Ukrainian Medical Stomatological Academy

THE DEPARTAMENT OF PATHOLOGICAL ANATOMY

WITH SECTIONSL COURSE

MANUAL

for the foreign students

GENERAL PATHOMORPHOLOGY

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Рекомендовано Вченою радою Української медичної стоматологічної академії як навчальний посібник для іноземних студентів – здобувачів вищої освіти ступеня магістра, які навчаються за спеціальністю 221 «Стоматологія» у закладах вищої освіти МОЗ України (протокол №8 від 11.03.2020р)

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A teaching manual in English, developed at the Department of Pathological Anatomy with a section course UMSA by Professor Starchenko II, Associative Professor Prylutsky OK, Assistant Zadvornova AP, Assistant Nikolenko DE.

The manual presents the content and basic questions of the topic, practical skills in sufficient volume for each class to be mastered by students, algorithms for describing macro- and micropreparations, situational tasks.

The formulation of tests, their number and variable level of difficulty, sufficient volume for each topic allows to recommend them as preparation for students to take the licensed integrated exam "STEP-1".

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INTRODUCTION TO PATHOMORPHOLOGY. SUBJECT MATTER AND TASKS OF PATHOMORPHOLOGY. MAIN STAGES OF DEVELOPMENT OF PATHOMORPHOLOGY. METHODS OF PATHOLOGY-ANATOMIC DIAGNOSTICS. METHODS OF PATHOMORPHOLOGICAL RESEARCH.

Pathomorphology - a discipline that gives the concept of the structural basis of human diseases for the in-depth assimilation of fundamentals of medicine and clinical picture of diseases with the subsequent use of the acquired knowledge in the practical work of the doctor.

Pathomorphology is based on pathological anatomy.

Pathological anatomy is a fundamental medical and biological science that studies the structural foundations of pathological processes and human diseases. Pathological anatomy (along with pathophysiology) is an integral part of pathology - a science that studies the patterns of occurrence and development of diseases, individual pathological processes and conditions.

Pathological anatomy studies the morphological manifestations of pathological processes at different levels (organ, tissue, cell and subcellular). Also widely used is the data obtained from the experimental modeling of pathological processes in animals.

The main tasks of pathological anatomy as a science:

1. Identification of the etiology of pathological processes, ie the causes (casual genesis) and conditions for their development.
2. Study of pathogenesis - the mechanism of development of pathological processes. The sequence of development of morphological changes is called morphogenesis. To refer to the mechanism of recovery (convalescence), the term "sanogenesis" is used, and the mechanism of dying (death) is tonatogenesis.
3. Characteristics of morphological picture of the disease (based on macro- and micromorphological features).
4. Study of complications and consequences of diseases.
5. Investigation of the pathomorphosis of diseases, that is, a stable and regular change in the picture of the disease under the influence of living conditions (natural pathomorphosis) or treatment (induced pathomorphosis).
6. Study of iatrogeny - pathological processes that have arisen as a result of diagnostic or therapeutic procedures.
7. Development of the theory of diagnosis.
8. Life-long and post-mortem diagnosis of pathological processes using morphological methods.

Pathological anatomy consists of two main sections:

1. General pathological anatomy - studies the common to all diseases patterns of their occurrence, development and completion. General pathology gives an idea of the typical pathological processes characteristic of a particular disease (metabolic disorders, dyscirculatory disorders, inflammation, immunopathological processes, adaptation and compensation processes, tumor growth, necrosis).
2. Special pathological anatomy - studies the morphological manifestations of certain diseases (nosological forms).

The main stages of development of pathological anatomy

In the history of pathological anatomy there are four main periods: anatomical (from antiquity to the beginning of the XIX century), microscopic (from the first third of the XIX century to the 50-ies of the XX century), ultramicroscopic (after 50-ies of the XIX century); modern, fourth period of development of pathological anatomy, characterized by the study of the basics of pathological processes at the molecular-genetic level.

The main methods of pathological anatomy research are *dissection, biopsy* and *experiment*. The objects studied by the pathologist can be divided into three groups: cadaveric material; substrates derived from patients during their lifetime (organs, tissues and parts, cells and parts, secretion products, liquids); experimental material.

Histological examination. This study is the subject of surgery and biopsy materials.

Biopsy (Greek. bios – life, opsis – vision) is a microscopic examination of vital tissue and cellular material obtained from a patient for the purpose of diagnosis, treatment, prognosis and scientific study.

The operating material includes tissues and organs removed during surgery. The study of surgical material allows us to confirm the diagnosis of the disease for which surgery was performed, and to determine its prognosis. Regardless of the purpose of surgical removal of pathologically altered tissues, they are necessarily subject to histological examination (keel sacs, appendices, tonsils, lungs, tumors, etc.).

For routine (daily) diagnostics, so-called universal (elective) methods of histological staining, which primarily include staining of histological sections with hematoxylin and eosin, are widely used. Tinctorial, that is, coloring, properties of hematoxylin are realized in a slightly alkaline environment, and the structures colored by this dye in blue or dark blue, commonly called basophilic. These include cell nuclei, lime salts and bacterial colonies. Weak basophilia may be caused by some types of mucus. Eosin, by contrast, at pH less than 7.0 dyes the so-called oxyphilic (eosinophilic) components in pink-red or red. These include cell cytoplasm, fibers, erythrocytes, protein masses and most mucus species. Also, micropreparations are painted according to the method of van Gizon, Hart, Perls and others.

Selective histological dyes are used for the purpose of identifying individual components of tissue or pathological substrates.

Method of coloring	*What turns out*	*Result*
Picrofuxin by van Gieson	Collagen fibers	Collagen fibers - crimson (red); nuclei, muscles, nerves, epithelial cells are bright yellow
Sudan III (orange)	Neutral fats	Orange color
Sudan IV	Neutral fats	Black color
Osmium acid	Neutral fats	Black color
Kos's reaction	Calcium	Calcium salts black
Congo red (rot)	Amyloid	Amyloid - bright red (brick), in polarization microscope - green
PAS reaction (McManus method)	Glycogen, neutral mucopolysaccharides	Glycogen (diastazolable) - dark crimson; neutral mucopolysaccharides - crimson
Toluidine blue	Acid mucopolysaccharides	Acid mucopolysaccharides are lilac, other structures are blue

Electron microscopy. For diagnostics of pathological processes on the material taken during the patient's life, in some cases electron microscopy is used (transmission - in a passing beam of light like light-optical microscopy and scanning - taking surface relief). Most often, such a need arises in oncomorphology and virology. For the diagnosis of certain types of histiocytosis, for example, histiocytosis-X, tumors from excised epidermal macrophages, the marker of which are Birbeck granules. Another example is rhabdomyosarcoma, the marker of which is Z-disks in tumor cells.

Immunohistochemical study. Histological and cytological preparations are applied with solutions with antibodies to antigens - tumor, viral, microbial, autoantigens and others. Antigens in normal histological staining are invisible. Serum antibodies carry a label: either fluorochrome, that is, a dye that glows in a dark field (in other words, which gives fluorescence), or a coloring enzyme. If a specific antigen is present in the tissues or cells under study, then the resulting antigen-antibody complex plus marker will accurately indicate its localization, amount, and help to study some properties.

In situ hybridization (ISH) is a method of direct detecting nucleic acids directly in cells or histological preparations. The advantage of this method is the ability not only to identify nucleic acids, but also to correlate with morphological data. The use of ISH can contribute to the diagnosis of viral infection in seronegative patients with AIDS, viral hepatitis. It can be used to study the role of viruses in carcinogenesis (thus linking the Epstein-Bar virus with nasopharyngeal carcinoma and Berkit's lymphoma, etc.).

Polymerase chain reaction (PCR) is a method of determining specific DNA or RNA sequences in any biological sample. PCR is an in vitro amplification (ie increase in copy number) of nucleic acids initiated by synthetic oligonucleotide primers.

Questions for self-control

1. Pathomorphology as a discipline.
2. The subject and tasks of pathomorphology.
3. The main stages of development of pathomorphology.
4. Methods of pathoanatomical diagnosis.
5. Methods of pathomorphological research.

MORPHOLOGICAL CHANGES OF CELLS AS RESPONSE TO STRESSOR AND TOXIC DAMAGE (PARENCHIMATOUSE / INTRACELLUAR DYSTROPHIES).

Alteration or **damage** (Latin alteratio - change) is a change in the structure of cells, intercellular matter, tissues and organs, which are accompanied by a decrease in their level of activity or its termination. Morphologically, alteration is manifested by dystrophy or necrosis.

Dystrophy (Greek dys - disturbance, tropho - feed) - morphological expression of metabolic disorders in cells.

Morphological essence of dystrophies

1) increase or decrease in the amount of any substances inherent in the body that are rapidly metabolized under physiological conditions;
2) change in quality, i.e. the physicochemical properties of substances inherent in the body in normal;
3) appearance of ordinary substances in an atypical place;
4) the appearance and accumulation of new substances that are not peculiar to these cells of the body.

The main causes of dystrophy:

I. Factors that impair cell autoregulation:
• toxic substances (including toxins of microorganisms);
• physical and chemical agents: high and low temperature, certain chemicals (acids, alkalis, heavy metal salts, organic substances), ionizing radiation;
• Acquired or inherited fermentopathy (enzymopathy);
• viruses.
II. Disorders of endocrine and nerve regulation:
• diseases of the endocrine organs (thyrotoxicosis, diabetes mellitus, hyperparathyroidism, etc.);
• diseases of the central and peripheral nervous systems (impaired innervation, brain tumors).
III. Impairment of the function of energy and transport systems that provide tissue (cell) metabolism.

The main mechanisms of development of dystrophies:

1. **Transformation** - the formation of products of one type of exchange from the common initial products that go to the construction of proteins, fats and carbohydrates. For example, carbohydrates are transformed into fats.
2. **Infiltration** - the ability of tissues or cells to accumulate excess amounts of any substance.
3. **Decomposition (phanerosis)** - the breakdown of intracellular and intracellular complex structures (protein-lipid complexes) that are part of the organelles membranes. For example, fatty cardiomyocyte dystrophy during diphtheria intoxication.
4**. Distorted synthesis**. At the distorted synthesis of cells form anomalous substances that are not inherent in the body. For example, in amyloid dystrophy, the cells synthesize an abnormal protein from which amyloid is then formed. In patients with chronic alcoholism, cells of the liver (hepatocytes) begin to synthesize foreign

proteins, from which the so-called alcohol hyaline (***Malory bodies***) is subsequently formed.

Principles of classification of dystrophies:

By reason and time of development	*By type of metabolic disorder*			*By prevalence of the process*
Acquired Hereditary	Protein	Fat	Carbohydrates	General Local

Protein dystrophy

By morphological manifestations and morphogenesis are divided into:

1. Hyaline-drop
2. Hydropic
3. Horny

Hyaline-drop dystrophy

Macroscopically: it has no characteristic manifestations, the appearance of organs and tissues varies little.

Microscopically: large hyaline-like protein aggregates and droplets of pink-red color (with hematoxylin and eosin staining) appear in the cytoplasm, which merge with each other and can fill the cell. It is more common in the kidney tubule epithelium.

By morphogenesis distinguish:

1. Dystrophies that develop due to the decomposition of organelle membranes, followed by the release of membrane proteins that coagulate into large rounded aggregates and are torn off into the tubular openings. Observed with acute anemia, shock, toxemia.

Consequences: The process is usually irreversible, culminating in the destruction of cells.

2. In persistent proteinuria, in patients with nephrotic syndrome, excess protein reabsorbed (infiltration) from the kidney tubules accumulates in the cytoplasm in large vacuoles in the form of large protein droplets.

Consequences: the process is reversed when proteinuria is eliminated.

Hydropic dystrophy

Localization: CNS neurons, skin epithelium and kidney tubules, hepatocytes.

Causes: Acute anemia, acute hypoxia, impaired water-osmotic balance.

Macroscopic: No typical changes in organs.

Microscopic: the appearance in the cell of vacuoles filled with cytoplasmic fluid. Often fills the entire cytoplasm and resembles a balloon - *balloon dystrophy*.

By morphogenesis distinguish:

1. *Cell edema* - the appearance in the cell of vacuoles filled with transparent cytoplasmic fluid. Fluid accumulates in endoplasmic reticulum cisterns and in mitochondria, sometimes in the nucleus of a cell.
2. *Cell swelling* - excessive hydration of the cytosol and the karyoplasm of the cell while increasing their volume. It develops in violation of the energy-dependent transport of ions and water through the plasmolem.

Consequences:
• in the case of short-term water-osmotic disorders, the dystrophy may be reversed,
• in case of acute anemia - unfavorable course, it can be transformed into balloon dystrophy (focal colliquative necrosis) and ends with total colliquative necrosis of the cell.

Horny dystrophy, or pathological keratinization

Classification:

By prevalence	By reason
- local - general	- congenital - acquired

Causes of development:
• chronic inflammation,
• the effects of physical and chemical factors,
• vitamin deficiency,
• congenital dysfunction of the skin, etc.

Types:

Hyperkeratosis - excessive formation of horny substance in keratinizing epithelium:
- local – skin horn,
- general – ichthyosis

Disceratosis – distorted keratinization.

Leukoplakia – pathological lesion on the mucous membranes covered with a multilayered flat non-keratinized epithelium (formation of the horny substance where it normally does not occur).

Localization: oral cavity, esophagus, uterine cervix.

Macroscopically: the area of gray-white color with clear borders, which rises slightly above the level of unchanged mucous membrane, is dense to the touch.

Microscopic: thickening of the multilayered flat epithelium, the phenomenon of hyperkeratosis and acanthosis.

Consequences:
• tissue repair may occur,
• cell death occurs in some cases.

Value:
• abnormal mucous membranes (leukoplakia) can be a source of cancer
• congenital severe ichthyosis is usually incompatible with life.

Fatty dystrophy

Fatty dystrophy of cells is manifested by an increase in the number of inherent lipids, the appearance of lipids of unusual composition, as well as their appearance in cells in which they are normally absent.

Reasons:
• oxygen starvation (tissue hypoxia);
• severe or prolonged course of infection (diphtheria, tuberculosis, sepsis);
• intoxication (phosphorus, arsenic, chloroform, alcohol);
• avitaminosis;

• eating disorders;
• heredity.

Fatty liver is manifested by a sharp increase in the content and change in the composition of lipids in hepatocytes.

Macroscopically: liver enlarged, yellow or guard-yellow in color, of a doughy consistency, with a greasy luster on the incision (***goose, clay liver***). When cut on the blade of the knife and the surface of the cut is visible fat.

Microscopically: small inclusions of lipids ***(powdered obesity***) appear first in the liver cells, then small droplets (***small droplets obesity***), which subsequently merge into large droplets (***large droplets obesity***) or into a fatty vacuole that fills all the cytoplasm ***("ring-shaped" cells***).

When staining tissue with hematoxylin and eosin in the cytoplasm of cells, the inclusion of fat have the appearance of optically empty vacuoles.

Histochemically, fats are detected by a number of methods:

- ***Sudan III - turns fats orange or red,***
- *Sudan IV and osmium acid - in black.*

By prevalence can be divided into:

• *disseminated:* Obesity is observed only in selected hepatocytes,
• *zonal*: obesity is occupied by hepatocyte groups,
• *diffuse* - Obesity spreads to the entire organ.

Fatty dystrophy of more than 50% of hepatocytes and excess of triglycerides in the liver by more than 10% was called ***liver steatosis***.

Consequences:

• fatty liver dystrophy is reverse;
• liver function in fatty dystrophy remains normal for a long time;
• when necrosis is associated, the function is impaired up to the development of liver failure and death.

Fatty myocardial dystrophy: triglyceride accumulation in cardiomyocytes.

Causes - chronic hypoxic conditions, especially in severe anemia, elderly patients with atherosclerosis, diphtheria.

Mechanism of dystrophy: **decomposition** or phanerosis (disintegration of lipoprotein complexes of membranes).

Macroscopically: in the myocardium from the side of endocardium the yellow stripes alternate with red-brown areas ("***tiger heart***"). The heart is enlarged in size, the cells are stretched, myocardium is pale, clay-yellow.

Microscopically: more often has a focal character; cardiomyocytes containing fat are located mainly in the course of venules, where the hypoxic factor is most pronounced.

Consequences: Myocardial contractility in fatty dystrophy is reduced and may lead to heart failure.

Cellular carbohydrate dystrophy

Carbohydrates found in humans are divided into:

• polysaccharides (glycogen)
• glycosaminoglycans - mucopolysaccharides (hyaluronic acid, heparin)
• glycoproteins (mucins, mucoids).

Parenchymal carbohydrate dystrophy may be associated with impaired metabolism of glycogen or glycoproteins.

Histochemically, polysaccharides, glycosaminoglycans and glycoproteins are detected by a *PAS reaction (pink color). Glycogen is stained with carmine Best in red.*

Disorders of glycogen metabolism:

• in diabetes mellitus

• glycogenoses (hereditary disorders of glycogen metabolism).

Diabetes mellitus is a disease characterized by absolute or relative insulin deficiency.

Clinical and morphological changes:

• hyperglycemia - increased blood glucose

• glucosuria - the appearance of glucose in the urine

• reduction of tissue reserves of glycogen in the liver with the development of fatty dystrophy

• infiltration of the renal tubule epithelium - polymerization of glucose into glycogen in the epithelium of the distal tubules. The epithelium becomes tall with light cytoplasm

• intercapillary (diabetic) glomerulosclerosis.

Glycogenoses are hereditary carbohydrate dystrophies that are associated with the absolute or relative insufficiency of enzymes involved in the breakdown of glycogen:

• without disturbing the structure of glycogen (Girke's, Pompe, Gers disease and others)

• with a disruption of glycogen structure (Forbes-Corey, Andersen disease)

Disorders of glycoprotein metabolism

Acquired mucous degeneration - inflammation (catarrhal) of the mucous membranes.

Hereditary mucosal dystrophy - cystic fibrosis.

Cystic fibrosis is a mucous dystrophy characterized by mucosal viscosity, which causes the development of retention cysts and sclerosis in the pancreas, bronchi, digestive and other glands.

Forms of cystic fibrosis:

• lung-intestinal

• pulmonary

• intestinal

• military

Pathomorphological changes.

Pancreas:

Macroscopically: without alteration or formation of small cysts

Microscopically: thick secretion in the ducts and acini of the gland, parenchyma atrophy (islet apparatus preserved), diffuse fibrosis and lymphohistiocytic infiltration of the interstitium.

Lungs: obstructive atelectasis with secondary infection and development of bronchitis, pneumonia, bronchiectasis, abscesses.

Intestine: coprostasis, intestinal obstruction.

Liver: Concentration of bile leading to cholestasis and biliary cirrhosis.

Macropreparations:

Fatty liver ("clay liver"): liver is enlarged in size, flabby, doughy consistency, yellow.
Fatty liver ("goose liver"): liver is yellowish-ochre color on the cut, doughy consistency.
Fatty heart dystrophy ("tiger heart"): myocardium is sluggish, pale yellow, the chambers of the heart are distended, the size of the heart is somewhat enlarged; under the endocardium, especially in the area of the papillary muscles, there is a yellow-white streak

Micropreparations:

Hydropic liver dystrophy (staining with hematoxylin and eosin): Hepatocytes contain transparent vacuoles of different sizes, filled with a translucent cytoplasmic fluid.
Hydropic dystrophy of the kidney (staining with hematoxylin and eosin): cells of the epithelium of tubules (nephrothelium) are enlarged, swollen, their contours are blurred. In the cytoplasm of cells, transparent vacuoles of different sizes filled with a translucent cytoplasmic fluid are determined.
Hyaline-drop liver dystrophy (staining with hematoxylin and eosin): hepatocytes contain homogeneous pink droplet-like inclusions (Melory bodies).
Fatty dystrophy of the liver (staining with hematoxylin and eosin): in the periphery (preferably) and in the centers of the liver lobules are detected hepatocytes, in the cytoplasm of which contain colorless vacuoles of different sizes. Large vacuoles in some hepatocytes push the nucleus to the periphery ("finger ring" cells).
Fatty liver dystrophy (staining with Sudan III): in the cytoplasm of hepatocytes, fat droplets of various sizes are colored in yellow-orange.

Questions for self-control

1. Dystrophy as a type of damage. Principles of classification of dystrophies.
2. Morphological nature and causes of dystrophies.
3. Mechanisms of development of dystrophies.
4. Parenchymatous dysproteinoses, general characteristics, classification.
5. Hyaline-drop dystrophy, morphological characteristics, consequences.
6. Hydropic dystrophy, morphological characteristics, consequences.
7. Horny dystrophy, morphological characteristics, consequences. Manifestations of horny dystrophy in the oral cavity.
8. Parenchymal lipidosis, morphological characteristics, consequences.
9. Parenchymal glycogenoses, morphological characteristics, consequences.

Examples of tests

Autopsy of a man who died from chronic cardiovascular collapse revealed "tiger heart". Sidewards of endocardium a yellowish-white banding can be seen; myocardium is dull, darkyellow. What process caused this pathology?

A. Fatty parenchymatous degeneration
B. Carbohydrate degeneration
C. Hyaline degeneration
D. Fatty vascular-stromal degeneration
E. Amyloidosis

A stillborn child was found to have thickened skin resembling of the tortoise shell, underdeveloped auricles. Histological examination of skin revealed hyperkeratosis,

atrophy of the granular epidermis layer; inflammatory changes were not present. What is the most likely diagnosis?

A. Ichthyosis
B. Leukoplakia
C. Xerodermia
D. Erythroplakia
E. Dermatomyositis

Microscopy of the kidneys from the dead patient who had suffered from chronic glomerulonephritis showed enlarged epithelial cells of the renal tubules, their cytoplasm was filled with vacuoles with transparent fluid, the nucleus was displaced to the periphery. Which parenchymatous dystrophy was present?

A. Hydropic
B. Horny
C. Hyalin drop
D. Protein
E. Fatty

Autopsy of the patient who had been ill with leukemia and died of increasing chronic anemia revealed an enlarged heart, dull, flabby, pale gray myocardium. There were yellow plaques and bands under the endocardium. Which pathologic process is observed in the heart?

A. Parenchymal fatty degeneration
B. Hyalin-drop degeneration
C. Mesenchymal fatty degeneration
D. Vacuole degeneration
E. Functional hypertrophy

Microscopic study of the biopsy material from the female patient who suffers from diabetes mellitus has revealed that the epithelium of narrow and distal segments of the tubules is high with light foamy cytoplasm. Staining with Best's carmine revealed red grains in the cytoplasm of the epithelium and tubules. Which parenchymatous dystrophy is present?

A. Carbohydrate
B. Fat
C. Hyalin-drop
D. Mucous
E. Protein

MORPHOLOGICAL CHANGES OF THE EXTRACELLULAR MATRIX (STROMA) AS AN ANSWER TO INJURY (STROMAL VASCULAR DYSTROPHY). PATHOMORPHOLOGY OF THE ACCUMULATION OF COMPLEX PROTEINS (HYALINOSIS) AND LIPIDS.

Stromal-vascular dystrophies are dystrophies that occur as a result of metabolic disorders in the connective tissue and are found in the fibrous-molecular matrix of organs and vessel walls.

Classification:

• protein (dysproteinoses)
• fatty (stromo-vascular lipidosis)

Disproteinoses (protein stromal-vascular dystrophies)

• mucoid swelling
• fibrinoid swelling
• hyalinosis

Mucoid swelling is the superficial and reverse disorganization of connective tissue. It is characterized by the accumulation in the paraplastic substance (in the main substance of the connective tissue) of glycosaminoglycans (mainly hyaluronic acid), which leads to increased vascular tissue permeability and the release of finely dispersed plasma proteins - albumins.

The mechanism of development is infiltration.

Causes: hypoxia, allergic, infectious diseases, collagenoses, atherosclerosis, endocrinopathy.

Localization: more common in the walls of arterioles and arteries, valves of the heart, parietal endocarditis.

Macroscopically: The organ or tissue is usually unchanged.

Microscopic: characteristic of **metachromasia**, especially with toluidine blue: in the focuses of mucoid swelling, the accumulation of glycosaminoglycans changes color from red-purple to red.

Significance: decrease in organ function.

Consequences:

• favorable - complete tissue repair,
• unfavorable - transition to fibrinid swelling.

Fibrinoid changes (fibrinoid swelling) - deep and irreversible disorganization of connective tissue, which is based on the destruction of the main substance of tissue and collagen fibers, which is caused by a sharp increase in vascular permeability and the formation of fibrinoid.

Fibrinoid is a complex substance composed of disintegrating proteins and polysaccharides of collagen fibers, of the main substance and blood plasma, of cellular nucleoproteins and the obligatory fibrin component.

The mechanism of development is infiltration and decomposition.

Macroscopic picture without changes.

Microscopic: Impregnation of plasma proteins by destroyed collagen fibers with yellow color by picrofuxin. Macrophages accumulate around the fibrinoid swelling zone. The latter are capable of producing monokines that promote the propagation of

fibroblasts. Thus, the area of fibrinoid swelling is replaced by connective tissue - sclerosis.
Metachromasia is not typical.
Significance: impaired or cessation of organ function - acute renal failure in malignant hypertension (fibrinoid necrosis and changes in arterioles).
Consequences: fibrinoid necrosis, hyalinosis, sclerosis.
Hyalinosis is characterized by the accumulation in the tissues of *translucent vitreous protein masses*, resembling hyaline cartilage, due to fibrinoid swelling, plasmorrhagia, sclerosis, necrosis.
Characteristics: homogeneous transparent dense masses of hyaline (fibrillar protein) are formed in the connective tissue, which are resistant to alkalis, acids, enzymes, PAS-positive, with picrofuxin colored in yellow or red, containing immune complexes, fibrin.
The mechanism of hyaline formation is the destruction of fibrous structures and their impregnation with fibrin and other plasma components (globulins, ß-lipoproteins, immune complexes, etc.).

Classification:

By prevalence	*By the organ specificity*
• local • systemic tissues • arterioles system walls	• hyalinosis of valves of heart and aorta at patients with rheumatism; • vascular hyalinosis in patients with hypertension and glomerulonephritis; • local hyalinosis in the capsule of the spleen ("glazed spleen") and at the bottom of chronic gastric ulcer (thickened translucent tissues of whitish color).

Hyalinosis of the valves of the heart and aorta in patients with rheumatism

It develops in rheumatism (rheumatic heart disease) in the mucoid swelling finale, fibrinoid changes and fibrinoid necrosis due to immune-complex damage to the valve stroma.
Macroscopically: in hyalinosis, the cusps of the valves of the heart are not transparent, dense, whitish color, thickened, fused together and sharply deformed. The atrioventricular opening is narrowed. The chordal filaments are thickened and shortened.
The consequence of rheumatism is unfavorable.

Hyalinosis of vessels

In the hyalinosis of vessels mainly small arteries and arterioles are affected.
Macroscopically: the arterioles are thick, dense, appear as gray translucent glass tubes with thick walls and a narrow opening.
Microscopically hyaline is detected in the subendothelial space, destroys the muscle cells, the vessel is tightened, the lumen is very narrow or completely closed.

Types of vascular hyaline:

• Simple - occurs due to the insudation of unchanged or unchanged components of the blood plasma (in hypertension, atherosclerosis);
• Lipohyaline - contains lipids and β-lipoproteins (in diabetes mellitus);
• Complex hyaline - built of immune complexes, destroyed structures of the vascular wall, fibrin (in diseases with immunopathological disorders - rheumatic diseases).

Consequences: hyalinized arterioles are unable to contract and dilate, contributing to persistent organ ischemia.
In hypertension due to hyalinosis arterioles develops arteriolosclerotic nephrosclerosis, or **primary wrinkled kidneys:** the kidneys decrease in size, compacted, their surface becomes fine-grained, the cortical layer becomes thinner.
The widespread hyalinosis of small vessels (mainly arterioles) underlies diabetic microangiopathy.

Hyalinosis of capillaries and glomeruli of kidneys at glomerulonephritis

Characterized by damage to immune complexes with the formation of fibrinoid necrosis in the walls of the capillaries, subsequently formed hyalinosis of glomerular capillaries and hyalinosis of the glomerulus of the kidneys.
Consequences: irreversible loss of nephrons, renal failure.

Pathomorphology of lipid accumulation

To stromal-vascular lipidosis include disorders:
1. Fat accumulation in fat depots (subcutaneous tissue, omentum, mesentery, mediastinal, epicardium) - **obesity.**
2. Disorders of fat metabolism (cholesterol and its esters) in the walls of the large arteries in atherosclerosis.

Obesity is an increase in lipids and adipose tissue in fat depots.

Classification of obesity:

According to the mechanism of development:
• alimentary;
• cerebral (in trauma, brain tumors);
• endocrine (in Frehlich and Cushing's syndrome, adiposogenital dystrophy, hypothyroidism, etc.);
• congenital.
Depending on the distribution of adipose tissue:
• android (apple) type (excess adipose tissue is localized in the abdomen);
• gynoid (pear-shaped) type (excess adipose tissue is localized in the thighs and buttocks);
• mixed type.
By percentage of excess body weight:
I degree - 20-29%;
II degree - 30-49%;
III degree - 50-99%;
IV degree - more than 100%.
By the number of adiposocytes and their size:
1) *hypertrophic* variant of general obesity: the number of adiposocytes is not changed, is formed by increasing their volume; has a malignant course;
2) *hyperplastic* variant of obesity: the number of adiposocytes is increased, their function is not broken; has a benign course.
Obesity of the heart develops with the general obesity of any genesis.
Macroscopically: the size of the heart is enlarged, the accumulation of a large amount of fat in the form of a case is determined under the epicardium, the fatty tissue sprouts into the stroma of the myocardium, the cardiomyocytes atrophy.

Consequence: is accompanied by the development of heart failure; a rupture of the right ventricle is possible in which the obesity is more pronounced.

Disorders of fat metabolism (cholesterol and its esters) in the walls of the aorta and large arteries underlies atherosclerosis.

Macroscopically: yellow spots and stripes are visible in the intima of the aorta, as well as white-yellow plaques that rise above the surface, some with ulcerations.

Microscopically: the formation of lipids in the form of droplets and cholesterol crystals, colored in orange, is visible in the coloring of Sudan III in the thickened aortic intimacy; fat inclusions are found in xantomic cells (macrophages, smooth muscle cells); among the lipid deposits is the growth of connective tissue.

Macropreparations

Hyalinosis of the capsule of the spleen: the capsule of the body is dense, whitish, translucent - "glazed" spleen.

Mitral valve hyalinosis: The mitral valve flaps are thickened, fused together, whitish, opaque, the left atrioventricular opening narrowed.

Simple obesity of the heart: the heart is enlarged in size, sluggish, under the epicardium considerable growth of adipose tissue, the chambers of the heart are enlarged, the heart muscle is cut in brownish brown color, the valves are thin, translucent, the chords and trabecular muscles are unchanged, the thickness is the walls of both ventricles are reduced.

Micropreparations

Hyalinosis of the capsule of the spleen (staining with hematoxylin and eosin): The capsule of the spleen is significantly thickened by the deposition of homogeneous eosinophilic substances. The parenchyma is not changed.

Hyalinosis of the arteries and white bodies in the ovary (staining with hematoxylin and eosin): the walls of small arteries are sharply thickened, homogeneous, pink. Their lumen is narrowed. White bodies have the appearance of homogeneous pink formations.

Questions for self-control

1. Classification of stromal-vascular dystrophies.
2. Mucoid swelling, morphological features, causes, consequences.
3. Fibrinoid swelling, morphological features, causes, consequences, significance.
4. Hyalinosis of the valves of the heart and aorta in patients with rheumatism, morphological features, causes, consequences, significance.
5. Systemic hyalinosis of arterioles in persons with hypertension, causes, morphology, consequences, significance for the body.
6. Obesity, types, causes, morphology, consequences, significance.
7. Obesity of the heart, causes, morphology, consequences, significance.

Examples of tests

Autopsy has revealed shrunken kidneys weighing 50 mg, with finegrained surface and uniformly thinned substance. Microscopic investigation has shown the thickening of arteriole walls due to accumulation of homogeneous anhistic pink-coloured masses in them. Glomerules were undersized, sclerotic, with atrophied tubules. What disease are these changes characteristic of?

A. Essential hypertension
B. Pyelonephritis with kidney shrinkage

C. Renal amyloidosis
D. Acute glomerulonephritis
E. Membranous nephropathy

Autopsy of a 78-year-old patient revealed that retroperitoneal tissue was soaked with blood, the abdominal aorta had a sacciform protrusion including a defect with irregular edges. The wall of the aorta was here and there of stone-like density. This is the complication of the following disease:

A. Atherosclerosis
B. Essential hypertension
C. Systemic vasculitis
D. Visceral syphilis
E. Marfan syndrome

Autopsy of a 58 year old man revealed that bicuspid valve was deformed, thickened and unclosed. Microscopically: foci of collagen fibrilla are eosinophilic, react *positively to fibrin*. The most probably it is:

A. Fibrinoid swelling
B. Fibrinous inflammation
C. Mucoid swelling
D. Hyalinosis
E. Amyloidosis

Autopsy of the man revealed the signs of rheumatic heart defect, i.e. thickened deformed cartilage-like valves with luster surface. Which process is present in the valves:

A. Hyalinosis
B. Fibrinoid necrosis
C. Fibrinoid swelling
D. Amyloidosis
E. Degenerative calcification

PATHOMORPHOLOGY OF THE CUMULATION OF PRODUCTS OF VIOLATED METABOLISM. DISORDERS OF IRON EXCHANGE AND METABOLISM OF HEMOGLOBOGENOGEN PIGMENTS.

PATHOMORPHOLOGIC MANIFESTATIONS OF IMPAIRED FORMATION OF MELANIN, EXCHANGE OF NUCLEOTOPROTEINS AND COPPER.CALCININOSIS OF TISSUE. CREATION OF STONES.

Pathomorphological manifestations of cumulation of products of impaired metabolism are observed in violation of the metabolism of complex proteins - **chromoproteins**, **nucleoproteins and lipoproteins**, as well as **minerals.**

Endogenous pigments (chromoproteins) are substances of various chemical nature that are synthesized in the body and have certain colors.

Disorders of the exchange and degradation of hemoglobinogenic pigments

Classification of endogenous hemoglobinogenic pigments:

Physiological	*Pathological*
Ferritin Hemosiderin Bilirubin	Hematoidin Hematins (hemomelanin, hydrochloric acid, formalin pigment) Porphyrin

Physiological hemoglobinogenic pigments:

Ferritin is normally in the inactive form associated with the disulfide group (SS-ferritin). In the absence of oxygen, the ferritin is reduced to the sulfhydryl active form (SH-ferritin), which has hypotensive and vasoparalytic properties.

Ferritin molecules are formed intracellularly by the binding of iron ions to the protein apopheritin:

a) *catabolic ferritin* - formed during the breakdown of red blood cells (including physiological) and destruction of hemoglobin mainly in monocytic-macrophage cells of the spleen, liver, bone marrow and lymph nodes

b) *anabolic ferritin* - binds iron ions delivered to the cell from the blood (iron ions are transported by protein transferrin).

Significant changes in the level of ferritin occur with massive and recurrent intravascular hemolysis.

With the polymerization of ferritin hemosiderin is formed.

Hemosiderin - large cytoplasmic grains of brown color, in a small amount formed under normal conditions with the natural breakdown (hemolysis) of red blood cells.

Microscopically: Erythrocyte degradation products are captured by cells of the reticulo-endothelial system of the liver, spleen, bone marrow and lymph nodes, where they are presented as brown grains of hemosiderin, which are formed in sideroblasts that contain siderosomes. Sideroblasts may retain hemosiderin, but at high concentrations the cells are destroyed and the pigment enters the stroma, staining it in a *rusty brown color*. In the **Perls reaction** (detection of iron ions by means of yellow blood salt in combination with hydrochloric acid), the granules become **blue-green (Berlin azure)**.

Pathological increase in hemosiderin - **hemosiderosis** (general and local).

General hemosiderosis occurs in intravascular hemolysis of erythrocytes: hemolytic anemia, leukemia; hemolytic poison poisoning; in infectious diseases (malaria, sepsis, typhoid fever, etc.); when transfused incompatible blood and rhesus conflict.

Macroscopically: the skin becomes brownish in color, the organs enlarged in volume, compacted, in the section brown or red.
Microscopically: hemosiderin is detected in the cells of the reticulo-endothelial system, as well as in the parenchymal cells of the liver, pancreas.
Consequences: In most cases, the accumulation of pigment in the organs does not lead to their dysfunction.
Local hemosiderosis develops in the foci of hemorrhage into the tissue during erythrocyte breakdown outside the vascular bed with hemoglobin release.
Brown lung induration - occurs with chronic venous stagnation in patients with chronic heart disease (stenosis of the mitral valve of the heart with rheumatism, cardiosclerosis, etc.).
Macroscopically: the lungs are enlarged, dense (induration) due to fibrosis, incised with numerous brown patches.
Microscopically: a large amount of brown pigment is detected in the lungs, which is found both in the stroma of the lungs and in the lumens of the alveoli and bronchi. The interveolar interseptions are significantly thickened by the growth of connective tissue.
Brain hematoma. At the site of bleeding, the brain tissue is destroyed, a cavity is formed, filled with blood clots and softened brain tissue (red softening of the brain). At the site of the hematoma a cyst with *rusty walls* and brownish contents due to hemosiderin is formed.
Bilirubin is found in the blood as indirect, i.e., albumin bound or unconjugated. Bilirubin is captured by hepatocytes, where glucuronic acid conjugates, and direct bilirubin enters the intestine.
Jaundice - the coloration of the skin and mucous membranes in yellow due to the increase in the amount of bilirubin in the blood plasma.
Jaundice can be congenital and acquired.

Types of jaundice by mechanism of development:

1) *hemolytic, or suprahepatic* - occurs as a result of increased hemolysis of blood in the vessels along with total hemosiderosis, the content of unconjugated bilirubin increases in the blood. Causes: hereditary anemia, bacterial infections, blood diseases, intoxication, transfusion of incompatible blood (patient needs hemodialysis). Consequences: Acute renal failure, hyperkalemia, acute anemia, nuclear jaundice.
2) *parenchymal, or hepatic*, occurs as a result of liver disease in which hepatocytes are unable to fully capture indirect bilirubin and conjugate it with glucuronic acid. Occurs with viral hepatitis, poisoning, hepatosis, cirrhosis and liver tumors. The content of conjugated and unconjugated bilirubin is increased in the blood. Consequences: hepatic coma, renal failure.
3) *mechanical or subhepatic* - occurs when obstruction of the common or hepatic ducts with stones, cancer of the fater papilla, atresia of bile ducts in newborns, tumors of the pancreas, etc. (the patient needs surgical treatment). It develops as a result of impaired intra-organ outflow of bile and causes cholestasis, which is accompanied by enlargement of the bile capillaries in the lobules, bile compaction and formation of bile clots. The walls of the biliary vessels are destroyed, the exit of bile beyond the bile capillaries leads to the death of hepatocytes. As a result, direct bilirubin and bile

acids enter the bloodstream, causing itching of the skin and small spot hemorrhages that are associated with high vascular permeability. Consequences: progressive hepatic-renal failure.

Macroscopically: the liver is enlarged, becomes yellow-green in color, intrahepatic ducts expand.

Microscopically: bilirubin is found in distended bile sinusoids, Kupffer cells (stellate reticuloendotheliocytes) and hepatocytes in the form of green-brown amorphous deposits.

Consequences: sclerosis and then cirrhosis.

Pathological hemoglobinogenic pigments

Hematoidin is a bright orange pigment that does not contain iron. It is formed during anaerobic destruction of erythrocytes and hemoglobin intracellularly, but, unlike hemosiderin, in cells does not remain and at their death is among necrotic masses. Hematoidin is found in the depths of obsolete hematomas, heart attacks with oxygen deficiency.

Hemomelanin, or malarial pigment, iron-containing, occurs only in malaria, as it is produced by the destruction of hemoglobin by malaria plasmodium. The pigment looks like *grains of black*. Organs enlarged, dense, in section of **gray-black** or **aspid color**. When excess pigment occurs aggregation of these grains - malarial stasis, which leads to ischemization of the CNS with subsequent necrosis and small hemorrhages. In addition, there is a general hemosiderosis, as well as the development of hemolytic jaundice.

Hydrochloric acid (hemin) is found at the bottom of erosions and gastric ulcers, where it is formed under the influence of enzymes of gastric juice and hydrochloric acid; the defect of the mucous membrane of the stomach thus turns **brown-black.**

Porphyrin is a pigment devoid of iron, the precursor of the prosthetic hemoglobin. Normally porphyrins are found in urine, blood, tissues and are melanin antagonists. In violation of the exchange of porphyrin (porphyria) increases the sensitivity to ultraviolet rays, skin erythema, dermatitis, porphyrinuria (**urine "color of portwine"**), staining of the spleen, teeth and bones in brown.

Pathomorphological manifestations of disorders of melanin formation

Melanin is a pigment of black color, synthesized by melanocytes. Tyrosine and tyrosinase enzymes are required for synthesis. Synthesis is regulated by the autonomic and endocrine systems. The autonomic (sympathetic) system increases its production, and the parasympathetic system reduces it. Endocrine system - adrenocorticotropic hormone stimulates, and melatonin suppresses. Melanin is found in the basal layer of the epidermis, the retina, the iris, the hair bulbs, the inner ear, and the soft meninge.

Disruption of melanin metabolism occurs through hyperproduction and hypoproduction. These disorders are widespread or local in nature and may be acquired or congenital.

Common hypermelanoses:

Bronze Disease (Addison Disease) - A acquired condition that exhibits increased diffuse skin coloration, hypotension, adynamia, and muscle weakness. The disease is caused by the adrenal gland (tuberculosis, amyloidosis, oncological processes). Under these conditions, ACTH is strongly synthesized.

Pigmented xeroderma is a hereditary disease that results from the deficiency of the enzyme endonucleasa involved in the disposal of melanin. The skin is dry, jaundice, with large pigment spots, exfoliates.

Local hypermelanoses are nevuses (birthmarks). This is a congenital malformation of the skin, characterized in that during embryogenesis there is a shift from the neuroectodermal tube of melanoblasts not only to the epidermis but also into the dermis. Sometimes a birthmark can be malignant in melanoma.

Total depigmentation:

Albinism is a congenital, genetically determined pathology associated with the absence or deficiency of tyrosinase enzyme production. Such people have white skin and hair, red iris, impaired thermoregulation and skin barrier function.

Local depigmentation:

Vitiligo - irregular depigmentation site, develops due to the appearance of antibodies to melanin, is hereditary.

Leukoderm is the area of rounded skin depigmentation resulting from exposure to pathogenic factors (syphilis, leprosy) on the skin. Initially, depigmentation appears on the skin of the neck and resembles a Venus necklace. Depigmentation can be after burns, synthetic substances, etc.

Disorders of lipoprotein metabolism

Lipofuscin is a pigment that looks like yellow pellets and is localized in or near the mitochondria. Normally, a small amount is contained in hepatocytes, cardiomyocytes and nerve cells.

Excessive amount of lipofuscin most often accumulates in the cells of the myocardium, liver, skeletal muscle during aging or depletion, which is accompanied by the development of so-called **brown organ atrophy**.

Brown atrophy of the heart.

Macroscopically: the heart becomes small, the amount of fatty tissue under the epicardium decreases significantly, the vessels become winding, the myocardium is thick, brown in color.

Microscopically: cardiomyocytes are reduced in size, granules of brown lipofuscin pigment are visible in the cytoplasm.

Brown liver atrophy.

Macroscopically: the liver is greatly reduced, its edge is sharp, the liver tissue is dense, brown in color.

Microscopically: liver beams are sharply thinned, in the cytoplasm of hepatocytes numerous brown granules of lipofuscin.

Pathomorphological manifestations of impaired nucleoprotein metabolism

Nucleoproteins are formed from protein and nucleic acids (DNA and RNA).

Their endogenous production and food intake are balanced by their disintegration and excretion of the final products of nucleic metabolism - uric acid and its salts by kidneys.

In violation of the exchange of nucleoproteins and excess formation of uric acid, its salts fall out in the tissues of the joints, kidneys and cause the development of gout, urolithiasis, uric acid infarction.

Gouty arthritis is the deposition of uric acid salts in the synovium and cartilage of small, ankle and knee joints, muscle sinews and joint bags. In response, necrosis and

inflammation (arthritis, bursitis) occur with the development of connective tissue and the formation of gouty *cones (tofu)*. There is deformation of the joints, movement in them is limited.
Microscopically: areas of necrosis with amorphous masses and crystals of uric acid are found in the gout cone, around them inflammatory infiltrate with giant multinucleated cells of foreign bodies and growth of connective tissue.
Due to the excess excretion of uric acid (hyperuricuria), ***urate (gouty) nephropathy*** is formed. Sodium urate is concentrated in the distal renal tubules and collecting tubes, causing obturation, deposited peritubularly in the form of crystals, causing inflammation of the interstitium.
Consequence: formation of gouty kidney with development of renal failure.
Urolithiasis - the formation of kidney stones.
Uric acid infarction - deposition of masses of uric acid sodium and ammonium in tubules and collecting tubules of kidneys in newborns.

Pathomorphological manifestations of copper exchange disturbance

Appears in hepatocerebral dystrophy (*Wilson disease*): copper is deposited in the liver, brain, kidneys, cornea (*Kaiser-Fleischer's ring* - greenish-brown ring on the edge of the cornea), pancreas, testicles and other organs, and leads to liver cirrhosis and dystrophic changes in the basal nuclei of the brain (lenticular nucleus, caudate body, pale orb).

Calcinosis (calcification) of tissues

Calcification - deposition of calcium salts in cells or intercellular substance.

Types of calcification:

1. *Metastatic (systemic) calcification* (calcareous metastases).

Reasons:
• parathyroid hormone hyperproduction,
• deficiency of calcitonin,
• myeloma disease,
• D. hypervitaminosis.

These conditions lead to persistent hypercalcemia and the loss of calcium salts in various organs and tissues (lungs, gastric mucosa, kidneys, myocardium, artery walls).

Macroscopically: the appearance of organs does not change. The incision surface sometimes shows whitish inclusions.
Microscopically: numerous small foci of dark purple are found, represented by inlaid calcium salts, necrotized cells (cardiomyocytes, epithelium of the kidney tubules, etc.), often with adjacent areas of stroma, around which inflammatory infiltration may occur.
The specific color for detecting the focuses of calcification is the silvering of Cossa, in which they are colored in black.
Consequences: usually metastatic calcification does not lead to impaired function, sometimes, due to lung damage, respiratory failure develops, and massive nephrocalcinosis can lead to renal failure.
2. Dystrophic (local) calcification (petrification) - the deposition of calcium salts is usually found in dead or dystrophied tissues. Occurs at a normal concentration of calcium in the blood and has a local character

The most common:
a) petrifices in the lungs arising from the healing of the foci of caseous necrosis in tuberculosis - foci of white color, stony density, surrounded by a connective tissue capsule;
b) calcificated atherosclerotic plaques (atherocalcinosis).
3. Metabolic calcification (calcium gout) occurs in the absence of dystrophy, necrosis and hypercalcemia. Importance is attached to the disturbance of the buffer systems or calcifaxia (increased sensitivity of tissues to calcium).

Formation of stones in organs

Stones (concretions) are dense formations that form in the hollow organs or excretory ducts of the glands.

Types of stones:

By shape	*By number*	*By surface relief*	*By color*
• round, oval (urinary bladder and gall bladder) • adolescent (in pelvis and calicies of kidneys) • cylindrical (in gland ducts)	• single • multiple	• smooth • rough (oxalates)	• white (phosphates) • yellow (urate) • dark brown and dark green (pigment)

The chemical composition of the stones are:
• bile (cholesterol, pigment, lime, mixed)
• Urinary (urate, phosphate, oxalate, cystine, xanthine)
• bronchial (compacted slimy mucus)
• intestinal (sealed intestinal contents)
• venous - petrified blood clots separated from the vein wall
Consequences of stone formation:
1) As a result of the pressure of stones on the tissue, its necrosis, bedsores, perforations, adhesions (gangrene of the gallbladder) may occur.
2) Inflammation of the mucous membranes (cholecystitis, cholangitis).
3) Violation of secretion outflow (mechanical jaundice).

Macropreparations

Brown induration of the lungs: lung is dense, brown on the cut.
Brown atrophy of the heart: the heart is reduced in size; fatty tissue under the epicardium is absent, the course of the vessels is winding; brown heart muscle due to deposition of lipofuscin pigment.
Pulmonary calcification (petrification): foci of dystrophic calcification (calcification) in the tissue of the lung at the focus of caseous necrosis (after healing of tuberculous foci), perifocal sclerosis around the foci of calcification.
Kidney stones: The kidney bowls contain concretions of gray-yellow with uneven edges. Renal bowls, renal cups sharply expanded, kidney tissue thinned, atrophic (hydronephrosis).
Gallstones: The gallbladder is filled with lots of yellow-brown stones of different sizes, the wall of the bladder is thickened, whitish in color.

Micropreparations

Liver with obstructive jaundice (staining with hematoxylin and eosin): the bile ducts and capillaries are sharply enlarged, full of bile. The deposition of yellow-brown pigment (bilirubin) is observed in the cytoplasm of several hepatocytes.
Calcium metastases in the myocardium (metastatic calcification) (staining with hematoxylin and eosin): calcium salts in the form of numerous violet formations of various sizes are deposited in myocardiocytes and stroma of the heart.
Brown induration of the lung (staining with hematoxylin and eosin): granules of brown pigment are determined in the cytoplasm of cells (sideroblasts, siderophages) and extracellular space. Pigmented cells are located in the lung stroma and the cavities of the alveoli. The interalveolar septa are thickened, sclerotized. Vessels of the lung are full-blooded, enlarged; there are hemorrhages in the interalveolar septa.
Brown induration of the lung (Perls reaction): the pigment hemosiderin stains blue (the formation of Berlin's azure) in the cytoplasm of cells (sideroblasts and siderophages).

Questions for self-control

1. Definition of mixed dystrophies.
2. Classification of endogenous pigments (chromoproteins) by origin.
3. Types of hemoglobinogenic pigments that are formed in the body in normal and pathology.
4. Hemosiderosis: classification, causes, types depending on the mechanism of development, macro- and microscopic characteristics, method of histochemical detection of hemosiderin.
5. Pathomorphological manifestations of bilirubin metabolism disorders: types of jaundice by mechanism of development, morphological manifestations.
6. Hematoidin: mechanism of formation, localization of pigment.
7. Hematins: hemomelanin, hematin hydrochloric acid; causes of formation, localization of pigments, morphological changes in organs.
8. Porphyria: causes, morphological manifestations.
9. Pathomorphological manifestations of melanin metabolism disorders depending on the change in the amount of melanin; causes, prevalence, macro- and microscopic manifestations.
10. Lipofuscinosis: causes, morphological manifestations in the affected organs.
11. Pathomorphological manifestations of impaired nucleoprotein metabolism: clinical and morphological characteristics.
12. Calcinosis (calcification): the essence of the process, types of calcification, depending on the mechanism of development.
13. Pathomorphology of copper exchange disturbances, main causes and complications.
14. Concretes: classification, main causes of formation and complications.

Examples of tests

A patient died from acute cardiac insufficiency, among clinical presentations there was gastrointestinal haemorrhage. Examination of mucous membrane of sromach revealed some defects reaching muscle layer; their edges and bottom were mostly even and loose, some of them contained dark-red blood. What pathological process was revealed?

A. Acute ulcers

B. Chronic ulcers
C. Erosions
D. Thrombosis
E. Inflammation

A 49-year-old man complains of pain in his metatarsophalangeal joints and joint deformation. In blood hyperuricemy can be observed. X-ray has revealed metatarsophalangeal joint space narrowing, erosion, periarticular calcification of the both joints, osteoporosis. Microscopy has revealed inflammatory granulomatous reaction surrounding necrotizing masses in the area of the first metatarsophalangeal joint. Choose the most likely diagnosis:

A. Gout (podagra)
B. Pyrophosphate arthropathy
C. Rheumatoid arthritis
D. Hyperparathyroidism
E. Urolithiasis

The patients with hypernephroid cancer of the kidney with multiple metastases developed bronze coloring of the skin, weakness, hypotension, adynamia. Which pigment is responsible for the changes in the color of the skin:

A. Melanin
B. Hemosiderin
C. Porphyrin
D. Lipofuscin
E. Biliverdin

Gastroscopy revealed an ulcer with dense herders and black-brown bed in the gastric mucosa. Microscopy revealed black-brown pigment on the necrotic layer in the ulcer bed. Which pigment is it?

A. Hydrochloric hematin
B. Porphyrin
C. Bilirubin
D. Ferritin
E. Hemosiderin

After a snake bite a woman developed hemolytic anemia, in spite of the intensive therapy the patient died on the 7th day. The autopsy showed brown spleen, bone marrow and lymph nodes. Microscopy revealed Pearls- positive pigment in the cytoplasm of macrophages of these organs. Which pigment was present in the tissues?

A. Hemosiderin
B. Hematin
C. Lipofiiscin
D. Bilirubin
E. Hematoidin

THE BASICS OF TANATOLOGY. NECROSIS. CLINICAL AND MORPHOLOGICAL FORMS OF NECROSIS. SELECTIVE LOSS OF SPECIALIZED CELLS: PATHOGEN-INDUCED APOPTOSIS, SELECTIVE CELL DEATH INDUCED BY THE IMMUNE SYSTEM, AND CELL DESTRUCTION BY ACTIVATED COMPLEMENT.

Thanatology - (Greek. Thanatos - death and logos - science) the science of the causes and mechanisms of death, as well as posthumous changes of the dead body.

Death is the cessation of life of the organism as a living biosystem.

Death Categories:

Violent death occurs prematurely as a result of the action on the body of various environmental factors - mechanical, thermal, chemical and more. Usually the circumstances of a violent death are examined by forensic experts on the instructions of law enforcement agencies.

Nonviolent death is a consequence of incompatibility of life with those changes in the body that occur in various pathological processes:

• physiological - occurs in old age due to the natural (physiological) deterioration of the body. It occurs very rarely: human life is reduced by disease and external damaging factors.

• sudden - when the disease causing the death develops rapidly (from a few minutes to 6 hours, such as acute myocardial infarction, hemorrhagic insult) or has a hidden course (aneurysm of the cerebral vessels, PE). The circumstances of sudden death are also often studied by forensic experts.

• from life-long diagnosed diseases: cardiovascular system, respiratory system, diseases of the gastrointestinal tract, urogenital, etc.

By the development of reversible or irreversible processes distinguish:

• Clinical death - characterized by cessation of blood circulation and breathing, but these changes in the body's activity within a few minutes are reversed.

• Biological death - irreversible changes in the life of the body, the beginning of autolytic processes.

Characteristics of clinical death. Clinical death is characterized by complete absence of pulse and breathing, but metabolism, although at a minimal level, is still preserved, so at this stage it is possible to revive the body (reanimation).

Agony is a profound inhibition of vital functions. Consciousness is lost, reflexes are diminished, heart and respiratory function are weak, signs such as arrhythmia, convulsions, sphincter paralysis, and pulmonary edema appear. The body temperature decreases.

Characteristics of biological death. Biological death is the stage of irreversible disorders of the life of the body.

Signs of death and post-mortem changes.

Indicative signs of death: can be observed in both biological and clinical death in a patient who is in a state of deep coma. Therefore, it is not possible to ascertain biological death on the basis of such features alone. The indicative features include: stationary position of the body, pallor of the skin, lack of breathing and heartbeat, no reflexes from the pupils, cornea, etc.

Certain signs are observed only after the biological death. Distinctive signs of death:

1. The cooling of a corpse develops due to the fact that the body stops producing heat and its temperature is aligned with that of the environment. If the patient had a high fever before death or had convulsions during the agonistic period, the corpse cooled more slowly.
2. A skeletal rigor is manifested by the compaction of the skeletal muscles. It is explained by the accumulation of lactic acid in the muscles. First, the facial muscles are tanned, then the neck, torso, limbs. In 2-5 hours the cadaveric rigor covers all muscles. It is stored for 2-3 days and disappears in the same sequence as it occurs. With the forced removal of a corpse rigor, it no longer appears.

Significant signs of death also include cadaveric changes such as:

1. Cadaveric drying is the result of evaporation of moisture from the surface of the body. Drying is associated with clouding of the cornea and the appearance of dry brown spots. The mucous membranes become dry, dense, brown in color. On the skin - parchment stains.
2. The redistribution of blood in a corpse is characterized by the plethora of veins and the obstruction of the arteries. Blood drains into the lower body parts and accumulates in them.
3. Corpse spots (cadaveric hypostasis) appear 3-6 hours after death and appear as dark purple spots that fade when pressed. Corpse hypostases are absent in areas that are subject to pressure (sacrum, buttocks, shoulder blades). When post-mortem hemolysis of erythrocytes occurs, corpse spots are impregnated with stained hemoglobin blood plasma. Late cadaver spots or cadaveric imbibition occur. These spots are reddish-pink in color and do not disappear when pressed.
4. Corpse decomposition is associated with the processes of autolysis and decay. Postmortem autolysis first occurs in the pancreas, liver, stomach.
5. Corpse emphysema. Autolysis is quickly joined by the processes of decay due to the multiplication of bacteria in the intestines and other tissues. The gases produced by decay inflate the intestines and enter the tissues and organs. The cadaveric emphysema develops.

Necrosis

Necrosis (Greek. *Nekros* - dead) - premature death and destruction of cells and tissues in a living organism under the influence of factors of critical damage.

Necrosis Factors:

Physical - mechanical damage, radiation, electricity, low and high temperature (frostbite and burn).

Chemicals - acids, alkalis, salts of heavy metals, enzymes, medicines and others.

Biologicals - microorganisms, their toxins, endo- and exoantigens, immune complexes.

Depending on the cause, there are *5 types of necrosis*:

1. Traumatic - occurs when exposed to physical (mechanical, temperature, radiation, etc.) and chemical (acids, alkalis, etc.) factors.
2. Toxic - occurs when exposed to bacterial and other toxins.
3. Trophoneurotic - associated with impaired microcirculation and tissue innervation in chronic diseases.
4. Allergic - develops in immunopathological reactions.

5. Vascular (infarction) - associated with impaired blood supply of the organ or tissue.

Depending on the mechanism of action of pathogenic factors distinguish:

Direct necrosis: caused by direct action of factors (traumatic, toxic).

Indirect Necrosis: Occurs indirectly through the vascular and neuro-endocrine systems (allergic, vascular, and trophoneurotic necrosis).

By prevalence:

• focal (partial) - death of part of an organ

• total - death of the whole organ.

Necrosis stages:

I. Paranecrosis - reversible changes similar to necrotic.

II. Necrobiosis - irreversible dystrophic changes.

III. Cell death - necrosis (criteria for determining the moment of cell death do not currently exist).

IV. Autolysis - the decomposition of a dead substrate by the action of hydrolytic enzymes released from a damaged cell.

Morphological signs of necrosis

Changes in nuclei at necrosis:

Karyopiknosis – wrinklage of nucleus

Karyorrhexis - decomposition of the nucleus into the grains

Karyolysis - dissolution of the nucleus

Changes in cytoplasm:

Cytoplasmic coagulation - denaturation of cytoplasmic proteins: it becomes homogeneous and expressed acidophilic.

Plasmorexis - decomposition of the cytoplasm into the grains.

Plasmolysis - hydrolytic melting of the cytoplasm due to the destruction of cell membrane structures.

Cytolysis - complete destruction of a cell with the formation of a granular homogeneous mass - tissue detritus, around which demarcating inflammation occurs. Its expediency consists in demarcation of the center of a necrosis, participation in resorption of necrotic masses with the subsequent organization (replacement by a connective tissue).

Clinico-morphological forms of necrosis.

I. Coagulative necrosis

II. Colliquative necrosis

III. Gangrene

IV. Sequestration

V. Infarction

I. Coagulative (dry) necrosis usually occurs in organs rich in proteins and poor in fluid (kidneys, myocardium, adrenal glands, spleen). Dead areas are dry, dense, crumbling, white or yellow in color.

Types of coagulative necrosis:

Caseous (cheese) necrosis develops in tuberculosis, sometimes syphilis, as well as in lymphogranulomatosis. In the internal organs there is a dry, limited area of whitish-yellow crumbling color.

Waxy or Zanker Necrosis - Necrosis of the muscles, most often the anterior abdominal wall and internal muscles of the thigh, with severe infections (typhoid fever). Necrosis sites externally resemble a stearin or wax candle.
Fibrinoid necrosis - occurs in connective tissue and vescular walls, as a consequence of fibrinoid swelling in immunopathological processes, allergic diseases. Necrotic masses are impregnated with plasma proteins, fibrinogen.
Consequences:
• Petrification - deposition of calcium salts at the site of necrosis that is not amenable to autolysis.
• Osification - bone formation in the area of necrosis, which is often observed in the lungs.
• Inlay - deposition of uric acid salts in necrotized masses.
• Encapsulation - the growth of connective tissue around the necrotic lesion.
• Organization - replacement of dead masses with connective tissue.
• Cavern - the formation of a cavity, which communicates with the environment, formed by the release of necrotic masses.
II. Colliquative (wet) necrosis develops in tissues relatively protein-poor and fluid-rich, where there are favorable conditions for hydrolytic processes. Cell lysis occurs as a result of the action of its own enzymes (autolysis). A typical example is a *gray softener (ischemic infarction) of the brain*. Secondary colliquation is melting of the masses of dry necrosis.
Consequences:
• Cyst - the formation of a cavity after absorption of tissue detritus.
• Erosion - superficial defect of epithelial coverings.
• Ulcer - a deep defect of the epithelial covering that penetrates the muscular or serous membrane and is formed after the removal of necrotic masses.
• Maceration - rejection of the dead epidermis.
III. Gangrene (Greek. *Gangraina* - fire) - necrosis of tissues that interact with the external environment and change under its influence.

Types:

1. *Dry gangrene* - necrosis of tissues poor in fluid, which are combined with the external environment, occurs without the participation of microorganisms. Necrotized tissues are black, dry, clearly separated from viable tissue. On the border with healthy tissues there is *demarcation inflammation*. The change in color is due to the conversion of hemoglobinogenic pigments into iron sulfide in the presence of hydrogen sulfide.
Examples:
- dry gangrene of the limb in atherosclerosis and thrombosis of its arteries (atherosclerotic gangrene),
- at obliterating endarteritis;
- during frostbite or burns;
- fingers in Raynaud's disease or vibrational disease;
- skin in typhus and other infections;
Consequences of dry gangrene:
• Mummification - drying and compacting dead tissue under the influence of air;

• Mutilation - the self-rejection of a necrotized part of a body or organ into the external environment.

2. *Moist (wet) gangrene* - develops usually in tissues rich in fluid as a result of attachment of a bacterial infection. Moisture gangrene can occur on the extremities, but more often - in the internal organs (in the intestine with obstruction of the mesenteric arteries (thrombosis, embolism), in the lungs as complications of pneumonia (influenza, measles), pulp of the tooth, as complications of caries. the reason that the necrotic area becomes swollen and red-black, not clearly distinguished from adjacent healthy tissue, ie, the demarcation zone is not expressed. As a result of the activity of bacteria, a specific odor occurs.

Consequences of wet gangrene:

• Self-amputation - rejection into the internal environment of a dead organ or tissue.

• Septic autolysis - purulent melting.

3. *Noma* (Gr. Nome - water cancer) - wet gangrene of the soft tissues of the cheeks, perineum, which develops in children weakened by infectious disease (usually measles, HIV).

4. *Bedsore (decubitus)* - a type of gangrene, characterized by the death of superficial areas of the body (skin, soft tissues), which are subjected to compression, usually between bed and bone, in long-standing, stationary patients. Bedsores appear more often in areas of spinous processes of vertebrae, sacrum, large femur, elbows, nape, etc. The morphogenesis of the bedsores is a trophoneurotic necrosis, because the vessels, nerves are constricted and this increases the disturbance of the trophicity of tissue.

5. *Gas gangrene* - an independent infectious disease that is caused by anaerobic microflora (*Cl.perfringens* and other microorganisms in this group) and is characterized by widespread tissue necrosis with gas formation as a result of bacterial enzymatic activity. The main manifestations are similar to wet gangrene, but with the presence of gas in the tissues and the appearance of crepitus (the phenomenon of cracking on palpation).

IV. Sequestration is a section of dead tissue that is not subject to autolysis, is not replaced by connective tissue and is freely placed among living tissues. Around the bone sequester, a sequestral capsule and cavity with pus are formed. (for example, chronic osteomyelitis).

V. Infarction is a type of vascular (ischemic) necrosis of the internal organs as results of extreme degree of ischemia.

Depending *on the size* of a infarction distinguish:

• total - infarction of the whole organ;

• subtotal - infarction of part of organ;

• microinfarction - detected only microscopically.

The shape of a infarction depends on the type of branching of the organ vessels.

a) wedge-shaped (triangular, cone-shaped) in organs with magistral type of branching of vessels and with poorly developed collaterals (spleen, kidney, lung). Such organs usually have anatomical formations - gates that contain blood vessels. The top of the wedge-shaped infarction is directed to the gates of the organ;

b) the irregular form of infarction is observed in organs with a scattered type of blood supply and a large number of anastomoses (myocardium, brain).

Types of infarctions

1. *White (ischemic)* - looks like a region of white and yellow, clearly separated from the surrounding tissues. It occurs in organs with insufficient collateral circulation, which excludes blood flow to the necrosis area. It occurs more often in the brain and spleen.

Ischemic cerebral infarction occurs more frequently in atherosclerosis and hypertension. Immediate causes of development: thrombosis, thromboembolism.

Macroscopic: foci of irregular shape, flabby mushy consistency, grayish color (***site of gray softening***).

Ischemic spleen infarction: the most common cause is thromboembolism.

Macroscopically: site of necrosis triangular in shape, white, dry, dense consistency, top turned to the gates of the organ, and the base is under the capsule; capsule in the infarct area rough, covered with fibrinous overlays.

2. *White infarction with hemorrhagic crown* - a site of necrosis of white-yellow color, surrounded by a zone of hemorrhages: a spasm of vessels at the periphery of infarction is replaced by their paretic expansion and occurrence of hemorrhages. Often occurs in the myocardium, kidneys.

Myocardial infarction.

Macroscopically: a lesion of irregular shape, sluggish consistency, surrounded by a zone of small hemorrhages and dilated blood vessels is determined in the wall of the left ventricle or interventricular septum.

Microscopically: cardiomyocytes without nuclei (karyolysis) are visible in the necrosis zone, with decay of the cytoplasm (plasmorexis); on the periphery of necrosis - demarcation inflammation in the form of blood vessels hyperemia and infiltration of tissue by polymorphonuclear leukocytes; in preserved areas of the myocardium - degenerative changes of cardiomyocytes.

Kidney infarction.

Macroscopically: a section of triangular shape, the base facing the capsule, surrounded by a dark red crown.

Microscopically: only the contours of the glomeruli and tubules are preserved in the necrosis zone, their nuclei (karyolysis) are absent in their cells, and in these regions, the structure of pink structures (necrotic detritus) is visible; on the periphery - zone of demarcation inflammation, in which there are full blood vessels, hemorrhages, accumulation of polymorphic-nuclear leukocytes; further determined preserved renal tissue, in the epithelium of the tubules - dystrophic changes.

3. *Red (Hemorrhagic)* - A section of dead tissue dark red, impregnated with blood (lungs, intestines), separated from the surrounding tissues. It usually occurs in **conditions of venous stagnation**.

Most often occurs in the lungs with thromboembolism or thrombosis of the branches of the pulmonary artery in conditions of venous plethora.

Mechanism: in conditions of stagnant plethora and closure of the branch of the pulmonary artery (thrombus, thromboembolism) blood from the bronchial artery is sent to the anastomosis under high pressure in the area of death. Thus there is a rupture of capillaries and seepage of dead tissue by erythrocytes.

Macroscopically: pulmonary infarction is triangular in shape, dark red, dense consistency, the base is turned to the pleura, on the pleura in this area - fibrinous overlays.
Microscopically: the rupture of the interveal septa, the absence of nuclei in the cells forming the interveal septa, and in the alveolar epithelium are determined in the necrosis site; the area of necrosis is impregnated with blood. In the area of demarcation inflammation - leukocyte accumulation.
Infarction stages:
• necrotic
• organizations
In the stage of organization in the area of demarcation inflammation appears young connective (granulation) tissue, which gradually replaces the necrosis and, when ripe, leads to the formation of scarring at the site of infarction.
In the brain, a cyst is formed at the infarct site, sometimes (with microinfarctions) - a glial scar.
The *cyst* is a hollow formation that is filled with blood after a hemorrhagic stroke and after ischemic stroke with necrotized brain tissue. Over time, the contents of the cyst are resorbed by phagocytic glial cells. After ischemic infarction cyst walls are gray, after hemorrhagic infarction cyst walls are brown (brown, rusty cyst) due to the presence of hemosiderin (local hemosiderosis).

Infarct morphology

Organ	Type of infarction	Type of necrosis
Heart	White with hemorrhagic crown	Coagulative with secondary colliquation
Lungs	Red	Coagulative
Kidneys	White with hemorrhagic crown	Coagulative
Brain	White and red	Colliquative
Spleen	White	Coagulative
Intestine	Red	Colliquative

Apoptosis

Apoptosis is a gene-programmed death of a cell that occurs under physiological conditions in the self-healing of cell populations at the end of the life cycle of any cell.
Pathogen-induced apoptosis is prematurely programmed by genes for cell death triggered by factors of critical alteration.
Apoptosis, in contrast to necrosis, is an active process. After exposure to etiological factors, a genetically programmed cascade of reactions is triggered, accompanied by the activation of certain genes, synthesis of proteins, enzymes that lead to the efficient and rapid removal of cells from the tissue.

Causes and significance of apoptosis:

1. During embryogenesis, apoptosis plays an important role in the destruction of various tissue germs and the formation of organs.
2. Aging cells that have completed their development cycle are subject to apoptosis.
3. In growing tissues, part of the daughter cells to be apoptotic is determined.
4. Weak effects of damaging factors that at higher intensity can lead to necrosis (hypoxia, radiation, toxins).

Morphological manifestations of apoptosis:

• *Reduction in cell size*, compaction of the cytoplasm; Organelles that look relatively normal are more compact.

• *Condensation of chromatin* under the nuclear membrane. Nucleus can be broken into two or more fragments.

• *Formation of apoptotic bodies*. In the apoptotic cell, deep projections of the cell membrane are formed, which leads to the exfoliation of the cell fragments - the formation of membrane-surrounded apoptotic bodies, consisting of cytoplasm and tightly located organelles, with / or without nucleus fragments.

• *Phagocytosis* and destruction of apoptotic cells are carried out by surrounding healthy cells in their lysosomes.

Apoptosis, unlike necrosis, is not accompanied by an inflammatory response.

Selective cell death induced by the immune system and cell destruction with activated complement.

Immune-induced cell death involves two processes: recognition by the immune system of target cells as foreign and their immediate destruction.

This way destroys infected, tumor, transplanted cells, as well as normal cells of the body, recognized as foreign in autoimmune diseases. The immune destruction of target cells is carried out by either immunocytes (immunocellular destruction) or activated complement.

Immuno-cellular destruction of cells occurs by phagocytosis and immuno-cellular killing. Phagocytosis is the absorption and destruction of cell fragments in phagolysosomes of phagocytes.

Immunocellular killing (cell-mediated cytotoxicity) is the destruction of target cells by immune cells without their absorption. Keeling is carried out by T-killers (cytotoxic T-lymphocytes), natural killers (NK cells, or null cells), K-cells, and, probably, macrophages.

The complement is able to activate on blood cells pre-labeled with antibodies or immune complexes and cause their death.

Macropreparations

Foot gangrene (dry): Toes wrinkled (mummified), black with a clear border between healthy tissue and necrotic areas.

Intestinal gangrene (wet): area of the intestine is dirty gray, swollen, without clear borders.

Ischemic myocardial infarction with a red crown: in the thickness of the myocardium of the left ventricle of the heart there is a clear section of gray-yellow color, irregular in shape, limited by a red rim (crown).

Ischemic infarction of the spleen: a section of white-gray color with clear borders, wedge-shaped, the base turned to the capsule of the spleen, and the apex to the gate of the spleen; at the apex of the infarction is determined by a vessel with a blood clot.

Micropreparations

Pancreatic necrosis (staining with hematoxylin and eosin): An unstructured homogeneous eosinophilic region is defined, in the periphery of which the preserved structure of the pancreas is located.

Necrosis of the epithelium of the kidney's tubules (staining with hematoxylin and eosin): at a large magnification there are no nuclei (karyolysis) in the majority of

tubule epitheliocytes, their cytoplasm are homogeneous, eosinophilic, luminal contours of the cell are not clear. The structure of the glomeruli is partially preserved.
Necrosis of the lymph node in tuberculosis (staining with hematoxylin and eosin): The homogeneous pink masses of tissue detritus are determine, around which an infiltrate of epithelioid, lymphoid cells and single cells of Pirogov-Langhans.
Lung infarction (staining with hematoxylin and eosin): There are foci of necrosis in a lung, with hemorrhages in the cavity of the alveoli are defined. The interalveolar septa are destroyed. Blood clots are in blood vessels.

Questions for self-control

1. Fundamentals of tonatology - the doctrine of death, its causes, mechanisms and features.
2. Necrosis: definitions, terms and stages of development.
3. Morphological characteristics of coagulative necrosis, its consequences.
4. Morphological characteristics of colliquative necrosis.
5. Definition, types and morphological characteristics of gangrene.
6. Definition and morphological features of the sequester.
7. Definition, classification, types and morphological characteristics of infarction.
8. Apoptosis: definitions, molecular mechanisms, term of development, microscopic manifestations, consequences.
9. Selective cell death induced by the immune system and cell destruction with activated complement.

Examples of tests

Autopsy of the dead patient who died from pulmonary edema revealed a large yellow-grey area in the myocardium, and a fresh thrombus in the coronary artery. What is the most likely diagnosis?

A. Myocardial infarction
B. Cardiosclerosis
C. Myocarditis
D. Amyloidosis
E. Cardiomyopathy

A patient died from acute cardiac insufficiency. The histological examination of his heart revealed the necrotized section in myocardium of the left ventricle, which was separated from undamaged tissue by the zone of hyperemic vessels, small hemorrhages and leukocytic infiltration. What is the most likely diagnosis?

A. Myocardial infarction
B. Myocardial ischemic dystrophy
C. Focal exudate myocarditis
D. Diffuse exudate myocarditis
E. Productive myocarditis

Acute renal impairment caused death of a patient with hemorrhage. Autopsy revealed enlarged kidneys with broad pale-pink cortical layer expressively demarcated from dark-red renal pyramids. Macroscopic examination revealed lack of epithelial nuclei of convoluted tubules, tubulorrhexis, phlebostasis. The cell nuclei of choroid glomus and straight tubules were present. What pathology is it?

A. Necronephrosis
B. Infarction

C. Glomerulonephritis
D. Pyelonephritis
E. Nephrosis

A patient with femoral neck fracture, who for a long time had to remain in bed in a forced (supine) position, has developed dark-brown lesions along the backbone; soft tissues are swollen, in the areas of maceration there is a foul-smelling liquid. Name the clinicopathologic type of necrosis:

A. Bedsore
B. Infarction
C. Sequestrum
D. Coagulation necrosis
E. Dry gangrene

Autopsy of a woman with cerebral atherosclerosis revealed in the left cerebral hemisphere a certain focus that is presented by flabby, anhistic, greyish and yellowish tissue with indistinct edges. What pathological process is the case?

A. Ischemic stroke
B. Multifocal tumor growth with cystic degeneration
C. Multiple foci of fresh and old cerebral hemorrhage
D. Focal encephalitis
E. Senile encephalopathy

ACUTE AND CHRONIC SYSTEMIC DISORDERS OF CIRCULATION. REGIONAL DISORDERS OF CIRCULATION (HYPEREMIA, ISCHEMIA, PLASMORRHAGIA, BLEEDING, AND HEMORRHAGE). DYSFUNCTION OF THE FORMATION AND CIRCULATION OF LYMPH.

Circulatory disorders - a violation of blood circulation along the bloodstream as a result of pathology of the circulatory system, neurohumoral regulation of the heart, structural breakdown at the level of the heart, blood vessels, microcirculatory bed, lymphatic vessels.

Principles of classification of circulatory disorders:

1. By the prevalence in the body:
• general (system);
• regional (local).
2. By the time of development:
• acute circulatory disorders;
• chronic circulatory disorders.
3. By type of blood circulation disorders:
• increased blood flow - plethora (hyperemia):
• arterial;
• venous.
• reduction of blood supply - anemia (ischemia)
• violation of the permeability of the vessel wall:
• plasmorrhagia;
• bleeding;
• hemorrhage.

Acute systemic circulatory disorders

Acute systemic circulatory disorders occur most often in pathological conditions, which are accompanied by the development of acute heart failure.

Acute heart (myocardial) insufficiency is a syndrome characterized by a decrease in cardiac output with normal or increased venous return.

Reasons:

• reduction of myocardial contractility (acute heart attack, myocarditis);
• pathology of the heart valves (tear of the mitral valve cusp), which changes the volume of the cavities of the heart;
• heart tamponade.

At the same time, the pumping function of the left ventricle and its cardiac output are rapidly reduced, resulting acute general **venous plethora.**

In acute heart failure in the **internal organs** due to hypoxia and increased hydrostatic pressure, the capillary permeability is sharply increased.

In the stroma of the organs, plasma seepage (plasmorrhagia) and swelling, stasis in the capillaries and multiple diapedesis hemorrhages develop; in parenchyma - dystrophic and necrotic changes. First of all, it concerns the vessels of the small circle of circulation: the **alveolar pulmonary edema** develops (lung enlargements and airless due to flooding of the alveoli). Renal dystrophy and necrosis of the tubule appear in the kidneys. Centrolobular hemorrhages and necrosis develop in the liver.

Circulatory disorders in shock

Shock is a critical disturbance of microcirculation in vital organs, caused by acute mismatch of vascular bed capacity and circulating blood volume (BV).

Reasons:

• a sharp drop in pumping function of the heart (cardiogenic shock);

• rapid expansion of vascular bed capacity (vascular tone decline and persistent vasodilation) with unchanged BV;

• a sharp decrease in BV (bleeding, hypovolemia, etc.).

Types of shock:

1. Hypovolemic shock. The basis is a sharp decrease in BV (severe blood loss, fluid loss in burns, irritable vomiting and diarrhea, etc.).

2. Cardiogenic shock. It occurs as a result of a decrease in cardiac output (in large-sized myocardial infarction and other conditions that lead to acute heart failure).

3. Septic shock (toxic-infectious). Most often associated with microorganisms that secrete endotoxins (endotoxic shock).

Massive damage of the endothelium (cells lining the lumen of the blood vessels) by toxin leads to the activation of the internal blood coagulation system (Hageman factor) and the development of disseminated intravascular coagulation (DIC).

4. Vascular shock:

a) anaphylactic;

b) neurogenic (traumatic shock).

Stages of shock:

1. Non-progressive (early) stage. Start mechanisms of compensation of the reduction of cardiac output to support the perfusion of vital organs.

2. The progressing stage. Exhaustion of compensatory mechanisms: tissue hypoperfusion and metabolic acidosis develop, blood is "sequestered" in a sharply expanded capillary bed; a deep collapse occurs.

3. Irreversible stage. Organ damage and metabolic disorders that are incompatible with life develop.

Morphological manifestations of shock:

• In the internal organs there are hypoxic lesions in the form of dystrophy and necrosis, stasis and micro thrombi in the system of microcirculatory bed combined with signs of increased capillary permeability, hemorrhages.

• Often joins the DIC syndrome, which is characterized by the formation of multiple blood clots in the microcirculatory system with the development of consumption coagulopathy.

• Sharp decrease in most coagulation factors. Stimulation of fibrinolysis lead to the development of hemorrhagic syndrome: there are multiple hemorrhages on the skin, mucous membranes and serosa, in the internal organs.

In addition to the above, due to the peculiarities of the structure and function of the various internal organs, they have a kind of relatively typical changes - **shock organs:**

In the **kidneys** - necrotic nephrosis (acute renal failure).

In the **lungs** there are atelectasis sites, serous hemorrhagic edema with fibrin loss in the lumen of the alveoli (hyaline membranes), stasis and blood clots in the microcirculatory bed, which causes the development of acute pulmonary insufficiency - respiratory distress.

In the **liver** - centrolobular necrosis.
In the **brain**, there are foci of necrosis, small hemorrhages.
In the **gastrointestinal tract** there are hemorrhages, numerous erosions and ulcers.
The death of the patient occurs due to irreversible multiple organ failure.

Chronic systemic circulatory disorders.

Chronic systemic circulatory disorders develop in the presence of a *chronic heart failure.*
In chronic heart failure (due to cardiosclerosis, heart defects, etc.), the pumping function of the heart gradually decreases and the **overall chronic venous plethora (hyperemia)** progresses. Maintaining tissue hypoxia for a long time, general chronic venous plethora leads not only to plasmorrhagia, edema, stasis and hemorrhage, dystrophy and necrosis, but also to atrophy and sclerosis: congestive **sealing (induration)** of organs and tissues develops.
Chronic heart failure is divided into:
- right ventricular;
- left ventricular.

Manifestations of *chronic right ventricular insufficienc*y: acrocyanosis, lower extremity edema, trophic ulcers, cyanotic induration of kidneys and spleen, nutmeg liver, hydrothorax, hydropericardium, ascites.
• ***ascites*** - accumulation of transudate in the abdominal cavity;
• ***hydrothorax*** - accumulation of transudate in the pleural cavities;
• ***hydropericardium*** - accumulation of transudate in the cavity of the pericardium;
• ***anasarca*** - general cavity and peripheral edema.
The **skin** (especially the lower extremities) is cold and cyanotic. Veins of skin and subcutaneous tissue dilated, full of blood; lymph vessels are also enlarged and lymphatic. Dermal and subcutaneous tissue edema, growth in connective tissue in the skin is expressed.
The **kidneys** become large and cyanotic (***cyanotic induration***), especially the full-blooded veins of the medullary layer and the intermediate zone. Lymphostasis develops. Hypoxia leads to dystrophy of the parenchymal elements and to the growth of connective tissue, causing the organ to tighten.
The **spleen** is enlarged, dense, dark cherry in color, does not give a pulp scraping.

Liver

Macroscopically: the liver is enlarged, dense, the edges are rounded, the surface of the incision is mottled, gray-yellow with a dark red speck and resembles nutmeg - **"nutmeg liver".**
Microscopically: full-blooded only central parts of lobules, where hemorrhage, hepatic cell discomplexation and hepatocyte death are noted - these sections appear dark red in the section of the liver. At the periphery of the lobules, hepatocytes are in a state of fatty dystrophy, which explains the gray-yellow color of the liver tissue. The distribution of venous plethora from the centers to the periphery of the lobes is prevented by high pressure in the sinusoids of the periphery of the lobes - the area of confluence of the branch of the hepatic artery.
As a result of chronic venous stagnation in the liver *"muscat"* fibrosis develops; sometimes with prolonged venous stagnation sclerosis in the liver progresses, the

liver tissue undergoes reconstruction and the process ends with the formation of small-node cirrhosis of the liver ("muscat", cardiac cirrhosis).
Manifestations of chronic left ventricular failure: brown lung induration.
Macroscopically: lungs are enlarged, dense, brown in color.
Microscopically: in the alveoli, bronchi, interveal sections, sideroblasts and siderophages are found in a considerable amount, active proliferation of fibroblasts with the phenomena of pneumosclerosis. *When Perls reaction* brown pigment - hemosiderin gives a *positive reaction to iron*, its grains turn blue-green (Berlin azure).

Systemic disorders of the bloodstream associated with increased blood flow (general hyperamia)

General arterial hyperemia - is observed with an increase in the volume of circulating blood (plethora) or the number of erythrocytes (erythremia).

Types of arterial hyperemia:

a) physiological:
• when climbing (alpinists);
• mountain dwellers;
• in newborns after umbilical cord dissection;
b) pathological:
• people with chronic lung diseases;
• Vaquez's disease (true polycythemia).
Macroscopically: redness (hyperemia) of the skin, visible mucous membranes, increased blood pressure.

Systemic circulatory disorders associated with decreased blood flow (general hypoemia)

General hypoemia can have both **acute** and **chronic** course.
Acute general hypoemia develops with rapid high blood loss, that is, a decrease in circulating blood volume (BV) in the circulatory system over a short period of time.
Reasons:
• various injuries with damage to organs, tissues and blood vessels;
• rupture of a large, pathologically altered vessel or heart (rupture of an aortic aneurysm for syphilis, atherosclerosis);
• rupture of a pathologically altered organ (fallopian tube in ectopic pregnancy, infectious spleen - in malaria, typhoid fever, massive blood loss in tuberculosis, gastric ulcer, tumors of different localization).
Macroscopic: ischemic tissue becomes pale, flabby, cold, organ shrinks, capsule shrinks. Spotty hemorrhages under the endocardium of the left ventricle of the heart (spots of Minakov).
Microscopic - dystrophic and necrotic changes in organs.
Chronic general hypoemia or **anemia** - reduction of erythrocyte number and / or hemoglobin content per unit volume of blood. The total volume of circulating blood in the body does not change.
Reasons:
• diseases of the hematopoietic organs (hemoblastosis, anemia);
• chronic infectious diseases (tuberculosis, syphilis);
• chronic parasitic diseases (helminth infestations);

• exogenous intoxication (lead, arsenic, carbon monoxide poisoning);
• endogenous intoxication (poisoning by products of nitrogen metabolism - in kidney diseases, bile acids in mechanical jaundice, endogenous poison in malignant tumors, etc.);
• starvation (full or partial), avitaminosis;
• minor frequent bleeding (with gastric ulcer and duodenal ulcer, pulmonary tuberculosis, uterine and hemorrhoidal bleeding).
Macroscopically:
• pallor of the skin, mucous membranes, internal organs;
• dystrophic changes of parenchymal organs (often fatty dystrophy);
• total hemosiderosis.
Consequences: atrophy of parenchymal cells and sclerosis.

Regional (local) circulatory disorders

Arterial hyperemia

Local arterial hyperemia - increased blood flow to the organ or part of the organ, accompanied by local redness and fever. It can be physiological (with excitement, increased function of organs), or be observed in pathological processes.
According to the mechanism of development:
• *Inflammatory* - a constant satellite of inflammation due to the action of biologically active substances - mediators of inflammation (histamine, serotonin, etc.).
• *Angioneurotic* - in case of irritation of the vasodilator nerves or paralysis of the vasoconstrictive nerves.
• *Collateral* - in case of obstruction of blood flow on the main vessel, and as a result of this blood flow to the bypass (collateral) vessels, whose diameter is much smaller.
• *Vacate* - when the barometric pressure is reduced: (divers, caisson workers, when using medical jars).
• *Hyperemia after elimination of compression or spasm of an artery* - rapid elimination of anemia after removal of a tumor, ligature, fluid in the cavities.
Of all types of arterial hyperemia, the greatest danger is represented by hyperemia after elimination of compression or spasm of the artery. Brain ischemia is possible due to blood redistribution.

Venous hyperemia (plethora)

Local venous plethora (hyperemia) occurs when there is an impeded outflow of venous blood from a specific organ or part of the body due to the closure of the lumen of the vein (thrombus or embolus) or compression from outside (tumor). The tissues and organs get a bluish tint, enlarge in volume through interstitial swelling, and feel cold.
Types of local venous plethora:
• *Swelling and induction of the lower extremity* - develops with thrombosis of its veins. Soft tissue swelling occurs, which causes an increase in volume and tightness of the limb.
• *Portal hypertension syndrome* - occurs in cirrhosis due to sclerosis of the periportal fields and is characterized by a triad of symptoms: congestive splenomegaly, varicose veins of port anastomoses and ascites.

• *Budd–Chiari syndrome* - occurs when inflammation and thrombosis of hepatic vein, which leads to the formation of "nutmeg" liver with a high risk of developing "nutmeg" cirrhosis.
• *syndrome of the superior vena cava* - develops at obstructive thrombosis of the superior vena cava after its catheterization. It is manifested by increasing swelling of the tissues of the upper part of the body, neck and head, which threatens the development of brain edema.

Ischemia

Ischemia is a reduced blood supply of the tissue, organ, body part due to insufficient blood flow.
Types by time of development:
1. Acute ischemia lasts from one to several hours.
2. Chronic ischemia lasts from several days to several years.
Types (*by cause and conditions*):
• angiospastic - artery spasm due to pain, negative emotions, hypertensive crisis;
• obstructive - partial or complete closure of the artery with a thrombus, embolus, atherosclerotic plaque, growth of connective tissue;
• compression - compression of the artery from outside by the tumor, effusion, ligature, plait;
• redistribution - occurs after removal of transudate from the abdominal cavity and may be accompanied by short-term collapse and fainting of the patient;
• because of a functional mismatch between the flow of blood and the high demand for it of the organ that is working hard (when exercising).
Consequences: due to oxygen-metabolic starvation of organs and tissues, their atrophy occurs with subsequent sclerosis and the development of organ failure. Organ shrinks in size, compacts, and the surface becomes fine-grained.

Plasmorrhage

Plasmorrhage is the plasma exit from the bloodstream. It is most common in arterial hypertension, atherosclerosis, decompensated heart defects, infectious, infectious-allergic and autoimmune diseases.
Microscopically: vascular wall looks thick, homogeneous. Fibrinoid necrosis occurs at the extreme degree of plasmorrhagia.
Consequences: vascular sclerosis or vascular hyalinosis.

Hemorrhage

Hemorrhage (bleeding) - the exit of blood from the lumen of a blood vessel or cavity of the heart into the environment or surrounding tissue.

Causes of bleeding:

1. Bleeding as a result of *rupture* of a vessel (heart) - haemorhagia per rhexin;
2. Bleeding due to *corrosion* of vascular walls - haemorhagia per diabrosin;
3. Bleeding due to *increased permeability of the vascular wall* - **diapedesis** (haemorhagia per diapedesis).

There are external and internal bleeding.

External bleeding - the release of blood into the external environment:
Haemoptoe - pulmonary bleeding;
Epistaxis - nosebleeds;
Haemotemesis - vomiting of "coffee grounds" (with gastric bleeding);

Maelena - tar-like stools (with gastric bleeding);
Metrorrhagia - uterine bleeding;
Haematuria - renal bleeding.
Internal bleeding - accumulation of blood outside the vascular bed in the cavities of the body.
Haemothorax - bleeding into the pleural cavity;
Haemopericardium - hemorrhage into the pericardium;
Haemoperitontium - hemorrhage into the abdominal cavity;
Haemarthrosis - hemorrhage into the joint cavity.

Hematoma

Hematoma - accumulation of blood from the blood vessels in the tissues.
Bruising - plane hematomas in the skin and mucous membranes.
Hemorrhagic infiltration - massive infiltration of tissues without destroying its main structural components.
Petechiae - point hemorrhages into the skin.
Ecchymoses - point hemorrhages into the skin that rise above its surface.
Hemorrhagic stroke (insult) – hematoma in the brain.
Subdural hematoma - hematoma under the dura mater.
Subarachnoid hematoma - hematoma under the arachnoid mater.
Consequences of hematoma:
• blood resorption;
• formation of a "rusty" cyst;
• encapsulation;
• organization;
• suppuration of hematoma.

Disorders of formation and circulation of lymph

These processes are closely interrelated and are often manifested by insufficient outflow (insufficiency of the lymphatic system).
Types of insufficiency of the lymphatic system by the mechanism of development:
• dynamic insufficiency: most often occurs with inflammation, when the lymphatic system does not have time to remove excess interstitial fluid;
• resorption insufficiency: with insufficient resorption of the interstitial fluid due to an increase in osmotic pressure in the intercellular space;
• mechanical failure: caused by contraction, constriction or obstruction of a lymphatic vessel by a tumor, inflammatory or sclerotic process.
Pathomorphological manifestations of lymphatic circulation disorders:
• **lymphedema** - observed in erysipelas and is characterized by tissue swelling due to lymphostasis;
• **elephantiasis** - persistent enlargement of the lower extremities due to chronic lymphatic congestion due to congenital malformation of the lymphatic system or infection with filamentous helminths;
• **lymphorea** - leakage of lymph from lymphatic vessels in lymphostasis, lymphangitis, mastectomy;
• **chylothorax** - accumulation of lymph in the pleural cavity with damage to the thoracic lymphatic duct;

• **chiloperitoneum** - accumulation of lymph in the abdominal cavity with damage to lymphatic vessels or lymphostasis in the abdominal cavity.

Macropreparations

"Nutmeg" liver: liver is enlarged, dense, the edges rounded, the surface of the incision is gray-yellow with a dark red speck, similar to nutmeg.

Diapedetic hemorrhage into the brain: the shape of the organ is preserved, the size is not increased; brain pale yellow, marked border between white and gray matter; small inclusions of brown color up to 1 mm in diameter.

Brain hematoma: a large blood clot of brown color is present in brain tissue, brain structures are displaced; the brain tissue in the area of hemorrhage is destroyed.

Hemopericardium: The heart is slightly enlarged in size, with a brownish mass of blood under the pericardium.

Cyanotic induration of the spleen: spleen increased in size, dense, bluish color.

Micropreparations

Pulmonary edema (staining with hematoxylin and eosin): Edematous contents of pink color, single cells are in the lumen of the alveoli. The blood vessels are sharply enlarged with the phenomena of plethora.

Hemorrhages in the brain (staining with hematoxylin and eosin): Small foci of erythrocytes are around the blood vessels, the substance of the brain is swollen.

Nutmeg liver (staining with hematoxylin and eosin): The central veins are greatly expanded. In the centers of the lobules the sinusoidal capillaries are dilated, filled with blood. Hepatic beams located between them, are narrowed (atrophy from pressure), some of them are not determined at all. On the periphery of the lobes the congestion is much less pronounced, the liver beams and capillaries have a normal appearance, hepatocytes with the phenomena of fatty dystrophy.

Questions for self-control

1. Circulatory disorders, definition, classification.
2. Acute systemic circulatory disorders, causes, morphological characteristics of changes in internal organs.
3. Chronic systemic circulatory disorders, causes, morphological characteristics of changes in internal organs.
4. Systemic disorders of the circulation that are associated with an increase in blood flow (general hyperemia), morphological characteristics.
5. Systemic disorders of the circulation, which are associated with a decrease in blood flow (general hypoemia), morphological characteristics of changes in the organs.
6. Regional (local) circulatory disorders: arterial hyperemia (plethora) venous hyperemia (plethora), morphological characteristics.
7. Hemorrhage and hematoma. Definition of terms, classification of bleeding by mechanism of origin; consequences of bleeding.
8. Chronic hypoemia (ischemia) - definition, causes, mechanism of development, morphological manifestations, consequences, significance.
9. Stasis, plasmorrhagia - causes, mechanism of development, morphological manifestations, consequences, significance.
10. Shock, classification, pathoanatomical manifestations.

Examples of tests

A 63 year old male patient who had been suffering from chronic diffuse obstructive disease, pulmonary emphysema, for 15 years died from cardiac insufficiency. Autopsy revealed nutmeg liver cirrhosis, cyanotic induration of kidneys and spleen, ascites, edemata of lower limbs. These changes of internal organs are typical for the following disease:

A. Chronic right-ventricular insufficiency
B. Acute right-ventricular insufficiency
C. Chronic left-ventricular insufficiency
D. Acute left-ventricular insufficiency
E. General cardiac insufficiency

While playing volleyball a sportsman jumped and then landed across the external edge of hisfoot. This caused acute pain in the talocrural articulation, active movements became limited, passive movements remained unlimited but painful. In the region of the external ankle a swelling appeared, the skin turned red and became warmer to the touch. What type of peripheral circulation disorder has developed in this case?

A. Arterial hyperaemia
B. Stasis
C. Embolism
D. Venous hyperaemia
E. Thrombosis

A section of the left lung was found to have an area of dense red tissue. The area was coneshaped, stood out distinctly from the healthy tissue, with its base directed to the pleura. The dissected tissue was granular, dark-red. What is the most likely diagnosis?

A. Haemorrhagic infarction
B. Lung abscess
C. Lung gangrene
D. Primary tuberculous affection
E. Croupous pneumonia

A patient died under conditions of cardiovascular insufficiency. Autopsy results: postinfarction cardiosclerosis, myocardium hypertrophy and dilatation of its cavities, especially of its right ventricle. Liver is enlarged, its surface is smooth, incision revealed that it was plethoric, with dark-red specks against the background of brownish tissue. Histologically: plethora of central parts of lobules; peritheral parts around portal tracts contain hepatocytes in a state of adipose degeneration. How are these liver changes called?

A. Nutmeg liver
B. Pseudonutmeg liver
C. Amyloidosis
D. Liver cirrhosis
E. Liver steatosis

During autopsy of a man, who had been suffering from mitral stenosis, the lungs are revealed to be dense and brown-colored. What pathologic process had occurred in the lungs?

A. Hemosiderosis

B. Hemochromatosis
C. Jaundice
D. Hemomelanosis
E. Lipofuscinosis

HEMOSTASIS DISORDERS: HEMORRHAGIC SYNDROME, THROMBOSIS, DIC, EMBOLISM. PULMONARY ARTERY THROMBOEMBOLISM

Violations of the hemostasis system are manifested by:

• decreased blood clotting and increased bleeding - *hemorrhagic syndrome*;
• blood clotting in the lumen of a vessel or heart cavity - *thrombosis*;
• *thrombohemorrhagic syndrome.*

Causes of hemorrhagic syndrome:

• quantitative or qualitative thrombocytes pathology (congenital or acquired);
• pathology of the plasma hemostasis system (congenital or acquired);
• pathology of vessels, characterized by their increased permeability.

This syndrome is characterized by internal hemorrhage and external bleeding.

Thrombosis - a life-long blood clotting in the lumen of vessels or chambers of the heart. A clot of blood is called a **thrombus**.

Stages of thrombus morphogenesis:

I - platelet agglutination;
II - coagulation of fibrinogen with the formation of fibrin;
III - agglutination of erythrocytes;
IV - precipitation of blood plasma proteins.

Pathogenesis of thrombus formation:

1. Local factors:
• changes in the vascular wall (damage to the internal membrane of the vessels);
• slowing and disruption of laminar flow.
2. Common factors:
• disturbance of balance between coagulation and anticoagulation systems of blood;
• change in the composition (quality) of blood.

Thrombus morphology. The thrombus consists of the head, body and tail.

Types of thrombi:

Depending on the predominance of blood cells:
• *white thrombus*: formed slowly, near the fast laminar blood flow in the arteries, consists of leukocytes, platelets and fibrin;
• *red thrombus*: contains more red blood cells, formed quickly in slow blood flow, more often in the veins;
• *mixed thrombi*: layered leukocytes alternate with erythrocytes and fibrin, occur in heart cavities, aneurysms, varicose veins;
• *hyaline thrombus*: formed in the vessels of the microcirculatory bed, does not contain fibrin, consist of destroyed erythrocytes, leukocytes, proteins of blood plasma.

In relation to the lumen of the vessel:

• parietal;
• obstructive;
• thromboendocarditis.

Consequences of thrombosis:

A. Favorable:
• aseptic thrombus autolysis;
• organization, canalisation and vascularization.

B. Unfavorable:
• thromboembolism;
• progressive thrombosis;
• septic thrombus autolysis.
Thrombosis values:
Protective - determined by stopping bleeding from a damaged vessel.
Unfavorable - the development of necrosis, thromboembolism, thrombophlebitis, *heart attacks, disorders of the blood supply*.

Differences thrombus from post-mortem blood clotting

Characteristic	***Thrombus***	***Post-mortem blood clot***
Density	Dense	Soft
Surface	Striped Rough	Glossy Smooth
Connection with the endothelium	Attached to the wall of the vessel in the place of its damage.	It is freely located in the lumen of the vessel

Disseminated intravascular coagulation syndrome

DIC syndrome - the widespread formation of small blood clots (fibrin, erythrocyte, hyaline) in the microcirculatory bed of the whole organism in combination with the violation of anticoagulation system of the blood, which leads to multiple massive hemorrhages. In the base of it - discoordination of functions of coagulation and anticoagulation systems responsible for hemostasis.

Stages of development of DIC syndrome:

Stage I - stage of hypercoagulation and intravascular cell aggregation. In the microcirculatory system there are microthrombi, which is clinically characterized by the development of shock.
Stage II - stage of hypocoagulation and consumption coagulopathy. It is characterized by the progression of secondary hypocoagulation and the development of bleeding; blood vessels or their components (fibrin) disappear from the vessels.
Stage III - activation of fibrinolysis. There is the lysis of microthrombi with complete restoration of blood flow at the level of the microcirculatory bed.
Stage IV - the stage of recovery or development of fatal organ failure. It is characterized by dystrophic and necrotic changes in the organs (cortical kidney necrosis, focal pancreatic necrosis, hemorrhagic necrosis of the adrenal glands).

Forms of DIC syndrome:

Acute form: 50% is obstetric pathology - embolism of amniotic fluid, placental abruption, hypoxia of newborns.
Chronic form: kidney disease, stomach cancer, lung.

Embolism

Embolism (*Greek. Emballon - throw in*) - circulation in the blood (or in the lymph) of particles or substances that do not occur under normal conditions and clogging of vessels. These substances are called **emboli**.

The direction of movement of the emboli:

• orthograde - by blood flow;
• retrograde - against blood flow (with insufficient vein valves and expansion of their lumen);

• paradoxical embolism - the embolus, bypassing the lungs, from the left half of the heart enters the right through openings in the interatrial or interventricular septum.

Types of embolism:

1. Thromboembolism (the most widespread), mainly emboli become thrombi of veins of a large circle of circulation, or those which are formed on valves of heart at endocarditis - there is, as a rule, hemorrhagic pulmonary infarction.
2. Fat embolism - emboli are fat droplets (with mechanical damage of subcutaneous tissue, fractures of tubular bones, pancreatic necrosis, intravenous injection of fat-soluble solutions).
3. Tissue (cell) embolism - in the destruction of tissue during trauma or pathological process, which leads to the ingress of tissue pieces (cells) into the bloodstream. More often - cells of malignant tumors (metastasis).
4. Gas embolism - with rapid change of high barometric pressure to low (caisson works). With rapid decompression, dissolved nitrogen in the blood can not be excreted in the lungs and its vesicles appear in the blood - "the blood boils".
5. Air embolism - in the case of injury to the neck veins, which have negative pressure; uterine contractions in postpartum atony, pneumothorax.
6. Microbial embolism - colonies of microorganisms clog the lumen of the vessel.
7. Embolism by foreign bodies - when the fragments of bullets, mines, pieces of petrifices, cholesterol crystals of atherosclerotic plaques enter the lumen of the vessel.

Consequences.

Unfavorable consequence of embolism of arterial vessels is the obstruction of the lumen of the vessel and the development of infarction, ie ischemic necrosis, of the organs.

Unfavorable consequence of embolism in the venous system is the sudden death due to the development of the **pulmonary-coronary reflex** when the thromboembol enters the pulmonary artery (pulmonary embolism, PE).

Pulmonary embolism (PE)

Pulmonary embolism is the closure of the lumen of the large, medium or small branches of the pulmonary artery by a thrombus, which is most often formed in the large veins of the lower extremities or pelvis and the right cavities of the heart.

There are:

1. Pulmonary embolism or major pulmonary arteries - leads to sudden death (lightning form) or death due to cardiac arrest, acute right ventricular failure, or acute cardiovascular collapse (acute form).
2. Thromboembolism of the partial pulmonary arteries with the development of massive hemorrhagic pulmonary infarctions and acute respiratory failure.
3. Thromboembolism of segmental and subsegmental branches of the pulmonary arteries with the development of subsegmental hemorrhagic infarctions and atelectasis of the lung with acute respiratory failure.

Macropreparations

Peripheral thrombus in the aorta in atherosclerosis: the aortic intimacy is uneven, whitish plaques are visible, the grayish-white masses are located near them, their surface is corrugated, uneven, dim, the masses adjoin the wall of the vessel.

Thrombus in the vein: in the lumen of the vein, a blood clot is defined, red, rough, completely covers the lumen of the vein and is located along the vessel - an obstructive progressive red blood clot.
Pulmonary embolism: in the area of the bifurcation of the pulmonary trunk there is a congestion of blood lying free, dark gray, rough.

Micropreparations

Fatty embolism of lung vessels (staining with sudan III): Most of the lung capillaries are filled with fat droplets that are colored in red and orange.
Fatty embolism of the vessels of the lung (staining with hematoxylin and eosin): The lumen of the blood vessel is filled with fat cells, the cytoplasm of which has an "optically empty" appearance.
Microbial embolism of the kidney vessels (staining with hematoxylin and eosin): Basophilic homogeneous masses - colonies of microorganisms - are determined in the blood vessel.
Thrombus with the phenomena of organization and canalization (staining with hematoxylin and eosin): in the lumen of the vessel there is an obstructive thrombus. A significant part of the thrombotic masses is replaced by a connective tissue that grows from the side of the intima. You can see the cracks in which the elements of the blood are determined - the canalization of the thrombus.

Questions for self-control

1. Violation of hemostasis, types.
2. Definition of the term "thrombosis", phases and mechanism of thrombosis.
3. Types of thrombi, differences of thrombi from post-mortem blood clots, the consequences of thrombi.
4. DIC syndrome, definition, classification, consequences.
5. Determination of types of emboli depending on the origin of the embolus. The effects of emboli on the body.
6. Pulmonary embolism, causes, types, consequences.

Examples of tests

2 hours after a skeletal extension was performed to a 27 year old patient with multiple traumas (closed injury of chest, closed fracture of right thigh) his condition abruptly became worse and the patient died from acute cardiopulmonary decompensation. Histological examination of pulmonary and cerebral vessels stained with Sudan III revealed orange drops occluding the vessel lumen. What complication of polytrauma was developed?

A. Fat embolism
B. Gaseous embolism
C. Microbal embolism
D. Thromboembolism
E. Air embolism

A patient suffering from trombophlebitis of the deep crural veins suddenly died. Autopsy has shown freely lying red friable masses with dim crimped surface in the trunk and bifurcation of the pulmonary artery. What pathologic process was revealed by morbid anatomist?

A. Tromboembolism
B. Thrombosis

C. Tissue embolism
D. Embolism with foreign body
E. Fat embolism

A patient with thrombophlebitis of lower extremities had got chest pains, blood spitting, growing respiratory failure that caused his death. Autopsy revealed multiple pulmonary infarctions. What is the most probable reason of their development?

A. Pulmonary artery embolism
B. Pulmonary artery thrombosis
C. Bronchial artery thrombosis
D. Bronchial artery embolism
E. Pulmonary venous thrombosis

The pulmonalis embolism has suddenly developed in a 40-year-old patient with opened fracture of the hip. Choose the possible kind of embolism:

A. Fat
B. Thrombus-embolus
C. Air
D. Tissue
E. Foreign body

A patient with chronic heart failure presents with increased blood viscosity. Capillaroscopy detected damage to the vessel walls of the microcirculation system. What disorder is possible in the given case?

A. Blood ”sludge” phenomenon
B. Thrombosis
C. Embolism
D. Arterial hyperemia
E. Venous hyperemia

INFLAMMATION: CAUSES, MORPHOGENESIS. PATHOMORPHOLOGY OF EXUDATIVE INFLAMMATION.

Inflammation – local vascular-mesenchymal response of tissues to injury.

The inflammation is aimed at:

• demarcation of the damage area;
• the destruction (neutralization) of agents that have caused inflammation;
• tissue regeneration and restoration of organ function.

Signs of inflammation

1) temperature rise (calor)
2) redness (rubor)
3) tissue enlargement in volume (tumor)
4) pain (dolor)
5) impaired function (functio laesa)

Etiology of inflammation

Inflammation factors:

a. Biological (exogenous and endogenous):
• microorganisms and products of their vital activity;
• endogenous factors: antigens and immune complexes, bilirubin and bile acids.
b. Physical: radiation, electricity, high and low temperatures, trauma.
c. Chemicals: drugs, toxins, poisons, acids, alkalis, heavy metal salts.

Pathogenesis of inflammation: phases of inflammation:

1) alteration
2) exudation
3) cell proliferation and repair of damaged tissue.

The **phase of alteration** is tissue damage, which morphologically manifests itself by various types of dystrophies and necrosis.

In this phase of inflammation is the release of biologically active substances - inflammatory mediators. This is the trigger of the inflammation.

Inflammatory mediators:

1. Plasma inflammatory mediators:
- activation of fragments C3, -4, -5 of the complement system causes:
• vasodilation and increased vascular permeability,
• increased adhesion and chemotaxis of leukocytes, as well as the release of eicosanoids (arachidonic acid derivatives),
• release of mediators of inflammation by labrocytes (mast cells),
• activation of phagocytosis by neutrophils and macrophages.
- activation of kallikrein-kinin system:
• kallikrein increases leukocyte chemotaxis,
• bradykinin causes enlargement of the arterioles and increased vascular permeability,
- activation of the Hageman factor of blood coagulation leads to:
• an increase in the concentration of kinin in the blood plasma, as well as the formation of thrombin and fibrin, which causes thrombosis of damaged microvessels,
• increased thrombin adhesion of leukocytes and proliferation of fibroblasts,
- activation of the fibrinolytic system: plasminogen activators are released from the damaged endothelium and leukocytes, which cleave plasminogen to form plasmin.

Plasmin causes fibrin lysis, forming fibrinopeptides that increase vascular permeability and leukocyte chemotactic activity.
2. Cellular inflammatory mediators:
- eicosanoids - released by any damaged cells. This leads to spasm, then dilation of vessels, increase their permeability and promote inflammatory tissue swelling
- cytokines (interleukins of 1,6,8 families and tumor necrosis factor) cause inflammatory hyperemia and cause repair of damaged tissue
- mediators of activated platelets increase vascular permeability, promote leukocyte migration
- vasoactive amines (histamine, serotonin) secreted by labrocytes (mast cells) and platelets, increase the permeability of venules and cause spasm of arterioles
- nitric oxide, which is synthesized in excess by the endothelium and macrophages, causes vasodilation.

The ***exudation phase*** is a vascular reaction with the formation of exudate and inflammatory cell infiltrate, which is completed by purification of the inflammation site from pathogens and destroyed tissues.
Exudation quickly follows the alternation and release of mediators.

Exudation sub-phases:

1) the reaction of the microcirculatory bed with impaired rheological properties of blood;
2) increasing the permeability of microvessels and migration of the liquid part of the blood plasma (water, proteins, salts);
3) migration of blood cells (leukocytes, monocytes, lymphocytes, erythrocytes).

In the first 6-24 hours neutrophils migrate to the inflammation site, within 24-48 hours monocytes. As a result, a liquid exudate or inflammatory cell infiltrate is formed outside the vessel.

Phase of cellular proliferation and repair of damaged tissue - the final phase of inflammation, aimed at restoring the original structure of the tissue or scar formation and reparative remodeling of the damaged tissue.

Classification of inflammation:

By development time:
1) acute - lasts 2-3 weeks
2) subacute - lasts more than 1 month
3) chronic - lasts for months and years

Due to development:
1) banal (non-specific) - caused by physical, chemical, biological factors
2) specific - caused by special pathogens of tuberculosis, syphilis, leprosy, scleroma.

By morphogenesis:
1) alternative inflammation (mainly acute)
2) exudative inflammation (mainly acute)
3) proliferative inflammation (mainly chronic)

Exudative inflammation

It is characterized by the predominance of the reaction of the vessels of the microcirculatory bed with the formation of exudate, while the alternative and proliferative components are less pronounced.

According to the morphology of the exudate are:

1) serous,
2) fibrinous,
3) purulent,
4) putrid,
5) hemorrhagic,
6) catarrhal

Serous inflammation

Causes: chemical, thermal factors, bacteria.
Localization:
• serous membranes of the internal organs - serous pleurisy, serous pericarditis, serous peritonitis
• internal organ parenchyma - serous hepatitis, serous nephritis
• skin - serous dermatitis
• mucous membranes
Characteristics of the exudate:
Macroscopic: watery, colorless or yellowish liquid.
Microscopically:
• 2-5% protein (mainly albumin)
• a small number of leukocytes
• peeled cover cells
Consequences: usually favorable - resorption of serous exudate occurs and tissue structure is restored.
Complications: sclerosis - in the case of prolonged serous inflammation in the organs due to stagnation of the lymph.

Fibrinous inflammation

Causes: bacteria, viruses, exo- and endogenous toxins.
Characteristics of the exudate:
Macroscopically: *white-gray (yellow-gray) filamentous or pellicular structures*.
Microscopically: in addition to leukocytes, lymphocytes, monocytes, macrophages, there is a lot of fibrinogen that turns into fibrin in damaged (necrotized) tissue.
Localization:
• serous membranes of internal organs
• mucous membranes
• lungs.
Classification according to the depth of the necrosis and the type of epithelium covered by the mucous or serous membrane:
• croupous
• diphtheritic
Croupous - develops on the mucous membranes covered with a cylindrical epithelium at shallow necrosis, or on serous membranes covered with a single-layered flat epithelium - mesothelium, where the epithelium hase loose connection with the underlying tissue. Therefore, the resulting pellicles can be easily separated from the epithelium even with deep impregnation of fibrin.
Examples:
• tracheitis, bronchitis
• croupous pneumonia

• fibrinous pericarditis ***("hairy heart"***)
• fibrinous pleuritis
• fibrinous peritonitis
When removing the pellicles - hyperemia of the mucous membrane and the formation of erosion.
Consequences:
• complete regeneration of the epithelium;
• in serous cavities, fibrin masses are subject to organization, which leads to the formation of connections between visceral and parietal pleura leaves (adhesive pleurisy), peritoneum, around the visceral pericardium (adhesive pericarditis with the development of pulmonary heart failure).
Diphtheritic - on mucous membranes covered with multilayered flat or multilayered transitional epithelium with deep tissue necrosis and seepage of necrotic masses with fibrin (oral cavity, tonsils, epiglottis, true vocal cords). The fibrinous **pellicles is tightly soldered** to the underlying tissue, and when it is rejected, a deep defect occurs.
Consequences:
• the formation of erosion, which heal by the complete restoration of necrotic tissue;
• the formation of deep ulcers that heal by scarring.

Purulent inflammation

Characteristic:
• Macroscopic pus - **a turbid, creamy yellow-green liquid**
• the predominance of neutrophil leukocytes and purulent bodies in the exudate (the dead leukocytes), which together with the liquid part of the exudate, form a pus containing various active enzymes, including proteases. Therefore, purulent inflammation is accompanied by tissue lysis.
Localization: in any organ and tissue.

Forms of purulent inflammation:

1) abscess
2) phlegmon
3) empyema
4) furuncle
5) carbuncle.

1) Abscess - focal confined purulent inflammation with the formation of a cavity filled with pus, separated from the normal tissue by a pyogenic capsule (producing pus).

By the course: acute and chronic.

Acute abscess: pyogenic capsule is represented by granulation tissue or organ tissue.
Chronic abscess has two membranes - internal (granulation tissue) and outer (dense connective tissue).
2) Phlegmon - diffuse purulent inflammation that spreads diffusely between the tissue elements (interfascial, intermuscular spaces or between the membranes of the hollow organs).
Types: depending on the activity of proteolytic enzymes:
• soft - has a diffuse appearance, ie has no clear boundaries, the consistency is doughy, turbid purulent fluid flows from the incision surface,

• dense - characterized by the presence of necrosis in the area of inflammation, also has no clear boundaries with the surrounding tissues, dead tissues are gradually separated, the consistency is more dense.

3) empyema - purulent inflammation with accumulation of pus in relatively or completely isolated anatomical cavities or cavities that do not drain well:

• pleural cavity - pleural empyema,
• pericardial cavity - pericardial empyema,
• abdominal cavity,
• in the gallbladder,
• piosalpinks - inflammation with accumulation of pus in the fallopian tube.

4) Furuncle - purulent inflammation of the hair follicle and associated sebaceous gland.

5) Carbuncle - purulent inflammation of several, along the hair follicles and sebaceous glands, with skin and subcutaneous tissue death.

Putrid inflammation *(gangrenous)*

Characteristic:

• occurs as a result of the anaerobic flora, which releases gases (indole, scatol) with an unpleasant odor, to the foci of inflammation,
• characterized by large foci of necrosis,
• macroscopically enlarged organ, looks like cooked meat.

Consequence: acute intoxication, parenchymatous dystrophy of internal organs with development of their functional deficiency.

Hemorrhagic inflammation

It is *characterized* by the presence of a large number of red blood cells in the exudate. Increasing vascular permeability - great importance in its development.

The *course* is acute.

Examples:

• hemorrhagic pneumonia in influenza (large "variegated" lung),
• anthrax meningitis ("cardinal's hat")
• serous hemorrhagic nephritis
• croupous pneumonia in the stage of red hepatization
• carbuncle of the skin

Reasons:

• endogenous intoxication (with nitrogenous slag in chronic renal failure)
• highly virulent pathogens of particularly dangerous infections (plague, anthrax, influenza, in the past - with smallpox).

Consequence - adverse, often fatal (influenza).

Catarrhal inflammation (Greek catarrheo - drain) or catarrh.

Localization: mucous membranes that have many glands.

Types:

• serous catarrh (upper respiratory tract)
• mucus catarrh (upper respiratory tract and gastrointestinal tract)
• mucus-purulent catarrh

Course:

• acute - reverse process
• chronic - possible mucosal atrophy (atrophic chronic rhinitis, gastritis)

Consequences of a chronic course: formation of polyps (nose, stomach, intestines, uterus) and pointed condylomas, atrophy of mucous membranes.

Macropreparations

Fibrinous pericarditis ("hairy heart"): on the surface of the epicardium, fibrin deposits in the form of filaments of gray are observed. The serous membrane becomes rough, as if covered with a hairline - filaments of fibrin.

Purulent leptomeningitis: in the area of the cerebral hemispheres, the soft meninges are thickened, dim. A large accumulation of greenish-yellow viscous fluid is under the shells. These changes are particularly clearly presented on the basal surface of the brain and on the convex surface of the anterior hemispheres in the form of a "cap." The furrows and convolutions of the brain are smoothed, there is a sharp hyperemia of the vessels of the brain.

Chronic liver abscess: a non-contracting cavity with a diameter of 5 cm, has a dense wall with an uneven inner surface, is observed in the liver parenchyma.

Rotting endometritis: The uterus is significantly enlarged in size, its wall thick, dirty gray, disintegrates, looks like cooked meat.

Micropreparations

Liver abscess (staining with hematoxylin and eosinone): focus of destroyed tissue infiltrated with neutrophilic leukocytes surrounded by liver tissue.

Purulent leptomeningitis (staining with hematoxylin and eosin): significant leukocyte infiltration, single filaments of fibrin are present in the soft cerebral membrane, in the subarachnoid space. Brain tissue without significant changes.

Fibrinous pericarditis (staining with hematoxylin and eosin): on the epicardium - homogeneous purple layers - fibrin films. In the epicardium - moderate leukocyte infiltration, myocardium without significant changes.

Croupous pneumonia (stage of gray hepatization) (staining with hematoxylin and eosin): enlarged lumps of alveoli filled with exudate, consisting of filaments of fibrin, neutrophilic leukocytes, individual alveolar macrophages; the capillaries of the alveolar septum become empty, invisible.

Questions for self-control

1. Definition of the concept of inflammation, its biological essence. Etiological factors of inflammation and phases of inflammatory reaction.
2. Alteration: definitions, types and mechanism of action of inflammatory mediators.
3. Exudation: definitions, stages of development, their morphological essence.
4. Proliferation: definition, cellular composition of proliferate, biological essence.
5. Determination of exudative inflammation, types.
6. Serous inflammation, causes and localization; morphology, consequences.
7. Fibrinous inflammation: composition of exudate, causes, localization; varieties.
8. Purulent inflammation: causes, phases, types, morphological picture.
9. Hemorrhagic inflammation: causes of development, morphological characteristics.
10. Putrid inflammation: causes, morphology, consequences.
11. Catarrh inflammation: localization, species, morphological characteristics, consequences.

Examples of tests

A 17 year old boy fell seriously ill, the body temperature rose up to 38,5oC, there appeared cough, rhinitis, lacrimati-on, nasal discharges. What inflammation is it?

A. Catarrhal
B. Serous
C. Fibrinous
D. Purulent
E. Hemorrhagic

Colonoscopy of a patient with dysentery revealed that the mucous membrane of the large intestine was hyperemic, edematic, and its surface was covered with grey-and-green layerings. What morphological form of dysenteric colitis is it?

A. Fibrinous
B. Catarrhal
C. Ulcerous
D. Purulent
E. Necrotic

A man died 8 days after the beginning of the disease. He was diagnosed with dysentery. At the autopsy it was found out a thickened wall of the sigma and rectum, fibrinous membrane on the surface of mucous membrane. Histologically: there is a deep necrosis of mucous membrane with infiltration of necrotic masses with fibrin. What kind of colitis does correspond to the changes?

A. Diphtheritic
B. Catarrhal
C. Ulcerative
D. Chronic
E. Gangrenous

Autopsy of a patient, who died of bilateral bronchopneumonia, shows in the left lung lower lobe a cavity 5 cm in diameter, filled with liquid yellowish-white substance. What complication of the patient's pneumonia had developed?

A. Abscess
B. Gangrene
C. Granuloma
D. Sequestrum
E. Tuberculoma

A 40-year-old patient with the progressing staphylococcal purulent periodontitis developed purulent inflammation of bone marrow spaces of the alveolar process, and then of the body of mandible. Microscopy revealed thinning of bone trabeculae, foci of necrosis, bone sequesters surrounded by the connective tissue capsule. What is the most likely diagnosis?

A. Chronic osteomyelitis
B. Acute osteomyelitis
C. Parodontome
D. Chronic fibrous periostitis
E. Purulent abscess

PROLIFERATIVE (PRODUCTIVE) INFLAMMATION: WITH THE FORMATION OF A POINTED CONDYLOMAS, AROUND ANIMAL PARASITES, INTERSTITIAL PRODUCTIVE INFLAMMATION, GRANULOMATOUS INFLAMMATION. SPECIFIC PROLIFERATIVE INFLAMMATION.

Proliferative (productive) inflammation develops with prolonged action of the pathogenic factor on the tissues.

Characteristics: the prevalence of cell reproduction with the formation of cell infiltrate, consisting of immunocytes, local mesenchymal cells and hematogenous cells.

Course: often - chronic, sometimes acute.

Characteristics of cell infiltrate composition

1. Immunocytes:
• T lymphocytes (carry out cellular immune responses)
• B lymphocytes (provide humoral immune responses)
• plasma cells (synthesize immunoglobulins)
• monocytic macrophages (phagocytes of pathogens and damaged cells).
• derivatives of macrophages - epithelioid cells, multinucleated giant cells
2. Local mesenchymal cells:
• cambial mesenchymal cells
• fibroblasts, fibrocytes
• endothelial cells, newly formed microvessels
• cambial cells of epithelial covers
• labrocytes (mast cells), which are activated during allergic reactions
• cells of bone marrow and mesenchymal stem cells.
3. Hematogenous cells - blood cells that have migrated from vessels:
• neutrophils - play the role of microphages (bacterial phagocytes). They usually appear in small numbers and short period of time
• eosinophils, activated basophils - have receptors for immunoglobulins and appear in allergic reactions.

Classification of cellular infiltrates

According to the prevalence in the organ:
• focal cellular infiltrate
• diffuse cellular infiltrate

By topography in the organ:
• perivascular - around the vessels
• periductal - around the duct
• interstitial - between specialized microstructures and organ cells
• around the foci of necrosis.

Banal proliferative inflammation

Causes: occurs in response to damage of the body:
• biological agents: viruses, fungi, protozoa, parasites
• exogenous physical factors: foreign bodies, gaseous toxins and allergens.

Types of proliferative inflammation:

1. Interstitial (intermediate) productive inflammation
2. Granulomatous

3. Productive inflammation with the formation of polyps and pointed condylomas
4. Productive inflammation around animal parasites and foreign bodies

1. Interstitial (intermediate) productive inflammation

Characteristic and localization: the formation of widespread inflammatory immune cell infiltrate in the stroma of the organ, that is, in the layers of connective tissue (interstitium) between its specialized microstructures and cells.

The composition of the inflammatory infiltrate:

• in the initial period: T- and B-lymphocytes, plasma cells, macrophages, labrocytes (mast cells), eosinophils, single neutrophils

• as antigens are eliminated: the number of immunocompetent cells decreases, instead, small-sized fibroblasts appear which gradually increase.

Examples:

• interstitial myocarditis
• interstitial hepatitis
• interstitial nephritis
• interstitial pancreatitis
• interstitial pneumonia

Consequences:

Fibrosis (sclerosis) is an overgrowth of the fibrous connective tissue in the stroma of the organs:

• cardiosclerosis
• nephrosclerosis
• pneumosclerosis

Cirrhosis - growth of scar connective tissue with deformation of the organ:

• liver cirrhosis
• nephrotic cirrhosis
• pneumocirrhosis

2. Granulomatous inflammation

Granulomatous inflammation is a variant of productive inflammation, in which the dominant cell type is activated macrophages (or their derivatives), and the **granuloma** is the main morphological substrate.

A granuloma, or nodule, is a focal cluster of cells of monocyte-macrophage origin capable to phagocytosis.

Granuloma morphogenesis (developmental stages):

1) accumulation in the foci of damage of young monocytic phagocytes;
2) maturation of these cells in macrophages and formation of macrophage granuloma *(phagocytoma, simple granuloma);*
3) maturation and transformation of monocytic phagocytes and macrophages into epithelioid cells with the development of *epithelioid-cell granuloma;*
4) transformation of epithelioid cells into giant multinucleate (Langhans and / or foreign bodies) and formation of *giant cell granulomas.*

Features of giant cells of Langhans:

• large sizes (up to 40-50 microns),
• the presence of a large number (up to 20) of nuclei, which are located eccentrically in the form of a horseshoe.

Features of a giant cell of a foreign body: the number of nuclei is up to 30 (sometimes 100), but they are located mainly in the center of the cell.
Giant cells do not have lysosomes and therefore, capturing various pathogenic factors, they do not digest them, that is, phagocytosis in them is replaced by endocytobiosis.

Granuloma classification

According to the characteristic of cellular composition:
1) macrophage granuloma (simple granuloma, or phagocytoma)
2) epithelioid-cell granuloma
3) a giant cell granuloma consisting mainly of Langhans cells.
According to the microscopic structure:
• caseous granulomas with necrosis in the center (mainly infectious)
• non-caseous epithelioid-macrophage granulomas without tissue necrosis (non-infectious)
By morphogenesis:
1. Granulomas of infectious-antigenic genesis, in which antigenic alteration is caused by:
• infectious agents (bacteria, viruses, rickettsiae, fungi)
• some antigenic factors (excess immune complexes in the blood, inhaled gases and small particles, a parenterally administered protein drug).
Examples:
• Aschoff granuloma - in rheumatism.
Microscopically: in the center - a small foci of fibrinoid necrosis, surrounded by single-core macrophages (histiocytes) with impurities of lymphocytes and plasmocytes.
• Typhoid granuloma
Microscopically: in the center are monocytes and very large single nuclei cells with a light cytoplasm and a pale nucleus (macrophages), called typhoid cells, around a small number of lymphocytes, histiocytes and reticular cells.
• Popov's granuloma for typhus in the brain
Microscopically: the focus of endo- or perivascular infiltration, around - a wide area of proliferating microglial cells (vascular gliogranulomatosis).
• brucellous granuloma - in all organs
Microscopically: epithelioid and giant multinucleated cells mixed with plasma cells and eosinophils, many blood vessels.
• tularemia granuloma - fingers (more often right)
Microscopically: epithelioid, lymphoid, giant cells, polymorphonuclear leukocytes, in the center of the granuloma - necrosis.
The consequences of granulomatous inflammation of infectious nature:
• - complete restoration of the organ structure
• - formation of small focal sclerosis on the site of granuloma.
2. Granulomas of foreign bodies: suture surgical material, fragments of glass, shells, particles of organic and inorganic dust (wool, silicosis, talcosis, asbestosis).
Microscopically: in the center of such granulomas - foreign material, surrounded by giant multinucleated cells of foreign bodies with admixtures of epithelioid cells, lymphocytes, sometimes - single leukocytes.

Consequences:
• resorption of foreign material with gradual restoration of the structure of the damaged tissue
• formation of the scar around the foreign body.
3. Granulomas of unknown etiology: in sarcoidosis, Crohn's disease, primary biliary cirrhosis, Wegener's granulomatosis, etc.

Specific granulomas (features):

1. A specific pathogen that causes only a specific disease
• mycobacterium tuberculosis - tuberculosis
• pale treponema - syphilis
• mycobacterium leprae - leprosy
• rhinoscleromous klebsiella - scleroma
• pathogenic fungi - histoplasmosis,
2. Chronic undulating course: exacerbation periods are replaced by periods of remission.
3. The change in inflammatory tissue reactions is caused by a change in the body's immunological reactivity (attack - B-lymphoid reaction, remission - T-lymphocytes).
4. The formation of focal productive inflammation (specific granuloma), which have a characteristic structure depending on the pathogen.
5. The tendency of specific granulomas to necrosis.

Tuberculosis granuloma (nodule, tubercle)

Localization: all organs, but more often the lungs
Macroscopically: numerous white and yellow nodules the size of millet grain.
Microscopically:
• in the center - **caseous** (cheesy) **necrosis**
• on the periphery - a shaft of epithelioid cells with admixtures of lymphocytes, macrophages and plasma cells
• Among these cellular elements are the typical **Langhans** giant multinucleate cells.
The effects of tuberculosis granuloma:
• necrosis
• caverns
• ulcers
• scarring
• encapsulated foci
• calcification of scars

Syphilitic granuloma (gumma)

Characteristic to the tertiary period of syphilis (which occurs after several years).
Localization: oral cavity, genitals, liver, aorta.
Macroscopically: single (solitary) or multiple rounded formations up to several centimeters in diameter of rubbery consistency, localized in bones, skin, brain, liver, kidneys, etc.
Microscopically:
• in the center - a large lesion of rubbery or caseous necrosis,
• on the periphery - granulomatous tissue with numerous lymphocytes, plasma cells and admixtures of epithelioid cells, fibroblasts, single cells of Langhans type,
• a large number of small vessels with phenomena of **productive endovasculitis**.

• a connective tissue capsule is formed around the periphery.
Consequence: early sclerosis, scarring and cirrhosis.

Leprosy granuloma

Localization: skin, lungs, liver, lymph nodes, mucous membranes, bones.
Macroscopically - nodes of different sizes.
Microscopically cell infiltrate consists of:
• macrophages, lymphocytes, and plasma cells
• **Virchow cells** - *large macrophages*, in vacuolated light cytoplasm, which, when stained with Ciel-Nielsen, detect mycobacteria of leprosy, packed as cigarettes in a pack.
Consequence:
• peptic ulcer complications
• mutilation (rejection) of the phalanxes of the fingers or toes
• scarring.

Scleromous granuloma

Localization is the mucous membrane of the upper respiratory tract.
Microscopically cell infiltrate consists of:
• large number of plasma cells with admixtures of epithelioid cells, lymphocytes
• **hyaline globes - Roussel bodies** *(dead plasma cells)*
• **Mikulich cells** - large *macrophages with light foamy cytoplasm*.
Consequence: granulomas are very quickly exposed to sclerosis and hyalinosis, which leads to stenosis and sometimes asphyxia.

Mycotic granuloma

Etiology: causative agent of histoplasmosis, coccidioidomycosis and others.
Microscopically histoplasmic granulomas do not differ from tuberculosis (the patient is diagnosed with a positive intradermal test with histoplasmin).

3) Productive inflammation with the formation of polyps

Conditions - chronic inflammation.
Localization: on ***the mucous membranes covered with a single-layer prismatic epithelium*** (nasal cavity, additional paranasal sinuses, stomach, colon, uterus, gallbladder).
Macroscopic: papillary formation on a peduncle of cylindrical shape protruding above the surface of the mucous membrane of the organ.
Microscopic: the growth of the glandular (prismatic) epithelium together with the underlying connective tissue and inflammatory cell infiltrate.
Consequences: After chronic tissue damage is eliminated, the polyp usually regresses.

Productive inflammation with the formation of a pointed condylomas

Conditions: chronic inflammation by infection with sexually transmitted viruses and bacteria.
Localization: on the border of the multilayered flat epithelium (skin) and single-layer prismatic epithelium near the openings - anal, genital tract.
Macroscopic: sharp papillary conical form.
Microscopic: Expansion of the covering epithelium with keratinization and inflammatory cell infiltrate.

Consequences:
• favorable: recurrence of condylomas after rehabilitation of the body from infection
• unfavorable: when infected with carcinogenic viruses of human papillomas can be transformed into cervical cancer.

4) Productive inflammation around animal parasites and foreign bodies

Parasites:
• echinococcal tapeworm - echinococcosis of the liver, lungs
• roundworms - trichinosis (transverse musculature - root of the tongue, diaphragm)
• tapeworms - cysticercosis of the anterior chamber of the eye, brain.

Foreign bodies - a fragment of a bullets, filaments in the surgical suture, around which develops granulomatous inflammation with the presence of giant cells of foreign bodies.

Mechanism of development: under the action of parasites toxins, necrosis develops, around which a connective tissue capsule is formed, followed by the deposition of calcium salts.

The *consequence* is sclerosis, scarring with the formation of a fibrous capsule around the parasite, followed by petrification.

Macropreparations

Miliary pulmonary tuberculosis: the lung is low-air, under the pleura and in the section are noticeably multiple, diffusely arranged, aphids, greyish, dense consistency tubercles with a diameter of 0.1-0.2 cm. Significantly enhanced mesh pattern of lung tissue (due to the growth of connective tissue - sclerosis). Some areas of the pleura are thickened (sclerosed), with scraps of adhesions.

Liver solitary gums: The liver is enlarged in size, represented by a large number of different humps (gums).

Uterine polyp: papillary mucosa formation on the stem.

Echinococcus of the liver: in the liver there is a rounded cavity, clearly separated from the surrounding tissue by a dense capsule with whitish, dense crumbling walls.

Micropreparations

Interstitial myocarditis (staining with hematoxylin and eosin): Inflammatory infiltration with a predominance of lymphocytes, plasma cells is in the stroma (layers of connective tissue) of the myocardium.

Giant Pirogov-Langhans cells (staining with hematoxylin and eosin): The very large cells contain many nuclei located along the periphery of the cytoplasm as a horseshoe.

Syphilitic granuloma (gum) (staining with hematoxylin and eosin):The focus of necrosis is surrounded by an inflammatory infiltrate consisting of lymphocytes, plasmocytes, epithelioid cells, around - connective tissue with a large number of blood vessels, the phenomenon of endovasculitis is in some of them.

Tuberculosis granuloma (staining with hematoxylin and eosin):Around the focus of caseous necrosis there is a layer of epithelioid cells, lymphocytes with the presence of macrophages, among which there are the giant multinucleated
cells of Pirogov-Langhans.

Adenomatous polypus (staining with hematoxylin and eosin):There is a proliferation of glandular (prismatic) epithelium together with the underlying connective tissue, in which the phenomena of edema and inflammatory infiltration are noted

Pointed condyloma (staining with hematoxylin and eosin):There is a proliferation of connective tissue, which forms papillae covered by multilayered squamous epithelium with keratinization.

Echinococcosis of the liver (staining with hematoxylin and eosin):A capsule which constructed of connective tissue is formed around the helminth. In areas of the capsule adjacent to the chitinous membrane of the helminth inflammatory infiltration is determined.

Questions for self-control

1. Definition of the concept of productive inflammation, its main morphological features, the nature of the course, causes, classification.
2. Interstitial inflammation: causes, morphological characteristics, localization, consequences.
3. Granulomatous inflammation: determination of granuloma, stage of morphogenesis; types of granulomas depending on cellular composition.
4. Granuloma classification: by etiology and pathogenesis.
5. Specific granulomas, general characteristics.
6. Macro-microscopic characteristics of tuberculosis granuloma, consequences.
7. Pathomorphology of syphilitic granuloma (gumma), consequences.
8. Scleromous granuloma: etiology, localization, macro- and microscopic characteristics, consequences.
9. Leprosy granuloma: etiology, localization, macro- and microscopic characteristics, consequences.
10. Polyps and condylomas: causes, localization, macro- and microscopic characteristics.

Examples of tests

Study of the biopsy material revealed a granuloma consisting of lymphocytes, plasma cells, macrophages with foamy cytoplasm (Mikulicz cells), many hyaline globules. What disease can you think of?

A. Rhinoscleroma
B. Leprosy
C. Syphilis
D. Tuberculosis
E. Actinomycosis

A patient died from progressive heart failure. Autopsy revealed that the heart was enlarged in diameter, flabby. The muscle section exhibited irregular blood supply. Histological study of myocardium revealed hyperemia, the stroma was found to have lymphohistiocytic infiltrates with degeneration of cardiomyocytes. The revealed morphological changes are indicative of:

A. Non-purulent interstitial myocarditis
B. Venous plethora
C. Cardiomyoliposis
D. Cardiosclerosis
E. Myocardial infarction

A man is 28 years old. Histological investigation of the cervical lymph node revealed a change of its pattern due to proliferation of epithelioid, lymphoid cells and macrophages withhorseshoe-shaped nuclei. In the center of some cell clusters there

were non-structured lightpink areas with fragments of nuclei. What disease are these changes typical of?

A. Tuberculosis
B. Hodgkin's disease
C. Actinomycosis
D. Tumor metastasis
E. Syphilis

A microscopic examination of the tissue dissected from some postoperative infiltrate revealed granulomata with giant multinucleate cells around the suture material. What kind of granulomata did they belong to ?

A. Foreign-body
B. Rheumtic
C. Lepromatous
D. Tuberculous
E. Mycotic

A microscopic examination of the aorta in a male, who died from a rupture of its aneurysm, revealed in the medial coat of the aorta some foci of destruction of elastic fibres and an inflammatory infiltrate consisting of lymphoid and plasma cells around the «vasa vasorum». Which of the diagnoses listed below was the most probable?

A. Syphilis
B. Atheroscleros
C. Tuberculosis
D. Leprosy
E. Rheumatism

MOLECULAR-PATOMORPHOLOGICAL BASES OF IMMUNE RESPONSE. THE IMMUNE SYSTEM IN THE PRENATAL AND POSTNATAL PERIOD. PATHOLOGY OF IMMUNE PROCESSES: AMYLOIDOSIS, HYPERSENSITIVITY REACTIONS, TRANSPLANT REJECTION REACTION. IMMUNE FAILURE. AUTOIMMUNE DISEASES.

The immune system protects the body from any infections, the appearance of mutant, damaged, tumor and transplanted cells, as well as from third-party endogenous and exogenous molecular antigens that come with food, air or parenterally introduced into human tissues. Infections, cells, and molecules that the immune system recognizes as foreign are called *antigens*.

The immune system includes:

• central organs - thymus, red bone marrow

• peripheral organs: lymph nodes, pharyngeal tonsils, lymphatic follicles in the intestinal wall, lymphocytes in the peripheral blood, spleen.

Molecular-pathomorphological basis of the immune response.

Permanent participants in the immune response are recycling immunocytes (T- and B-lymphocytes, plasmocytes, monocytes, macrophages and natural killers), cytokines (interleukin-1, -2, -3, -4, -5, -6; interferon-α, -β, -γ; tumor necrosis factor, transforming and colony-stimulating factors, numerous growth factors), as well as C3 and -4 complement fragments. Other cells may also be involved in the immune response: neutrophils, eosinophils, basophils, and labrocytes (mast cells), as well as K cells (newer generations of T lymphocytes, natural killers, macrophages, and eosinophils acquiring the Fc receptor for immunoglobulins).

Phases of normal immune process:

• immune recognition of antigens;

• an immune response characterized by three features:

1) specificity (develops on a well-defined antigen);

2) potentiation (acceleration and enhancement upon re-entry of antigen);

3) immunological memory of contact with each antigen due to the presence of B- and T-cells memory.

Types of immune response: cellular and humoral.

Cellular immunity is performed by T-lymphocytes (T-killers, T-suppressors, T-helper cells). They are formed in the thymus. In the implementation of cellular immunity, an important role belongs to cytotoxic cells (T-killers), which carry out direct damage to cells by their lysis. In addition, T cells synthesize lymphokines (cytokines): interleukins, interferon, and others that regulate the function of macrophages and other lymphocytes. An important role in this process is played by T-helper (CD4) and T-suppressor (CD8).

Humoral immunity is carried out by B-lymphocytes, which are transformed into plasmocytes and synthesize immunoglobulins (antibodies).

The immune system in the prenatal and postnatal periods

Embryo-fetal hemo- and lymphocytopoiesis begins in a three-week human embryo in the extra-germinal (mesenchymal) tissue of the yolk sac, and at the 3-6th month of fetal life occurs in the liver. Bone hematopoiesis begins on the 4-5th month of the fetal period in parallel with the formation of skeletal bones and becomes significant

by the 6th month of fetal life. In the last 3 months of pregnancy, as well as after birth, the bone marrow in humans is the main site of hemo- and lymphocytopoiesis.

The *thymus* begins to develop as an epithelial-stromal organ at the 2nd month of embryogenesis, at the 9th week of embryogenesis it is settled by lymphocytes. By birth, the thymus mass is 10-15 g. In the first two years of life, its size and mass increase very rapidly; a further increase is noted until puberty, when it reaches the maximum size and mass of 30-40 g. Subsequently, the gland undergoes age-related involution, which is characterized by even atrophy of its lobules, preserving the reticuloepithelium, lymphocytes and stem cells, as well as the development of the gingival tissue.

The *spleen* begins to develop on the second month of embryogenesis, by the 5th month in it develops a hematopoietic and lymphoid tissue. The mass of the spleen of the newborn is 9 g.

Lymph nodes begin to develop at the 3-4th month of embryogenesis, but lymphatic follicles develop in them only during the first month after birth. Settlement of lymph nodes by B- and T-lymphocytes stabilizes during the first 3-5 years of life. The stimulus to stable colonization of lymphocytes by lymph nodes is the flow of antigens that collapses on the baby after birth.

Synthesis of immunoglobulins (Ig) in the newborn is not sufficiently strong, so the level of circulating IgM and IgG remains low. Synthesis of IgA and IgE in a baby is formed during the first month of life. Being immune to a baby's infection in the first weeks of life is related to the transmission of the immunoglobulin G and complement from the mother in the second trimester. The system of synthesis of immunoglobulins reaches the capacity of the adult body up to 2-5-10 years of age.

Immunoglobulin G is the only class of immunoglobulins that passes through the placenta. The large amount of IgG transmitted from the mother provides the child with "bestowed immunity" in the first months of life and enables him to form his own antibody-forming system. Maternal immunoglobulin disappears in a child by 3 months after birth. Synthesis of own IgG becomes significant in a child only at the end of the 1st month of life and gradually reaches the level of the adult organism only at the age of 8 years. Thus, in the first years of a child's life there is a relative lack of IgG, which explains its sensitivity to pathogenic flora.

The level of i*mmunoglobulin* M up to 4 months after birth is 50% of the rate of adults and reaches the values of such in adults in boys by the end of the 1st year of life, in girls - in the 2nd year of life. That is, children have relative IgM deficiency, which can be a cause of increased sensitivity to gram-negative bacteria.

The level of *immunoglobulin* A in children by the end of the 1st year of life is only 30% of that in adults and reaches the last indicator only by 10 years. IgA deficiency in children explains their sensitivity to viral diseases and fungal damage to the upper respiratory tract.

Thus, the relatively low power of immunoglobulin synthesis in children provides early protection of the body against low-pathogenic and saprophytic flora, however, against highly pathogenic infections, immune protection is not effective enough.

THE PATHOLOGY OF IMMUNE PROCESSES

By morphogenesis and clinical manifestations, the following main types of immunopathological processes are distinguished:

• amyloidosis;
• hypersensitivity reactions;
• immunodeficiency syndromes;
• autoimmune diseases;
• tumors of lymphatic tissue.

Amyloidosis

Amyloidosis - characterized by the appearance in the stroma of the organs and in the walls of the vessels of a complex protein - amyloid, which is not found normally.
The disease was described by K. Rokitansky and was called "sebaceous disease", as a macroscopic sign of amyloidosis is a ***sebaceous luster of the organ***.
Amyloid falls out in the course of reticular (perirethicular amyloidosis) or collagen (pericollagen amyloidosis) fibers.
The amyloid consists of a fibrillar protein (F-component) bound to plasma glycoproteins (P-component). Amyloid fibrils are synthesized by macrophages, plasma cells, cardiomyocytes, vascular smooth muscle cells, apudocytes, etc. from precursor proteins.
Macroscopically: the organs are enlarged in size, dense, fragile, easily broken, the edge of the incision is sharp, since the amyloid is deposited under the membrane of the vessels, causes them to narrow, ischemia develops and the organ becomes pale. Amyloid gives the organ a characteristic **sebaceous luster**.
When dissected on the organs, a macroscopic Virchov test for amyloid is used. The sample is performed on fresh, non-fixed organs: a plate from the organ, wash with water from the blood and pour with Lugol's solution, and after 30 minutes the organ is watered with 10% solution of sulfuric acid. When blue-green appears, the sample is considered positive.
Microscopic diagnosis of amyloid:
a) when stained with hematoxylin and eosin, the amyloid is represented by amorphous eosinophilic masses;
b) in **Congo red** staining (specific amyloid staining), amyloid is colored **brick-red**;
c) when viewing the colored Congo red specimens in the polarization microscope revealed two-color - dichroism: reddish and green-yellow glow;
d) when viewing thioflavin T-stained specimens, a specific green glow is detected in the fluorescence microscope.
There are several theories of the pathogenesis of amyloidosis, among which the most common *universal theory - mutational*. Mutagenic factors affect cells, thereby causing mutations, and the mechanism that leads to the formation of amyloidoblasts cells is triggered.

Types of amyloidosis (by a reason):

1. Idiopathic (primary)
2. Hereditary (family, genetic)
3. Secondary (acquired)
4. Aging (elderly)

The *primary amyloidosis* is characterized by:
• absence of primary or concomitant disease
• impressions of predominantly cardiovascular system, stript and smooth muscles, nerves and skin

• tendency to form nodular deposits of amyloid in tissues.

Hereditary amyloidosis is characterized by:

• Predisposition of certain ethnic groups (Jews, Portuguese, British, Arabs, Armenians, Danes, Americans)

• kidneys, peripheral nerves are most commonly affected.

Secondary amyloidosis is characterized by:

1. The development of amyloidosis as a complication of a number of diseases ("second disease"):

• chronic nonspecific lung diseases (bronchiectatic disease, chronic lung abscesses);

• cavernous form of tuberculosis;

• chronic osteomyelitis;

• rheumatoid polyarthritis;

• malignancies (leukemia, lymphogranulomatosis, cancer).

2. Damage of many organs and tissues (generalized amyloidosis).

Aging amyloidosis is characterized by:

• predominance of local forms of amyloidosis (atria, brain, aorta, pancreas);

• often associated with atherosclerosis, diabetes.

Features of amyloidosis in some organs

In the ***spleen***, amyloid is deposited perireticularly or pericollagenically. In the first case, there is an accumulation of amyloid in the spleen follicles, in the white pulp and looks like white grains, which are similar to sago grains **("sago" spleen**). In the second, amyloid is spread throughout the stroma. The spleen is significantly enlarged in size, dense, on incision a brown-red with a greasy luster. It was called the "**greasy**" spleen.

In the ***kidney***, the amyloid appears under the membranes of the glomerular capillaries, the vessels of the cerebral and cortical layer, the convoluted and straight tubules, and in the stroma of the kidney along the reticular fibers.

Macroscopically - a large "sebaceous" kidney: the body is significantly enlarged in size, thick and sufficiently pale cortical layer with sebaceous gloss, pyramids swollen, crimson-blue.

Microscopically: amyloid is deposited in the glomeruli (basal membranes of capillaries, mesangium), in tubular basal membranes, in the walls of vessels, stroma. At this stage, the shrinkage of the kidney develops. Kidney failure leads to death.

In the ***liver***, the deposition of amyloid begins in the sinusoids between Kupffer cells, in the course of the reticular stroma of the particles, the hepatocytes are compressed and atrophied. The liver is large, dense, light with a sebaceous luster on the incision.

Consequence: leads to hepatocyte atrophy and development of liver failure; in case of difficulty of venous outflow in connection with the defeat of the central veins may be accompanied by portal hypertension.

In the adrenal glands, amyloid is deposited only in the cortical layer in the course of the capillaries, which leads to adrenal insufficiency, so any injury or stress can lead to the death of the patient.

In the ***intestine*** the small intestine is most often affected. Amyloid is deposited in the course of the reticular stroma of the mucous membrane, under the membrane of small vessels, which leads to atrophy, ulceration of the mucous membrane. There is a violation of the suction, develops exhaustion.

Hypersensitivity reactions

Immunological hypersensitivity - an individual reaction to the re-entry of antigens (chemicals, plant pollen, medicines, food), which in terms of severity and end result exceeds the measure of biological expediency. In all forms, the primary admission of a specific antigen (sensitizing dose) elicits a primary immune response (sensitization). After a short period (one or more weeks) during which the immune system is activated, a hypersensitive response occurs to any subsequent intake of the same antigen.

1st type (immediate reagent hypersensitivity)

Mechanism of development. The first antigen (allergen) intake activates the immune system, which leads to the synthesis of antibodies - IgE (reagents), which have specific reactivity against this antigen. After that, they are fixed on the surface membrane of tissue basophils and blood basophils. Synthesis of antibodies in sufficient amount for the development of hypersensitivity takes one or more weeks. Subsequent administration of the same antigen is the interaction of antibody (IgE) and antigen on the surface of tissue basophils or blood basophils, which causes their degranulation. From the cytoplasmic granules of tissue basophils into the tissues come vasoactive substances (histamine and various enzymes involved in the synthesis of bradykinin and leukotrienes), which cause vasodilation, increased vascular permeability and reduction of smooth muscle.

Disorders that occur with type 1st type hypersensitivity:

1. Local manifestations - local manifestation of type I hypersensitivity is called atopy. Atopy is a congenital tendency that is related to a pathological response to certain allergens. Atopic reactions are widespread and can occur in many organs.

Skin - Allergy gets into the skin with sudden redness, swelling (sometimes with blisters - urticaria) and itching; in some cases develop acute dermatitis or eczema.

Nasal mucosa - when inhaling an allergen (eg, plant pollen, animal hair), vasodilation and hypersecretion of mucus (allergic rhinitis) occur in the nasal mucosa.

Lungs - Inhalation of allergens (plant pollen, dust) leads to reduction of bronchial smooth muscle and hypersecretion of mucus, leading to acute airway obstruction and shortness of breath (atopic bronchial asthma).

Intestine - oral allergen (eg, nuts, shellfish, crabs) causes muscle contraction and fluid output, manifested as spastic abdominal pain and diarrhea (allergic gastroenteritis).

2. Systemic manifestations - anaphylaxis. The ingress of vasoactive amines into the bloodstream causes a contraction of smooth muscle, widespread vasodilation and an increase in vascular permeability with the release of fluid from the vessels into the tissues and the development of peripheral vascular insufficiency (***anaphylactic shock***).

Type II (antibody-mediated hypersensitivity)

Mechanism of development. Type II hypersensitivity is characterized by the reaction of the antibody with the antigen on the surface of the host cell, which causes the destruction of this cell. A specific antibody, mainly IgG or IgM, which is synthesized against the antigen interacts with it on the cell surface and causes cell damage in several ways:

1. Cell lysis
2. Phagocytosis

3. Cellular cytotoxicity
4. Changing cell function

Types of type II hypersensitivity reactions.

1. Reactions with destruction of erythrocytes:
A. Posthemotransfusion reactions
B. Hemolytic disease of newborns
C. Other hemolytic reactions.
2. Reactions with destruction of neutrophils.
3. Reactions with platelet destruction.
4. Reactions on the basal membrane.
5. Stimulation and inhibition in hypersensitivity. Some authors classify inhibition and stimulation that are associated with hypersensitivity as V type hypersensitivity.

Stimulation – ***Graves disease*** (primary hyperthyroidism) develops when antibodies (IgG) bind to TSH receptors on the thyroid follicular epithelial cells. This interaction leads to the stimulation of the enzyme adenylate cyclase, which leads to increased levels of cAMP and the secretion of increased amounts of thyroid hormones.

Inhibition - Inhibitory antibodies play a key role in severe myasthenia gravis, a disease characterized by impaired neuromuscular transmission and the appearance of muscle weakness. The disease is caused by antibodies (IgG) directed against acetylcholine receptors on the motor endplate. Antibodies compete with acetylcholine for the binding site at the receptor, thereby blocking nerve impulse transmission. The mechanism of inhibition also underlies pernicious anemia, in which antibodies bind to an internal factor and inhibit the absorption of vitamin B12.

Type III (immunocomplex hypersensitivity)

Mechanism of development. The interaction of antigen and antibody can lead to the formation of immune complexes - either locally in the site of damage or generalized in the bloodstream. The accumulation of immune complexes in different parts of the body activates complement and causes acute inflammation and necrosis.

Types of immunocomplex damage:

1. Reactions of the type of Arthus phenomenon - tissue necrosis occurs at the site of antigen administration. Repeated administration results in the accumulation of a large number of precipitating antibodies in the serum. Subsequent administration of the same antigen leads to the formation of large antigen-antibody complexes that settle locally in small blood vessels, where they activate the complement, accompanied by the development of severe local acute inflammatory reaction with hemorrhage and necrosis.
2. Serum disease type reactions - more common than type of Arthus type reactions. The course of the reactions depends on the antigen dose. Repeated delivery of a large dose leads to the formation of immune complexes in the blood. They pass through the endothelial pores of small vessels and accumulate in their wall, where they activate complement and lead to complement-mediated necrosis and acute inflammation of the vessel wall (necrotizing vasculitis).

Type IV (delayed or cell-mediated hypersensitivity)

Mechanism of development. Cells, not antibodies, are involved in cell type hypersensitivity. This type is mediated by sensitized T lymphocytes, which either directly exhibit cytotoxicity or by secretion of lymphokines. Type IV hypersensitivity

reactions generally occur 24-72 hours after antigen administration to a sensitized person.
Microscopically: cell necrosis and severe lymphocytic infiltration.

Morphological changes in organs with antigenic stimulation

Lymph nodes enlarged in size, full-blooded. In I-III types of hypersensitivity in the light centers of the follicles of the cortex and in the medullary helices of the medullary substance, a sufficient number of plasmoblasts and plasma cells are detected. T-lymphocyte count decreased. A large number of macrophages are noted in the sinuses. In type IV hypersensitivity, in the lymph nodes in the paracortical zone proliferate mainly sensitized lymphocytes, but not plasmoblasts and plasma cells. The expansion of T-dependent zones.
The spleen enlarges, becomes full-blooded. In I-III types of hypersensitivity in the section is clearly visible sharply enlarged large grayish-pink follicles. Microscopically marked hyperplasia and plasmatisation of pulp, a sufficient number of macrophages. In white pulp, especially in the periphery of the follicles, there are also many plasmoblasts and plasmocytes. In type IV hypersensitivity, the morphological remodeling is similar to the changes observed in lymph nodes in T-zones.
In addition, in the organs and tissues in which the reaction of immediate hypersensitivity (I, II, III types) develops, there is acute immune inflammation. It is characterized by the speed of development, the dominance of alterative and exudative changes. Alterative changes in the form of mucoid, fibrinoid swelling, and fibrinoid necrosis are observed in the base substance and fibrous structures of the connective tissue. In the focus of immune inflammation is expressed plasmorrhagia, found fibrin, neutrophils, erythrocytes.
In type IV hypersensitivity (delayed type hypersensitivity reaction), lymphocytic and macrophage infiltration in the foci of immune conflict is an expression of chronic immune inflammation.

Kidney transplant rejection reactions

The rejection reactions can be caused by donor antigens in the molecules of the major histocompatibility complex of classes I and II, as well as antigens of the AB0 system present on the renal cells.
An acute rejection reaction occurs after transplantation, renal vascularization of a recipient who already has antibodies to the donor AB0 antigens. Antibodies in blood vessels react with AB0 antigens of donor kidney cells, activate complement, attract and activate neutrophils and platelets that cause destruction of the basal membranes of capillaries and vessels, as well as the basal membranes of the tubules of the donor kidney.
Chronic rejection of transplanted kidney. When the recipient and donor are incompatible with the antigens of the molecules of the major histocompatibility complex of I and II classes, the antigens are recognized by antigen presenting cells, which in lymph nodes initiate the emergence of new generations of CD8 + -T-killers and CD4-T-helper cells. The killers destroy the endothelium and damage the kidney vessels, cause their thrombosis, and also destroy the epithelium of the renal tubules and together with the activated macrophages destroy the kidney tubules. CD4 + -T helper cells provide the emergence of new generations of B-lymphocytes that

differentiate into plasmocytes that synthesize rejection antibodies. Antibodies are fixed to the endothelium of the kidney vessels and cause antibody-mediated destruction.

Thymus changes in immunogenesis disorders

Types of thymic pathology associated with immunopathological conditions:
• Accidental involution;
• atrophy;
• agenesis, aplasia,
• hypoplasia;
• thymomegaly;
• hyperplasia.

Accidental involution - a progressive decrease in thymus mass due to the destruction of thymocytes under the influence of stressors.

Causes: infectious diseases, intoxication, trauma, stress, excess glucocorticoids, malignant tumors.

Microscopic changes. *There are 5 phases of changes of the thymus* (Ivanovskaya TE, 1978):

Phase 1 corresponds to the unchanged thymus of a healthy baby.

Phase 2 is characterized by the focal disappearance of lymphocytes from the cortical layer and their adhesion to macrophages, which creates the appearance of a "starry sky".

Phase 3 is characterized by a further decrease in lymphocytes from the cortical layer, which leads to inversion of the layers - the medullary substance becomes richer in lymphocytes compared to the cortical. There is activation of the reticuloepithelium, there are neoplasms of many thymic calves.

In the ***4th phase***, there is an increasing collapse of the lobes, the layers become indistinct, the thymic calves (Hassal) are large, often forming cystic cavities.

In the ***5th phase***, the lobules look like narrow strands, the connective tissue layers are enlarged, there are few lymphocytes and thymic calves, many of which are calcified, which can be regarded as acquired atrophy.

Consequences:

Favorable - restoration of the structure and function of the thymus.

Unfavorable - thymus atrophy with the development of immune deficiency and the development of viral bacterial infectious diseases with fatal consequences.

Thymus atrophy is accompanied by collapse of the epithelial cell lattice, diminished volume of parenchyma, scarring of the thymus cells, growth of fibrous connective and adipose tissue. Sharply reduced T-lymphocyte count. The lymph nodes are enlarged in the initial period, and then subject to atrophy and sclerosis.

Agenesia, aplasia, thymic hypoplasia are congenital developmental anomalies accompanied by cellular or combined immunity deficiency (immunodeficiency syndromes).

Thymomegaly - an increase in the weight and volume of the thymus gland above the age limit, while maintaining its normal structure. Types:

Congenital thymomegaly - combined with malformations of the nervous system, chronic insufficiency of the adrenal glands and gonads.

Acquired thymomegaly - occurs in adults with the development of chronic adrenal insufficiency.
Causes of death: infections, infectious-allergic diseases, endocrine disorders under stress.
Thymus hyperplasia occurs in autoimmune diseases.
Microscopic: accumulation of B-lymphocytes, plasma cells, appearance of lymphoid follicles, which do not occur normally, in the enlarged intraparticular perivascular spaces of the thymus parenchyma.

Insufficiency of the immune response

The extreme manifestation of immune system deficiency is immunodeficiency syndromes. They can be primary, caused by underdevelopment (hypoplasia, aplasia) of central and peripheral organs of immunogenesis - these are congenital or hereditary immunodeficiency syndromes, or secondary (acquired) that arise in connection with the disease or treatment.
Morphological manifestations of the primary deficiency of the immune response are usually associated with congenital thymus anomalies or a combination of these anomalies with underdevelopment of the spleen and lymph nodes.
Aplasia, thymic hypoplasia are accompanied by a deficiency of the cellular immune system or combined immune deficiency. At ***aplasia (agenesis)*** the thymus is absent completely, at a ***hypoplasia*** its sizes are reduced, division on a cortex and a medullary substance is broken, the number of lymphocytes is sharply reduced.
In the spleen, the size of the follicles is significantly reduced, light centers and plasma cells are absent. In the lymph nodes there are no follicles and cortical substance (B-dependent zones), only the surrounding cortical layer (T-dependent zone) is preserved.
Morphological changes in the spleen and lymph nodes are characteristic of hereditary immunodeficiency syndromes associated with defects in both humoral and cellular immunity.

Types of congenital immunodeficiency

• Severe combined immunodeficiency
• Thymic hypoplasia (Day-George syndrome) - lack of cellular immunity, combined with defects of the heart, large vessels and absence of parathyroid glands
• Neselof syndrome is a primary immunodeficiency caused by hypo- or dysplasia of the thymus. As a result of its functional deficiency, there is a violation of T-lymphocyte differentiation.
• Congenital agammaglobulinemia (Bruton's disease) - violation of humoral immunity (agammaglobulinemia) while maintaining cellular
• General variable immunodeficiency
• Isolated IgA deficiency
• Immunodeficiency associated with inherited diseases (Viscott-Aldrich syndrome, ataxia-telangiectasia syndrome, Bloom's syndrome)
• Complement deficiency.

Secondary (acquired) immunodeficiency

It occurs as a secondary phenomenon in various diseases or as a result of drug therapy and is very rarely a primary disease.

The morphology of acquired immunodeficiency syndrome (AIDS) has no specific pattern. Stages of change in secondary immunodeficiency:
• Follicular hyperplasia
• Pseudo-angioimmunoblastic hyperplasia
• Depletion of lymphoid tissue.
Follicular hyperplasia is characterized by a systemic enlargement of the lymph nodes up to 2-3 cm. Many sharply enlarged follicles fill virtually the entire tissue of the lymph node. The follicles are quite voluminous, with large germinal centers. They content immunoblasts. Mitoses are numerous. Morphometrically it is possible to ascertain disturbance of a ratio of subpopulations of T-cells, but they are variable and have no diagnostic value.
Lymphoid tissue depletion alters lymphoid hyperplasia at the final stage of immunodeficiency. The lymph nodes at this stage are small. The structure of the lymph node throughout is not determined, only the capsule and its shape are preserved. Sharply pronounced sclerosis and hyalinosis of bundles of collagen fibers. The T-lymphocyte population is virtually undetectable, and single immunoblasts, plasmoblasts, and macrophages are preserved. This stage of immunodeficiency is characterized by the development of malignant tumors.
The value of secondary (acquired) immunodeficiency.
Immunodeficiency is always accompanied by the development of opportunistic infections and in the final stage by the development of malignant tumors, most often Kaposi's sarcoma and malignant B-cell lymphoma.

Autoimmune diseases

Autoimmune diseases are diseases that result from autoimmunization. *Autoimmunization* is a breakdown of natural tolerance followed by a specific humoral and / or cellular response against the body's own tissues.
Depending on the mechanism of autoimmunization distinguish:
1. Organ-specific autoimmune diseases
2. Organ-nonspecific autoimmune diseases
3. Diseases with autoimmune disorders.
Organ-specific autoimmune diseases are a group of diseases that arise due to damage to the physiological barriers of immune organs and tissues, allowing the immune system to respond to their antigens by producing autoantibodies and sensitized lymphocytes.
Examples:
• thyroid gland (autoimmune thyroiditis - Hashimoto thyroiditis),
• brain (encephalomyelitis),
• peripheral nerves (polyneuritis),
• adrenal glands (idiopathic Addison's disease),
• testis (aspermatogeny),
• eye (sympathetic ophthalmia).

Morphological manifestations characteristic for delayed type hypersensitivity:
• lymphocytic infiltration;
• necrosis of parenchymal elements;
• sclerosis in the finale.

Non-organ-specific autoimmune diseases are disorders of the control of the immunological homeostasis by the lymphoid system, manifested by morphological changes, characteristic, mainly, for immediate-type hypersensitivity.
Examples:
• rheumatic diseases (rheumatism, rheumatoid arthritis, systemic lupus erythematosus, etc.),
• secondary hemolytic anemia,
• Trombocytopenic purpura.
Diseases with autoimmune disorders occur when the antigenic properties of tissues and organs change.
Reasons (examples):
• Antigen formation under the influence of bacterial antigens (glomerulonephritis, hepatitis, gastritis, enteritis);
• protein denaturation, radiation, viral infections (cirrhosis);
• hapten mechanism (agranulocytosis, drug disease).

Macropreparations:

Hashimoto's thyroiditis: the gland is enlarged in size, its consistency is dense, the surface is nodular. The section is pale yellow.

Micropreparations:

Autoimmune thyroiditis (Hashimoto thyroiditis) (staining with hematoxylin and eosin): a parenchyma of the gland with phenomena of atrophy, partially replaced by connective tissue, in the stroma - infiltration by lymphocytes and plasma cells, light lymphoid formation.

Questions for self-control

1. Molecular-pathomorphological basis of the immune response.
2. The immune system in the prenatal and postnatal period.
3. Amyloidosis, definition, morphological characteristics.
4. Classification and morphological characterization of hypersensitivity reactions.
5. Definition, etiology, pathogenesis of autoimmune diseases.
6. Classification of pathological changes in the immune response.
7. Morphological manifestations of transplant rejection reaction.
8. The concept of immunodeficiency states.
9. Macro-, microscopic manifestations of individual immunodeficiency states.

Examples of tests

A 45 year old male died from disseminated tuberculosis. On autopsy the symptoms of tuberculosis were confirmed by both microscopical and histological analyses. All the affected organs had epithelioid cell granulomas with caseous necrosis in the centre. What kind of hypersensitivity reaction underlies the process of granuloma development?

A. Delayed
B. Antibody-dependent cytotoxicity
C. Complement-dependent cytotoxicity
D. Anaphylactic
E. Immune complex

During pathomorphological renal investigation of a patient, who for a long time had been suffering from osteomyelitis and died of progressing renal failure, the following

was revealed: deposits of homogeneous eosinophilic masses in glomerular mesangium, arterial and arteriolar walls, and stroma, which colored red when stained with Congo red. What pathological process is this?

A. Amyloidosis
B. Mucoid swelling
C. Calcinosis
D. Carbohydrate degeneration
E. Hyalinosis

Autopsy of an 8-month-old boy, who died of severe pneumonia complicated with sepsis, revealed absence of thymus. Lymph nodes have no lymphoid follicles and cortical substance. In the spleen the follicles are decreased in size and have no light centers. What is the cause of such changes?

A. Thymus agenesis
B. Thymus aplasia
C. Thymus atrophy
D. Thymus hypoplasia
E. Accidental thymic involution

10 days after having quinsy caused by beta-hemolytic streptococcus a 6-year-old child exhibited symptoms of glomerulonephritis. What mechanism of glomerular lesion is most likely in this case?

A. Immunocomplex
B. Cellular cytotoxicity
C. Anaphylaxis
D. Atopy
E. Antibody-dependent cell-mediated cytolysis

A 50 year old man who was referred to the hospital for treatment of cervical lymphadenitis underwent test for induvi-dual sensitivity to penicillin. 30 seconds after he went hot all over, AP dropped down to 0 mm Hg that led to cardiac arrest. Resuscitation was unsuccessful. Autopsy results: acute venous plethora of internal organs; histological examination of skin (from the site of injection) revealed degranulation of mast cells (tissue basophils). Degranulation was also revealed in myocardium and lungs. What type of hypersensitivity reaction is it?

A. Anaphylactic
B. Delayed-type hypersensitivity
C. Complement-mediated cytotoxic
D. Immunocomplex-mediated
E. –

REGENERATION. STRUCTURAL BASIS OF PHYSIOLOGICAL ADAPTATION OF ORGANS AND CELLS. MORPHOLOGY OF CELL ACCOMMODATION PROCESSES. COMPENSATORY-ADAPTIVE PROCESSES.

Regeneration

Regeneration (Lat. Regeneration) - the process of restoring the structural elements of tissues and organs instead of lost ones.

Regeneration levels:

• molecular-membrane
• subcellular
• cellular
• tissue-organ

Types of regeneration:

1. Physiological
2. Reparative
3. Dysregeneration (disruption of regeneration)

1. *Physiological regeneration* - self-renewal of biostructures that have exhausted vital resources.

Physiological self-renewal of the cell population involves two major processes:

• mitotic division of maternal precursor cells
• differentiation (maturation, specialization) of daughter cells into cells capable of performing organ-specific functions.

Examples: continuous renewal of the epithelium of the skin, mucous membranes, secretory epithelium of the exocrine glands, cells lining the serous and synovial membranes, connective tissue cells, blood cells.

2. ***Reparative regeneration*** - restoration of destroyed or damaged cells and tissues in various pathological processes.

Ways of reparative regeneration

of populations of damaged specialized cells in the adult body:

• mitotic division of stem and cambial cells
• intracellular regeneration of mitochondrial and nuclear DNA, as well as damaged organelles in cells that have lost the ability to mitosis
• simultaneous combination of intracellular regeneration of organelles of damaged cells and mitotic division of similar intact cells.

Restoration of damaged organs

Damage to organs involves two successive stages:

• The ***first*** is the regeneration of the constituent components of the damaged organ through subsequent reparative processes:

1) reparative angiogenesis (recovery of the microcirculatory bed), which occurs on average within the first five days in the area of damage,
2) repair of damaged populations of specialized cells,
3) restoration of the intercellular molecular-fiber matrix and the basal membranes of the damaged organ,
4) repair of damaged specialized microstructures of the affected organ

5) restoration of the epithelium, which covers the damaged organ (serosa, epithelium of the skin and mucous membranes)

• The ***second*** is reparative remodeling of the damaged organ

Types of reparative organ regeneration.

• *Complete restoration* of the structure and function of the organ *(restitution*) - usually develops after shallow or small area damage of the organ, which includes specialized cells capable of mitotic division, or stem (cambial) cells that are capable of differentiation into specialized cells of the organ.

Examples: complete skin repair after superficial damage (abrasion); in the area of superficial erosion of the mucous membrane; liver, with minor lesions.

• *Incomplete structure restoration (substitution)* and reparative organ remodeling - develops as a result of deep or widespread organ damage, usually by replacing a number of specialized organ cells with a coarse connective tissue (scar).

Examples: the formation of connective tissue scar in the skin after deep damage, the formation of connective tissue scar in the heart after myocardial infarction.

3. ***Dysregeneration (disruption of regeneration)*** - distortion of the regenerative process due to disruption of the proliferation phase, or the phase of cell differentiation.

Types of pathological regeneration:

• Excessive regeneration (hyperregeneration) - due to the increase in the level of inductive germinal signals from the intercellular matrix to cell division.

Examples: formation of a keloid scar in the wound area, bone marrow, excessive granulation of the wound edges ("wild meat");

• Insufficient regeneration (hypo-regeneration) - due to lack of the necessary plastic substances for the growth of new cell generations.

Examples: sluggish healing of trophic ulcers in diabetes, too slow healing of bedsores.

The completeness of reparative regeneration of the damaged organ depends on the depth and prevalence of damage, on the mitotic activity of its cells, as well as on the completeness of the trophic support of regeneration.

Wound healing.

Types:

• Immediate closure of the epithelial defect - healing, which consists in "crawling" the epithelium to the surface defect and closing it with an epithelial layer.

• Healing under the scab - healing due to the proliferation of the epithelium under the crust (scab), which is formed from coagulated blood and lymph, which disappears after 3-5 days (mucous membranes, skin).

• Primary tension healing - in wounds with damage not only of the skin but also of the underlying tissue. The edges of the wound should be smooth, not infected. The wound is filled with blood clots, a day later these clots are removed (primary cleansing) and the proliferation of granulation tissue begins, which matures for 10-15 days and becomes covered with epithelium. A delicate scar remains at the site of the wound.

• Secondary tension healing - with significant wounds accompanied by tissue fracture and death with the onset of infection. Within 5-6 days there is a rejection of necrotic masses (secondary cleaning of a wound) and the beginning of development of

granulation tissue with subsequent closing of defect of an epithelium. A rough scar is in place of the wound.

COMPENSATORY-ADAPTIVE PROCESSES

Adaptation - a set of biological processes that ensure the ability of a biological species to exist when changing environmental conditions. By the adaptation maintains the stability of the internal environment of the body (homeostasis). Adaptation processes, to varying degrees, continue in the body constantly, throughout life - from birth to death.

The process of adaptation of cells to changes in the extracellular environment, which can be detected microscopically, is called ***"cell accommodation"***.

Compensation is a separate type of adaptation that develops in the body in the presence of a pathological process (illness, injury, etc.), aimed at compensating for the impaired function of the organ or tissue.

Thus, the compensatory reactions are one of the types of adaptations. Therefore, those processes that provide the body with the restoration of lost structures and impaired function in pathology, can be combined into one group called ***"compensatory-adaptive processes".***

Morphological manifestations of cell accommodation:

1***. Proliferation*** (increase in the number of dividing cells) and hyperplasia (increase in the number) of cells. Reproduction and timely differentiation of specialized cells enhances the functional activity of the organ.

2. ***An increase in the number of apoptotic cells*** as the level of apoptogenic signals from extracellular microenvironment increases.

3. ***Cell hypertrophy*** - increase in cell size / volume.

4. ***Endoreplication and polyploidy***. In the cell nucleus, the number of chromosomes is multiplied by a haploid (single) set of odd chromosomes.

5***. Amitosis with the formation of two- or multinucleated cells*** - the cells retain their functional activity, which almost completely ceases upon mitosis.

6. ***Cell atrophy*** - reduction of the cytoplasm and nucleus of cells by reducing the function of cells or reducing their trophic supply.

7. ***Cell metaplasia*** - stable substitution of differentiated cells of one type by differentiated cells of another type while maintaining the basic tissue species. Tissue metaplasia - the transition of one type of tissue to another within one germ sheet.

Examples of metaplasia:

• Transformation of the prismatic single-layer epithelium into a multilayer flat (squamous metaplasia) in the respiratory tract.

• Intestinal metaplasia ("enterolysis" of gastric mucosa) - transformation of gastric epithelium into intestinal.

• Metaplasia of coarse fibrous connective tissue in cartilage and bone (in healing foci of tuberculosis, in tumor stroma, etc.).

Significance: Metaplasia of the epithelium can be a background for the development of a malignant tumor (cancer).

Phases of compensatory-adaptive processes:

1. *Compensation phase* - inclusion of all structural and functional reserves of the injured organ and switching to economical mode of operation.

2. *Phase of fixing compensation* - the inclusion of additional specialized microstructures, cells and intracellular organelles, microvessels and metabolic reserves, which ensure the stable operation of the organ under increased load or deficiency of specialized microstructures.
3. *Depletion / decompensation phase* - inability to perform specific organ functions at an elevated level due to a shortage of specialized microstructures or a shortage of material substrates. Organ atrophy develops.
Changes in neuroendocrine regulation, functional load, and blood supply that accompany reparative organ remodeling cause adaptive changes in organ size, volume, and mass: hypertrophy, atrophy.

Hypertrophy

Hypertrophy (Greek *hyper* - excess, *trophe* - nutrition) - increase the size and functional activity of an organ by increasing the volume of its specialized cellular structures.

Types of hypertrophy depending on the mechanism of development

• *Neurohumoral (hormonal) hypertrophy* - develops against the background of changes in function (increase or decrease in the number of hormones produced) of endocrine organs.

Types of neurohumoral hypertrophy:

- *physiological* - uterine enlargement during pregnancy
- *in the case of pathology* - gigantism, acromegaly, (with hyperproduction of somatotropic hormone in the anterior pituitary).

• *Vicarious (substitute) hypertrophy* - compensatory hypertrophy of one of the paired organs (kidneys, lungs) in case of death due to the disease or after operative removal of the other, or odd (for example, liver) due death, or surgical removal of a part of it.
• *Compensatory (working) hypertrophy* - occurs in the body in case of increase of its functional load under conditions of adequate strengthening of blood supply and provision with plastic substrates.

Types of working hypertrophy

• *physiological* - skeletal muscle and myocardial hypertrophy in athletes and people with heavy physical labor,
• *in the case of pathology* - occurs in pathological processes, accompanied by increased work of the organ or part of the organ.

Examples of working hypertrophy in pathology:

• hypertrophy of the bladder wall with benign nodal hyperplasia of the prostate, which narrows the urethra;
• hypertrophy of the wall of the stomach or intestine above the area of the lumen stenosis;
• myocardial hypertrophy.

*Causes of **myocardial hypertrophy***:

• extracardial (arterial hypertension, aortic constriction; sclerosis of lung vessels)
• intracardiac (congenital and acquired heart defects)

Signs of hypertrophy of the heart at different stages of compensation.

1. The phase of formation of compensation (emergency stage) - inclusion of all structural and functional reserves and change of metabolism in the affected organ (system):

• a combination of marked pathological changes in the myocardium and the phenomena of acute heart failure with the mobilization of myocardial and body reserves;
• rapid (within weeks) increase in heart mass by 30-70%;
Microscopic - muscle fiber contracture.
2. Compensation phase (relatively stable hyperfunction stage) - restructuring of the structure and metabolism in the organ (system), which ensures their functionality under conditions of high load:
• myocardial mass increased by 100-120% and no longer increases;
• extension of the heart in the longitudinal direction (***tonogenic, active, concentric, compensatory dilatation***) due to the elongation of the aferent tract up to 11-13 cm, the deferent tract does not change;
• hemodynamic compensation;
Microscopically - an increase in the mass of sarcoplasm of muscle cells, the size of the nucleus, the number of myofilaments - hyperplasia of intracellular ultrastructures.
3. The phase of decompensation (the stage of gradual exhaustion) - increasing insufficiency of compensatory processes, which depends on many factors (age, duration and severity of the disease, the nature of treatment):
• loss of muscle fibers and replacement of connective tissue;
• transverse (***passive, myogenic, eccentric***) enlargement of the heart;
• heart failure and, subsequently, circulatory failure
Microscopically - fatty parenchymatous myocardial dystrophy, sclerosis phenomena.
The key mechanism for the development of decompensation in working heart hypertrophy is the inability of adequate blood supply of hypertrophied cardiomyocytes by the blood vessels of the myocardium. As a result, in cardiomyocytes develop dystrophic changes with subsequent death and growth of connective tissue.
False hypertrophy - an increase in the size of the organ due to the formation of cavities, the development of adipose or connective tissue with a decrease in its functional activity.
Example: False kidney hypertrophy develops with persistent obstruction by a stone of its ureter. The size of the kidney increases due to the increased volume of its pelvis and cups, the kidney tissue atrophy and the function of the kidney decreases.
False hypertrophy is not a compensatory-adaptive process.

Hyperplasia

Hyperplasia - an increase in the size of an organ or tissue as a result of an increase in the number of cells from which they are composed.

Types of hyperplasia depending on the mechanism of development

• *Reactive (protective*) - cell reproduction in lymph nodes in response to antigenic stimulation.
• *Neurohumoral (hormonal*) - develops due to changes in the number (increase or decrease) of some hormones.

Types of neurohumoral hyperplasia:

- physiological - breast enlargement during lactation
- pathological, examples:

• ***glandular cystic endometrial hyperplasia*** - occurs in ovarian dysfunction. Most often manifested by anovulatory uterine bleeding and may result in the development of cancer of the uterine body (optional pre-cancer)
Microscopically: the number of glands in the scraping is increased, some of them are enlarged (cystically altered), the number of cytogenic stroma cells is increased.
• ***Gynecomastia*** in men is observed with a decrease in the number of male sex hormones (androgens), or with a relative increase in female sex hormones. In the breast gland hyperplasia of the glandular lobes develops, which leads to a marked increase in the size of the whole gland.
Macroscopically: breast of elastic or dense consistency, well separated from surrounding tissues, large lobular structure, yellow, sometimes with a pink tinge, with varying amounts of adipose tissue.
Microscopically: The parenchyma of the gland consists mainly of a small amount of glandular acini and ducts, lined by a proliferating cubic or highly prismatic epithelium, sometimes located in several layers. In places, the epithelium can collect into folds, forming a kind of capillary projections in the lumen of the acini. The number of glandular ducts is increased, sometimes they retain a tubular structure, sometimes branching.
Complications: Breast cancer.
• Substitute - observed in the red bone marrow in case of blood loss.

Atrophy

Atrophy is an adaptive, lifelong reduction in organ mass and size, with a steady decrease in its functional load, innervation, or blood supply.

Types of atrophies:

Physiological - observed during life, but not associated with the action of pathological factors.
Examples:
• after birth: obliteration of the umbilical arteries, the ductus arteriosus, age-related involution of the thymus
• in the elderly: atrophy of the individual organs (genital atrophy, in the elderly - bones, intervertebral cartilage, etc.).
Pathological - develops due to the action of pathological factors.
Pathological atrophy, depending on the prevalence is:
• general (exhaustion, cachexia),
• local.
General atrophy (exhaustion), cachexia (Greek kakos - bad, exis - condition) or marasmus (Greek. Marasmos - exhaustion).
Reasons:
• nutritional exhaustion (fasting, eating disorders);
• Cancer cachexia (tumor depletion);
• pituitary cachexia (depletion in case of massive pituitary cell death);
• cerebral cachexia (depletion in case of hypothalamus disorder);
• exhaustion in chronic infectious diseases.
Appearance of the patient and changes of internal organs at exhaustion:
• sharp weight loss, lack of subcutaneous fat;
• dry, faded skin, muscle atrophy;

• reduction of internal organs in size, changing their color to brown due to the accumulation of lipofuscin pigment (brown atrophy);

Classification of local pathological atrophy depending on the mechanism of development:

1. Dysfunctional atrophy - a result of decreased organ function (muscle atrophy in bone fractures and joint diseases, optic nerve atrophy after eye removal, etc.).
2. Organ atrophy caused by insufficient blood supply - due to narrowing of the arteries that feed this organ and the development of local hypoxia (kidney atrophy with narrowing of the renal artery, myocardial atrophy in coronary sclerosis).
3. Compression (pressure atrophy) - due to the reduction of trophic and hypoxia (renal hydronephrosis in violation of urine outflow; compression and deformation of vertebral bodies with aortic aneurysm; hydrocephalus and brain tissue atrophy in violation of spinal fluid.).
4. Neurotic atrophy - a violation of the conductivity of the peripheral nerve trunks or their mechanical damage and inflammation (muscle atrophy in trauma and nerve rupture, etc.).
5. Atrophy under the influence of physical and chemical factors (under the influence of ionizing radiation bones and genital organs suffer; iodine, thiouracil suppress thyroid function; steroid hormones - adrenal cortex, etc.).

Morphological signs of atrophy:

Macroscopic:
• reduction of the organ in size;
• smooth (smooth atrophy) or granular (granular atrophy) organ surface;
• enlargement of the organ in size with hydrocephalus, hydronephrosis due to the accumulation of fluid in them and reduction of parenchymal elements;
• the growth of fat around the atrophied organ.

Microscopic:
• reduction of cell size due to compaction of the cytoplasm (atrophy of the parenchymal elements);
• growth of connective tissue.

Organization - Replacement of non-viable tissues (necrosis, thrombus) with connective tissue.

Encapsulation - the fusion of connective tissue and the delimitation of dead masses, animal parasites, foreign bodies by capsule from the rest of the body.

Fibrosis is an overgrowth in the stroma of the organs of the fibrous connective tissue.

Sclerosis is the replacement of parenchymatous elements or specialized structures of the internal organs with a dense connective tissue, which leads to diffuse or focal seals and loss of function.

Cirrhosis - sclerosis of the organ with its deformity and rearrangement.

A scar is a local area of sclerosis that replaces a defect or area of necrosis on the wound surface.

The etiology of sclerosis:

• hypoxia of different genesis;
• chronic productive inflammation of infectious-allergic or immunopathological origin, as well as caused by foreign bodies.

• systemic (rheumatic diseases, systemic congenital dysplasia) and local (keloid, Dupuytren's contracture) disorganization of connective tissue.
• necrosis and atrophy of organs and tissues with replacement of their connective tissue.

Mechanisms of sclerosis:

• neoplasm of young connective tissue due to the proliferation of fibroblasts and their production of collagen;
• transformation of young connective tissue into fibrous tissue.

The reverse of sclerosis is divided into:

• labile - reverse, after termination of pathogenic factor,
• stable - irreversible or partially reversible, for a long time or as a result of treatment,
• progressive - irreversible.

Macropreparations

Hypertrophy of the heart: the size of the heart is increased due to the outflow tract; wall of left ventricle thickened to 2 cm; there are no signs of necrosis and hemorrhage.

Hydronephrosis: the kidney is significantly enlarged in size, the cortical and cerebral layers are thinned; bowls and cups distended, parenchyma atrophied; there are stones in the cavity of the renal pelvis.

Large-focal cardiosclerosis: heart enlarged in size, increased thickness of left ventricular wall - more than 1.2-1.3 cm, increased volume of papillary and trabecular muscles, enlarged heart cavities. In the wall of the left ventricle myocardium is a large transmural scar of irregular shape, white color, dense consistency.

Micropreparations

Glandular cystic endometrial hyperplasia(staining with hematoxylin and eosin): The number of glands in the scraping is increased, some of them are enlarged (cystic changes), the number of cells of the cytogenous stroma is increased.

Granulating tissue (staining with hematoxylin and eosin):The tissue consists of a large number of thin-walled vessels and cellular elements of the macrophage-monocyte series, lymphocytes, low-specialized fibroblasts. The fibrillar component is poorly developed.

Cardiosclerosis (Van Gieson staining): Among the muscle tissues there are the areas of growth of coarse fibrous connective (fibrous) tissue, which is stained with picrofuxine in a yellow-red color.

Cardiosclerosis (staining with hematoxylin and eosin): There are areas of proliferation of coarse-fibrous connective (fibrous) tissue among hypertrophied muscle tissues.

Questions for self-control

1. Definition of the term "regeneration", its types, characteristics.
2. Definition of "adaptation" and "compensation".
3. The main types of compensation and adaptation processes.
4. Stages of development of compensatory-adaptive processes.
5. Determination of hypertrophy, classification by mechanism of development.
6. Working hypertrophy of the heart: causes, mechanism of development, macro- and microscopic changes in the stage of fixation (compensation) and in the stage of decompensation, consequences.

7. Definitions and types of hyperplasia.
8. Types of wound healing.
9. Determination of atrophy, its types by mechanism of development and prevalence.
10. Metaplasia: definitions, causes, morphology, consequences.
11. Definition of concepts: fibrosis, sclerosis, cirrhosis, etiology, consequences.

Examples of tests

On histological examination of uterine mucosa the following is detected: sinuous glands, serratiform and corkscrew-shaped elongated growths of stroma with cell proliferation. Make the diagnosis:

A. Glandular endometrial hyperplasia
B. Acute endometritis
C. Leiomyoma
D. Vesicular mole
E. Placental polyp

At autopsy the occipital lobe of brain was found to have a cavity 2,5x1,5 cm large filled with a transparent liquid. The cavity had smooth brownish walls. What process had developed in the brain?

A. Cyst on the site of a hemorrhage
B. Softening of the cerebrocortical grey matter
C. Brain abscess
D. Paracephalia
E. -

Histological examination of the biopsy material obtained from the lower third of the esophagus of a 57-year-old male with the symptoms of continuous reflux revealed the change of the stratified squamous epithelium to the singlelayer columnar glandular epithelium with signs of mucus production. Specify the pathological process in the mucous membrane:

A. Metaplasia
B. Hyperplasia
C. Hypertrophy
D. Organization
E. Regeneration

Examination of coronary arteries revealed atherosclerotic calcified plaques closing vessel lumen by 1/3. The muscle has multiple whitish layers of connective tissue. What process was revealed in the myocardium?

A. Diffusive cardiosclerosis
B. Tiger heart
C. Postinfarction cardiosclerosis
D. Myocarditis
E. Myocardium infarction

A patient who has been abusing tobacco smoking for a long time has got cough accompanied by excretion of viscous mucus; weakness after minor physical stress, pale skin. The patient has also lost 12,0 kg of body weight. Endoscopic examination of biosy material his illness was diagnosed as squamous cell carcinoma. Name a pathological process that preceded formation of the tumour:

A. Metaplasia

B. Hypoplasia
C. Hyperplasia
D. Necrosis
E. Sclerosis

ONCOGENESIS. MACRO-MICROSCOPIC PECULIARITIES AND TYPES OF GROWTH OF BENIGN AND MALIGNANT TUMORS. MORPHOLOGICAL CHARACTERISTICS OF THE MAIN STAGES OF THE DEVELOPMENT OF MALIGNANT TUMORS. CLINICAL AND MORPHOLOGICAL NOMENCLATURE OF TUMORS.

Oncogenesis is a complex process of tumor origin and development that is caused by changes in cellular genes, under the influence of exogenous (carcinogens) and endogenous factors.

Tumor (synonyms: neoplasia, neoplasm, blastoma - Greek. Blasto - sprout) is a pathological process characterized by uncontrolled, autonomous cell reproduction.

Clinical classification of tumors:

• Benign (differentiated)
• Malignant (undifferentiated)
• Tumors of marginal type

Ethiopathogenetic theories of tumor development:

1. Viral genetic (LA Silber theory, 1968);
2. Physico-chemical (R. Virkhov's theory, 1885; LM Shabad, 1969);
3. Dysontogenetic (theory of Y. Congame, 1839-1884);
4. Polyetiological (II Petrov's theory).

Etiology of the tumors

Tumor growth initiators are factors of different nature, under the influence of which tumor cells are formed.

Carcinogens are factors that, due to their properties, contribute to the emergence of a malignant tumor, causing irreversible changes in the genetic apparatus.

Tumor growth initiators (promoters)

Factors	The mechanism of influence and the organ of defeat
Physical: ultraviolet, ionizing, x-ray	DNA damage with irreversible mutations
Chemical: - Industrial carcinogens (benzidine, asbestos, nafilamine) - Medicinal carcinogens (diethylstilbestrol, bisulfan, thioteph) - Natural carcinogens (aflotoxin, benzpyrene, nitrosamines)	Genotoxic effects on organ tissues: *skin cancer, lung cancer* *cancer of the vagina, renal pelvis* *lung, skin, liver cancer*
Oncogenic viruses: - Epstein-Barr virus - HPV papilloma virus - T-lymphotropic viruses	Integration of viral oncogenes into host cell growth regulators: *Burkitt's lymphoma, cancer of the nasopharynx* *cervical cancer* *leukemias, lymphomas*
Hereditary	Defective tumor suppressor genes

Mechanisms of oncogenesis

Epigenetic mechanisms of oncogenesis are characteristic for the development of benign tumors:

• excess hormones and cytokines

• increased sensitivity of receptors to normal concentrations of hormones or cytokines

Genetic mechanisms of oncogenesis are characteristic for the development of malignant tumors:

• transformation of protooncogens into oncogenes (alteration of gene structure, gene amplification)

• inactivation (mutation) of anti-oncogenes (suppressor genes of uncontrolled cell division)

• inactivation (mutation) of genes of apoptosis regulators

• Mutation, hereditary defect or loss of DNA repair genes

Appearance of tumors:

Node (with clear boundaries):

• polypoid with narrow leg,

• papillae (cauliflower),

• mushroom-shaped with broad fixed leg.

Infiltrate - without clear boundaries.

Ulcer - the presence of a deep defect in the skin or mucous membrane of the organ.

Cyst is a thin-walled hollow formation with clear borders filled with contents (mucous, serous, colloid, etc.).

Tumor growth

Depending on the number of foci of origin:

• unicentric

• multicentric

In relation to the surrounding tissues:

Expansive growth (*delimited by a capsule or pseudocapsule)* - grows slowly "from the middle of itself", squeezing surrounding tissues, causing atrophy and fibrosis in them. It is typical for benign tumors.

Infiltrative growth (*invasive*; lat. In vasa - into a vessel) - tumor cells grow into surrounding tissues and destroy them, due to which the tumor has no clear boundaries. It is typical for malignant tumors.

Locally destructive growth has signs of infiltrative growth, but does not germinate vessels and does not metastasize (eg, ameloblastoma).

In relation to the lumen of hollow organs:

• ***endophytic*** - infiltrating tumor growth into the wall of the hollow organ

• ***exophytic*** - the growth of a tumor into the cavity of an organ, narrowing or completely closing its lumen

• ***exo-endophytic (mixed).***

Microscopic structure of the tumor

Tumors have parenchyma and stroma. The parenchyma is represented by tumor cells. The stroma is usually represented by connective tissue and blood vessels, free of lymphatic vessels and nerve fibers.

Atypism - a property of tumors that distinguishes it from normal tissue and is characterized by impaired structure, metabolism, function, antigenic structure, reproduction, delayed differentiation (*cataplasia*).

Types of atypism:

• Morphological (structural):

 tissue

 cellular
 ultrastructural
• Biochemical (histochemical)
• Antigenic
• Functional

Morphological (structural) atypism:

Tissue atypism is typical for benign and malignant tumors and characterized by:
• change in the ratio of parenchyma and stroma;
• changing the ratio between the number and architectonics of the individual structural components of the tissue (cells and fibrillar structures).

Cellular atypism is typical for immature, malignant tumors, manifested by:
• increase of mitotic activity, appearance of pathological mitoses
• polymorphism of cells, nuclei and nuclei both in shape and in size
• an increase in the nuclear-cytoplasmic ratio in favor of the nucleus
• impaired sexual chromatin division
• nuclear hyperchromia.

Ultrastructural atypism is characterized by changes in the plasmolemma, cytoskeleton, number and structure of cell organelles.

Depending on the severity of morphological atypism distinguish:
• *Homologous tumors* (benign) - mature, differentiated, similar to the parenchyma of the organ from which they originate.
• *Heterologous tumors* (malignant) - immature, low-differentiated, lost resemblance to the organ due to the high degree of cell atypia.

Biochemical atypism is manifested by metabolic changes in tumor tissue. Detect disorders of metabolic processes in the cell using histochemical methods of research (***histochemical atypism***).

Functional atypism is the reduction (loss) by tumor cells of specialized functions inherent in mature tissue or the appearance of a new function that is not peculiar to cells of this type.

Antigenic atypism - 5 types of antigens are detected in tumor cells:
• virus antigens associated with tumors;
• carcinogens-related tumor antigens;
• transplant type isoantigens - tumor-specific antigens;
• oncofetal (embryonic) antigens;
• heteroorganic antigens.

Secondary changes in tumors

• foci of necrosis and apoptosis are associated with the action of immune defense factors, cytokines, ischemia in insufficiently vascularized tumors, etc .;
• hemorrhages associated with imperfect angiogenesis in tumors and invasive growth;
• mucous transformation occurs as a result of changes in metabolic processes in tumor cells;
• lime deposition (petrification) is associated with a change in the alkaline acid balance in the tumor.

Implications for the body

Local influence	*General influence*
• atrophy and fibrosis of the surrounding tissue due to	• cancer intoxication,

compression; • closure of the lumen of the hollow organ: in the salivary gland - cyst, in the kidney - hydronephrosis, in the liver - jaundice; • ulcers; • inflammatory process - paracancreatic inflammation.	• cachexia • metastases

Stages of malignant tumor development

1. Pretumor stage - chronic inflammatory processes with pathological regeneration: hyperplasia, dysplasia, metaplasia, hypoplasia.

A) Precancerous conditions

Optional precancer - background of chronic disease, hyperplastic, dysplastic suprovodzhuyutsya processes that increase the likelihood of developing malignant tumors:

• oral mucosa - leukoplakia
• cervix - endocervicosis, leukoplakia
• uterine body - hyperplasia of the glands of the mucous membrane
• stomach - glandular polyps, reorganization of the mucous membrane by intestinal type
• large intestine - adenomatous polyps
• bronchial tubes - chronic bronchitis

Obligate precancer - almost always ends with the development of a tumor, usually congenital condition associated with an inherited predisposition:

• congenital polyposis of the colon
• pigmented xeroderma
• neurofibromatosis

B) Precancerous changes

Dysplasia (Greek: dys - disorders, plasis - formation) - disorders of epithelial proliferation and differentiation. The manifestations of dysplasia are disorders of the normal layered structure of the epithelium, loss of polarity of the epitheliocytes and the appearance of single atypical cells with mitoses.

1. Stage of a non-invasive tumor - the appearance of the first atypical cells, which rapidly divide and lose the ability to fully differentiate. At malignant epithelial tumors (cancer, carcinoma) atypical cells proliferate in the epithelial layer without invading the basement membrane - cancer "in situ".

2. The stage of invasive tumor growth is the penetration of tumor cells into surrounding tissues due to their destruction by lytic enzymes. Carcinomas, invading the basement membrane, propagate into the underlying tissues.

3. The stage of tumor metastasis.

Metastasis - the spread of tumor cells from the primary tumor to other organs with the formation of secondary tumor nodes - metastases.

Ways of metastasis:

1. Lymphogenic (orthograde, retrograde) - characteristic for carcinoma and melanoma.
2. Hematogenous - characteristic of sarcoma, melanoma.
3. Implantation (more often on serous membranes).
4. Perineural.

5. Liquorogenous (in the CNS for the current of cerebrospinal fluid).
6. Mixed

Differential diagnosis of tumors

Characteristics	**Benign tumors**	**Malignant tumors**
Morphological features	Homologous	Heterological
Growth	Expansive	Infiltrative Oppositional
	Locally-destructive	
Morphological atypism	Tissue	Tissue Cellular
Metastasis	Is not typical	Typical
Effect on the body	Local	General
Secondary changes	Hyalinosis Petrification	Necrosis Hemorrhage Mucous transformation
Consequences	In most cases favorable	Not favorable

Morphological classification of tumors according to histogenesis (WHO):
1. Epithelial tumors without specific localization (non-organ-specific)
2. Organ-specific epithelial tumors (tumors of exo- and endocrine glands, as well as epithelial coatings)
3. Mesenchymal tumors (tumors of soft and other tissues)
4. Tumors of melanin-forming tissue
5. Tumors of the nervous system and brain membranes
6. Tumors of hematopoietic and lymphatic tissue
7. Teratomas

Oncological classification - according to the International Classification of Diseases (ICD X), it takes into account the type and localization of tumors in certain organs (for example, cancer of the pyloric department of the stomach, hip sarcoma).

Process prevalence classification is an international TNM system for most malignant tumors, where:

T (tumor) is a characteristic of the tumor,

N (nodus) - the presence or absence of lymph node metastases,

M (metastasis) - the presence or absence of distant metastases.

Macropreparations:

Uterine polyp: formation on the peduncle in the form of a papilla 1.5 cm in size, protruding from the lumen of the cervical canal.

Uterine fibromyoma: A tumor of rounded shape, gray in color, with clear boundaries surrounded by a capsule, represented by fibrous structures intertwined in different directions.

Mushroom-shaped gastric cancer: a hilly knot of gray-pink color, which is located broadly, protruding into the gastric cavity (exophytic growth).

Cancer metastases to the liver: The liver is enlarged in size, the surface of its hilly, numerous and rounded nodes with clear outlines, gray-pink, are visible on the surface and incision.

Micropreparations:

Nodular hyperplasia of the prostate (staining with hematoxylin and eosin): there is a significant increase in the glandular elements, some of which are cystically altered, in others epithelial proliferation.

Perineural metastases (staining with hematoxylin and eosin): atypical glandular structures - adenocarcinoma metastases - are determined around the nerve trunk.

Metastasis of glandular cancer into the lymph node (staining with hematoxylin and eosin): atypical gland complexes - lymphogenous metastases of adenocarcinoma are determined in the lymph node under the capsule.

Questions for self-control

1. The concept of oncogenesis, current views on etiological factors and mechanisms of oncogenesis.
2. Give a definition of the tumor, classification of tumors by clinical course.
3. Appearance of tumors. Types of tumor growth.
4. Microscopic structure of tumors, types of atypism and their characteristics.
5. Secondary changes in tumors. Influence of tumors on the body.
6. Stages of development of a malignant tumor, the concept of optional and obligatory precancer.
7. Stages of malignant tumor development: characterization of stages of non-invasive and invasive tumor growth.
8. Stages of development of a malignant tumor: the concept of metastasis of tumors, the main ways of metastasis.
9. Differential diagnosis of benign and malignant tumors.
10. Nomenclature and principles of classification of tumors.

Examples of tests

In 40-year-old patient, the tumor, which grew under skin of spine was resected. The histologic diagnosis: a lipoma. What principle of the tumors' classification did the pathologist use when created his conclusion?

A. Gistogenesis
B. Of biochemical features
C. Of ultrastructural features
D. Of physico-chemical features
E. Macrostructure of an organ

2. During the laparotomy in 49 year-old male patient, the tumor has been found out in the field of a sigma with growth through all its layers and an occlusion of the lumen of an intestine. The biopsy has been taken and colonostoma has been overlapped. The clinical diagnosis after operation: a cancer of sigma. What kind of tumor is growth in relation to tissues?

A. Infiltrative
B. Expansive
C. Endophytic
D. Exophytic
E. Multicentric

3. A clinical study is performed with patients who had a diagnosis of breast canacer. Characteristics of the grade, stage, molecular biology, and histologic type are analyzed. Of the following characteristics, which is most likely to be associated with the best prognosis for these patients?

A. Decreased nuclear/cytoplasmic ratio
B. Increased expression of laminin receptors
C. Increased cathepsin expression
D. Decreased apoptosis
E. Decreased doubling time

4. A 45-year-old healthy woman has a routine check of her health status. She has no chest pain, cough, or fever. A chest x-ray taken and shows a peripheral 2.5 cm diameter ’’coin lesion" in the right mid-lung field. Which of the following biologic characteristics best distinguishes this lesion as a neoplasm, rather than a granuloma?

A. Uncontrolled (autonomous) growth
B. Recurrence following excision
C. Rapid increase in size
D. Sensitivity to radiation or chemotherapy
E. Necrosis

A patient died of cancerous cachexia with primary localization of cancer in the stomach. Autopsy revealed acutely enlarged liver with uneven surface and numerous protruding nodes; the nodes had clear margins in the section, rounded shape, gray-pink color, varying density, sometimes contained necrotic foci. Histologically: there are atypical cells in the nodes. What pathologic process occurred in the liver?

A. Cancer metastases
B. Abscesses
C. Regeneratory nodes
D. Infarction
E. Hepatic cancer

EPITHELIAL TUMORS: BENIGN NON- ORGAN-SPECIFIC TUMORS, CANCER (FEATURES OF DEVELOPMENT, METASTASIS, HISTOLOGICAL FORMS). GENERAL CONCEPTS OF ORGAN-SPECIFIC EPITHELIAL TUMORS

Epithelial tumors are divided into:

Non-organ-specific - develop from the epithelium, which does not perform any specific function: the epidermis, the epithelium of the oral cavity, esophagus, endometrium, urinary tract, etc.

Organ-specific - develop from the cells of a specific organ and retain the morphological, sometimes functional features characteristic of the organ, most commonly found in the glandular organs (liver, kidney, thyroid glands).

Depending on histogenesis, tumors are distinguished from:

• cover (flat, transitional)
• glandular epithelium.

In the course of the epithelial tumors are divided into:

• benign
• malignant.

Epithelial organ-specific tumors

Benign tumors

Papilloma (Latin papilla - papilla) is a benign tumor from a flat or transitional epithelium.

Localization: skin, oral mucosa, larynx, true voice, esophagus, vagina, ureter, renal pelvis, bladder.

Macroscopic: the formation of a spherical shape on a wide or thin basis, ranging from millet grain to large peas, dense or soft consistency, with papillae (similar to cauliflower); located on the surface of the skin or mucous membrane (*exophytic growth).*

Microscopic: Parenchyma in the form of overgrowth of the covering epithelium with an uneven increase in the number of layers, maintaining the polarity and complexity of cells and varying degrees of healing. Stroma is characterized by varying degrees of growth of connective tissue with excessive formation of small blood vessels.

Consequences: favorable, when removed it rarely recurs.

Adenoma (Greek. Aden- - gland, -oma - tumor) - benign tumor from glandular (prismatic) cells.

Macroscopically: It usually looks like a clearly delimited node, ranging from a few millimeters to tens of centimeters, soft or dense in consistency, in the section of white and pink, or as a cyst (*cystadenoma*).

The adenoma that localized in the mucosa and protrudes above its surface is called the *adenomatous (glandular) polyp*.

Microscopically: glandular structures formed from a prismatic or cubic epithelium located on the basal membrane with the preservation of complexity and polarity; excretory ducts are absent.

Types of adenoma depending on the ratio of parenchyma and stroma:

• simple adenoma (parenchyma predominates over stroma);
• fibroadenoma (approximately equal ratio of parenchyma and stroma);

• adenofibroma (pronounced stroma predominance, reminiscent of fibroma structure, but containing single glands).

Types of adenoma depending on the histological structure of the parenchymal component:

• acinar - develops from the alveolar part of the glands
• tubular - develops from the ducts of the gland
• trabecular - has a beam structure
• papillary - papillary growths in the lumen of cystic lesions.

Consequences: possible malignancy (adenocarcinoma).

Malignant tumors

Cancer (**cancer**, Latin cancer) is a malignant tumor from epithelial cells.

Histological forms of cancer

Differentiated	*Undifferentiated*
• Cancer in situ (carcinoma in situ) • Squamous cell carcinoma • Adenocarcinoma (glandular) • Transitional cell carcinoma	• Mucous (colloidal) • Solid • Small cell • Fibrosis (skin) • Medullary (adogenous)

Pathomorphological classification of differentiated forms of cancer

Cancer in situ (carcinoma in situ) is an intraepithelial, non-invasive carcinoma.

Macroscopically: unchanged.

Microscopically: atypical epithelium loses its polarity and complexity, the presence of pathological mitoses; tumor growth within the epithelial layer without passing into the underlying tissue (**does not destroy the basement membrane**).

Consequences: over time infiltration (invasive growth) occurs with destruction of the basement membrane of the epithelium, metastasis.

Squamous cell carcinoma (epidermoid cancer) is a malignant tumor originating from the squamous epithelium.

Localization: organs and mucous membranes covered with stratified squamous epithelium (skin, oral mucosa, lips, tongue, cervix, vagina, etc.), or on mucous membranes covered with a single-layer epithelium after a previous squamous metaplasia.

Macroscopic: fixed whitish, soft or dense node (plaque) with fuzzy borders, often with ulcers.

Microscopic: complexes of atypical flat epithelium, invasive growth. Depending on the degree of differentiation distinguish:

• *squamous cell carcinoma with keratinization* (highly differentiated cancer) is characterized by the formation of concentric eosinophilic structures - "**cancer pearls**" due to the ability of cells to synthesize keratogialin

• *squamous cell carcinoma without keratinization* (malodifferentiated cancer) is characterized by the formation of cancer complexes whose cells lose their capacity for keratinization.

Consequences: local and general effects on the body, relapses, metastasis.

Adenocarcinoma (Latin aden- - gland, cancer - cancer) - malignant tumor from the glandular epithelium.

Localization: mucous membranes of internal organs covered with a single-layer epithelium (gastrointestinal tract, respiratory tract, uterus), or glandular organs (mammary gland, ovary).
Microscopically: glandular complexes formed by atypical epithelium with cell polymorphism, invasive growth into the surrounding tissue.
Histological varieties of adenocarcinoma:
- acinar - the predominance of acinar structures
- tubular - predominance of tubular formations
- papillary - atypical papillary growths.

The degree of differentiation of adenocarcinoma is determined taking into account the severity of morphological atypism and the ratio between glandular and solid structures:
- highly differentiated - resembles adenoma in structure but cell polymorphism is present
- moderately differentiated - formed by glandular complexes of atypical cells
- low-differentiated - pronounced cell polymorphism, glandular structures are not always formed, solid ones predominate.

Consequences: local and general effects on the body, metastasis, recurrence.
Transitional cell carcinoma develops from the multilayered transitional epithelium of the bladder, renal pelvis, and ureter.
Pathomorphological classification of undifferentiated forms of cancer
Mucinous (colloid) carcinoma - characterized by morphological and functional atypism.
Macroscopically: colloidal or mucous masses.
Microscopically: adenogenic atypical cells are among the mucus.
Consequences: local and general effects on the body, metastasis.
Solid (trabecular) carcinoma (Latin solidus - dense)
Microscopically: complexes of cancer cells with marked atypism and a large number of pathological mitoses, located in the form of trabeculae, delimited by connective tissue layers.
Consequences: rapid growth, early metastasis.
Small-cell carcinoma
Microscopically: among a small number of stromas are monomorphic (**lymphocyte-like**) atypical cells with round nuclei and a narrow rim of the cytoplasm, many mitoses, necrosis sites.
Consequences: rapid growth, early metastasis.
Scirrhous carcinoma (Greek. Scirrhosus - solid) is an undifferentiated carcinoma characterized by the predominance of stroma over the parenchyma.
Microscopic: chains of atypical polymorphic cells with hyperchromic nuclei, which are located in the well-developed coarse fibrous connective tissue.
Consequences: early metastasis.
Medullary (adenogenic, brain-like) carcinoma is an undifferentiated carcinoma characterized by a predominance of the parenchyma over the stroma.
Microscopically: layers of atypical epithelium with pathological mitoses and a small amount of connective tissue, areas of necrosis.
Consequences: rapid growth, early metastasis.

Organ-specific epithelial tumors

Tumors of endocrine glands

Tumor source	Benign tumors	Malignant tumors
The ovaries		
Tubal-uterine epithelium	Serous cystadenoma Mucinous cystadenoma	Serous cystadenocarcinoma Pseudomycinous cystadenocarcinoma
	Tecoma	Malignant tecoma
Stroma of sex cord	Granulosa cell tumor	Malignant Granulosa cell tumor
Testicles: Leydig cells	Tumor from Leydig cells	Seminoma
Sertoli cells	Tumor from Sertoli cells	
Thyroid gland		
Cells A and B	Follicular adenoma	Follicular cancer Papillary cancer Undifferentiated cancer
Cells C.	Solid adenoma	Solid cancer with stromal amyloidosis (medullary cancer)
Parathyroid glands	Adenoma	Cancer
Adrenal glands:		
cortical layer	Adrenocortical adenomas	Adenocortical cancer
medulla	Pheochromocytoma	Pheochromoblastoma
Thymus gland	Timoma	Cancer
Pituitary glands	Adenoma	Cancer
Pancreas		
α-cells	α - insuloma	
β-cells	β - insuloma	Malignant insuloma
G - cells	G - insuloma	
Enterochromaffin cells	Carcinoid	Malignant carcinoid

Tumors of exocrine glands and epithelial coverings

Tumor source	Benign tumors	Malignant tumors
Liver: hepatocytes	Adenoma (hepatoma)	Hepatocellular cancer
The kidneys The epithelium of the tubules Methanephrogenic tissue	Adenoma	Renal cell carcinoma Nephroblastoma
Mammary gland Epithelium of alveoli and excretory ducts The epidermis of the nipple and areola; epithelium of the ducts	Fibroadenoma (pericyanalicular, intracranial)	Lobular "carcinoma in situ" Ductal "carcinoma in situ" Paget's disease (cancer)
Uterus Chorionic shell	Molar pregnancy	Destructive molar pregnancy Chorionepithelioma
Skin Sweat duct epithelium	Syringoadenoma	Cancer

The epithelium of the secretory departments of the sweat glands	Hydroadenoma	
Epithelium of hair follicles	Trichoepithelioma	
Epithelium of different departments of skin appendages		

Basalioma (basal cell carcinoma) is a skin tumor that is characterized by locally detectable growth and recurrence, but does not metastasize.

Macroscopically: localized mainly in open areas of the body (face, neck) has the appearance of a plaque with possible ulceration.

Microscopically: small cells with a small amount of basophilic cytoplasm (dark cells), without intercellular junctions, located in nests or strands. Sometimes there are formations that resemble the skin appendages.

Macropreparations

Central lung cancer: tumor in the form of a gray-white knot, exits the bronchial wall and germinates into the lung tissue without clear boundaries (invasive growth); bifurcation and peribronchial lymph nodes enlarged, replaced by tumor tissue of dense consistency, grayish-white color (lymphogenous metastases).

Gastric cancer: rounded, with thick whitish edges and ulcer in the center.

Cancer metastases to the liver: The liver is enlarged in size, its surface is hilly on the surface and in section are seen numerous nodes of rounded shape with clear contours, gray-pink.

Ovarian ovarian cystadenoma: macropreparation is represented by a single-chamber cystic formation of a rounded shape, with thin walls and transparent yellowish content. The inner surface of the cyst is smooth.

Micropreparations

Papilloma(staining with hematoxylin and eosin): In the tumor, a stroma is well expressed, represented by a connective tissue with a large number of blood vessels, which forms outgrowthspapillae. The papillae are covered with multilayer squamous epithelium, the number of layers of which is increased.

Keratinizing squamous cell carcinoma(staining with hematoxylin and eosin): The tumor consists of strands and layers of atypical squamous epithelium, which grow into the underlying tissue. Tumor cells are
polymorphic. There are foci of keratin formation inside epithelial layers in the form of concentric structures of rounded shape ("cancer pearls").

Adenocarcinoma(staining with hematoxylin and eosin): The tumor is represented by glandular complexes of various shapes and sizes, which are formed by atypical epithelial cells with hyperchromic nuclei with figures of pathological mitoses.

Scirrhous cancer (staining with hematoxylin and eosin): The tumor is represented by atypical hyperchromic cells, arranged in the form of chains among the coarse-fibrous connective tissue (stroma), the amount of which predominates over the parenchyma of the tumor.

Basalioma (basal cell carcinoma) (staining with hematoxylin and eosin): The tumor is built of small dark cells resembling the basal cells of the epidermis. Tumor cells form strands and nesting clusters.

Questions for self-control

1. The concept and classification of tumors of the epithelium.
2. Papilloma: definition, localization, pathomorphology, consequences.
3. Adenomas: definition, classification, localization, pathomorphology, consequences.
4. Definition of the term cancer and its classification.
5. Definition of the term "carcinoma in situ", meaning, implications
6. Morphology, types, consequences of squamous cell carcinoma.
7. Morphology, types, consequences of adenocarcinoma.
8. Morphology, types of consequences of undifferentiated epithelial carcinomas.
9. Classification, histogenesis of organ-specific epithelial tumors.
10. Pathomorphology, localization, effects of basalioma.

Examples of tests

Autopsy of a 50-year-old male who had tuberculosis revealed a dense gray-white nidus in form of a nodule 2 cm in diameter in the subpleural portion of the upper right lobe. The pleura in this region was thickened, in the pleural cavity there was a small amount of serous hemorrhagic fluid. Histological study of the region revealed some glandular structures with signs of cellular atypia and abnormal mitoses, which were found within the fibrous connective tissue. What other pathology had developed in the lungs?

A. Adenocarcinoma
B. Squamous cell carcinoma
C. Adenoma
D. Fibrosarcoma
E. Fibroma

Histological examination of the removed skin neoplasm revealed clusters and cords of atypical cells of stratified squamous epithelium, growing into the underlying tissue. What diagnosis can be assumed?

A. Non-keratinizing squamous cell carcinoma
B. Keratinizing squamous cell carcinoma
C. Carcinoma in situ
D. Papilloma
E. Adenoma

A 39-year-old woman has madescence in the region of mammilla, a small ulcer with inflammatory hyperemia and cutaneous edema. Histologic examination of tissue sampling from this area revealed in the malpighian layer of thickened epidermis atypical cells with light and optically empty cytoplasm, with no intracellular bridges. Such cells were also found in the orifice of big mammal gland ducts. What is the most probable diagnosis?

A. Paget’s disease
B. Intraductal cancer
C. Basal cell carcinoma
D. Epidermoid cancer
E. Melanocarcinoma

A patient has hoarseness of voice. During laryngoscopy a gray-white larynx tumor with papillary surface has been detected. Microscopic investigation has shown the

following: growth of connective tissue covered with multilayer, strongly keratinized pavement epithelium, no cellular atypia. What is the most likely diagnosis?

A. Papilloma
B. Fibroma
C. Polyp
D. Angioma
E. Angiofibroma

Histological examination of biopsy samples taken from the thickened edges of a gastric ulcer revealed small clusters of small, markedly atypical hyperchromatic epithelial cells that were localized in the overdeveloped stroma. Specify the tumor:

A. Scirrhous undifferentiated carcinoma
B. Medullary carcinoma
C. Adenocarcinoma
D. Undifferentiated sarcoma
E. Adenoma

MORPHOLOGICAL FEATURES OF BENIGN AND MALIGNANT MESENCHYME ORIGIN TUMORS. PECULIARITIES OF SARCOMA DEVELOPMENT AND METASTASIS. FIBROBLASTIC, MYOFIBROBLASTIC AND FIBROHISTIOCYTIC ORIGIN TUMORS. TUMORS OF FAT AND MUSCLE TISSUE.TUMORS FROM BLOOD VESSELS. MORPHOLOGICAL FEATURES OF MELANIN-PRODUCING TUMORS. NOMENCLATURE AND MORPHOLOGICAL FEATURES OF NERVOUS TISSUE ORIGIN TUMORS (ASTROCYTE, OLIGODENDROGLIA, EPENDYMAL, NEURONAL AND MENINGOVASCULAR TUMORS).CRANIAL AND SPINE NERVOUS ORIGIN TUMORS.

Non-epithelial tumors include:

A) tumors from tissues derived from mesenchyme:

• Fibroblastic, myofibroblastic and fibrogistiocytic genesis (tumors of loose and dense connective tissue)

• Tumors made of tissues with special properties (fat, cartilage, bone, muscle)

• Tumors of blood and lymphatic vessels.

B) tumors of nervous tissue

C) tumors of melanin-forming tissue

Classification of tumors of mesenchymal origin:

Tumor behavior is divided into:

• good quality

• malignant (***sarcoma***, sarcos – fish flesh)

• with locally detectable growth (invasive)

Histogenesis: develop from different derivatives of mesenchyme

Features of non-epithelial tumors:

• less common than epithelial tumors

• do not have organ specificity (found in any organ or part of the body),

• heterogeneous, due to the diversity of tissues derived from mesenchyme,

• sarcoma usually metastasize by hematogenous.

Pathomorphological characteristics of some non-epithelial tumors

Tumors from connective tissue

Fibroma is a benign tumor of fibrous connective tissue, which is quite common in the skin, ovaries, mucous membranes of the mouth, tongue and grows slowly, expansively.

Macroscopic: is represented by a rounded formation with clear contours, surrounded by a capsule, in the section of white-gray color, fibrous structure**.**

Microscopic: consists of bundles of collagen fibers and fibroblastic cells. The bundles go in different directions, their thickness is different, in some areas there are more cells, in others - fibers (tissue atypism).

Types of fibroma:

• dense - collagen fibers dominate over cellular elements,

• soft - consists of a large number of cells such as fibroblasts and fibrocytes. Special varieties of fiber include dermatofibroma and desmoid.

Dermatofibroma *(fibrous histiocytoma)* is a benign tumor of connective tissue that occurs much more frequently than fibroma and is localized frequently in the skin of the extremities, subcutaneous tissue.

Macroscopically: the tumor is represented by a small, painless nodule (rarely exceeding 1 cm in diameter) of brown color, exploding above the skin surface.

Microscopically: the tumor is localized in the dermis and subcutaneous tissue, represented by fibroblasts and histiocytes. Cells and collagen fibers are folded into short bundles, oriented in different directions, which gives the tumor a "moire pattern". Often, the tumor contains a large number of vessels. Histiocytic tumor cells can look like xanthoma cells (due to fat inclusions in the cytoplasm), siderophages (hemosiderin appears in the cytoplasm, the tumor turns brown), giant multinucleate cells (**Tutton cells**).

Desmoid is a tumor characterized by locally destructive growth.

By localization desmoids distinguish:

Abdominal desmoid - localized in the musculo-aponeurotic structures of the anterior abdominal wall. It occurs mainly in women of 20-40 years, more often during pregnancy and after childbirth. It often recurs.

Extra-abdominal desmoid - shoulder, chest, back, thigh.

Intra-abdominal desmoid - mesentery, pelvis.

Extra-abdominal and intra-abdominal desmoids occur in both sexes at infancy or young age.

Macroscopic: a dense whitish-colored tumor with fuzzy borders.

Microscopically, the desmoid is similar to dense fibroma.

Fibrosarcoma is a malignant tumor from connective tissue.

Macroscopically: the tumor usually has no clear boundaries (infiltrative growth), in the section of gray-pink color, reminiscent of ***"fish flesh",*** with focuses of necrosis and hemorrhage.

Microscopically: the lower the tumor differentiation, the less collagen fibers in it (atypical cells lose the ability to produce collagen). In low-differentiated fibrosarcoma, the cellular component prevails. Sharply expressed cellular atypism: cells and their nuclei of different size and shape, nuclei hyperchromic, nuclear-cytoplasmic ratio increased, numerous mitoses, among which there are atypical.

Fibrosarcoma, compared with other sarcomas, metastasizes less frequently, but recurs more often than other tumors.

Tumors from adipose tissue

Lipoma is a benign tumor of adipose tissue. It is more common in women in all age groups.

Macroscopically: a node with distinct borders, of different sizes, in the section of yellowish color, resembles adipose tissue. Intramuscular (diffuse) lipoma - a special type of infiltrate growth lipoma, located in muscle tissue, does not have a capsule.

Microscopically: The tumor is composed of mature adipocytes. Often has a pronounced fibrous stroma - *fibrolipoma*, may contain a large number of vessels - *angiolipoma*, or myeloid tissue - *myelolipoma*.

Hibernoma - a rare tumor of the brown fat.

Macroscopically: a node with clear borders along the section of the particle structure.

Microscopically represented by rounded or polygonal shaped cells with a centrally located nucleus, cytoplasm filled with fat vacuoles (granular or foamy cytoplasm)
Liposarcoma - a malignant tumor of adipose tissue, which is often localized in the retroperitoneal space, grows slowly, can reach gigantic sizes.
Macroscopically: it has the form of a single node or conglomerate with infiltration of surrounding tissues, dense consistency, the incision surface is juicy, mottled - with foci of mucous transformation, hemorrhage and necrosis. Often it is white, juicy, reminiscent of "fish flesh".
Microscopically: sharply expressed tissue and cellular polymorphism, consists of lipoblasts of varying degrees of maturity, giant cells with chimeric nuclei are found.
Distinguish: highly differentiated liposarcoma and polymorphocellular (low differentiated, rapidly progressing) liposarcoma.

Tumors from muscle tissue

Leiomyoma is a tumor of smooth muscle tissue, found in various organs that contain smooth muscle. In some cases, the source of tumor development may be smooth myocytes of the middle lining of the blood vessels. More often occurs in women 30-50 years in the uterus, where it can be multiple in nature. Tumor is sensitive to estrogens: usually increases during pregnancy and decreases in menopause.
Macroscopically: a node with clear borders (expansive growth), surrounded by a connective tissue capsule, in the section of white-pink color, fibrous structure. It can be located in the myometrium (intramurally), under the endometrium (submucosally) and under the serous membrane (subserous).
Microscopically: the tumor is represented by bundles of mature smooth muscle cells of different thickness, located in different directions (tissue atypism). The tumor in the structure resembles fibroma.
For differential diagnosis using staining with *picrofuxin according to van Gizon:* connective tissue stroma of the tumor is stained in red, bundles of smooth muscle cells turn yellow (unlike fibroma, in which bundles of collagen fibers are the main component of the tumor, stained in red).
Leiomyosarcoma is a rare malignant tumor of smooth muscle tissues.
Occurs in retroperitoneal space, uterus. More often occurs de novo and is not associated with malignancy of leiomyoma. An important diagnostic criterion for the degree of malignancy that allows you to differentiate it from leiomyoma is the number of mitoses, including pathological ones.
The *prognosis* is unfavorable: more than half of patients die within 2 years.
Rhabdomyoma is an extremely rare tumor of transversely striated muscle cells. It occurs in children in the nasopharynx, in the thickness of the muscles.
Macroscopically: the tumor is represented by a node with clear borders, red.
Microscopically, it consists of cells resembling rhabdomyocytes and with indistinct darkness and glycogen in the cytoplasm.
Rhabdomyosarcoma is a very rare malignant tumor that grows from grows cross-striated muscles in the form of a dense node with areas of hemorrhage and necrosis. It usually occurs in children.
Localization: head, neck, retroperitoneal space. The *forecast* is very poor.
Granular-cell tumor *(Abrikosov's tumour)* is usually small in size, has a capsule, localized in the tongue, skin, esophagus. Consists of the broad fascicles of tumour

cells arranged in nests or sheets infiltrating the dermis and dermal structures. The tumour cells are large in size, with small, uniform, eosinophilic granules filling the cytoplasm, and small, round-to-oval nuclei. Mitoses are rare. It is thought to have a neural origin, probably derived from Schwann cells.

Tumors from blood and lymph vessels

Hemangiomas are tumors from blood vessels that occupy an intermediate position between the hamartoma and the true tumor.

Classification (depending on the type of vessels and other features):

Benign

• capillary hemangioma
• cavernous (venous) hemangioma
• glomosangioma
• hemangiopercytoma
• lymphangiomas (capillary, cavernous, cystic)

Malignant

• hemangioendothelioma
• lymphangiosarcoma
• Soft tissue angiosarcoma (malignant hemangioendothelioma)
• malignant hemangiopercytoma
• Kaposi's sarcoma.

Capillary hemangioma is more often found in the skin of newborns.

Macroscopically, the formation of intense purple color, slightly increased over the surface of the skin ("strawberry nevus").

Microscopically: the tumor is composed of numerous capillary-type cleft vessels.

Cavernous hemangioma - a congenital formation that is more often localized in the skin, the liver (the most common primary tumor of the liver). Increases with growth of the body. It does not disappear spontaneously. May be accompanied by thrombosis, ulceration, infection.

Macroscopically: Has the appearance of deep red spots ("port wine spots ") or a node of red-bluish color with clear borders.

Microscopically: consists of many thin-walled vascular cavities lined by endothelial cells without signs of cellular atypism. Cavities of various shapes and sizes (tissue atypism) filled with blood and thrombotic masses.

Glomus angioma (glomus tumor, Barre-Masson tumor) - is more often localized at the tips of the fingers (in the area of the nail bed).

Macroscopically: painful knot of purple color.

Microscopically: the tumor is composed of blood vessels, mainly with a slit lumen, which are lined by the endothelium and surrounded by mufts of epithelioid (glomus) cells. On the periphery of the tumor hemoglomus in the form of vessels of venous type is observed.

Lymphangioma is a tumor that consists of lymphatic vessels of various shapes and sizes filled with lymph.

Hemangiosarcoma is a rare tumor that occurs in the skin, skeletal muscle, and liver. The occurrence may be due to chemical carcinogens: arsenic, torotrost (used in angiography), as well as polyvinyl chloride.

Kaposi's sarcoma.

Clinical forms:
• sporadic
• endemic
• epidemic.
Sporadic form (classic version) is a rare tumor. Occurs in elderly men (predominantly Jews), may occur in persons with kidney transplantation on the background of immunosuppressive therapy.
Localization: Tibia skin, oral mucosa, often symmetrical lesions.
Macroscopically: bluish or purple spots and plaques, often with ulcers, spontaneous scarring of foci may occur.
The tumor of low degree of a malignancy, is characterized by a long course with a possible metastasis in the final.
The endemic form is widespread in some parts of Africa, accounting for up to 10% of all malignant tumors.
The epidemic form is associated with the HIV infection. Often occurs (along with lymphomas and some other tumors) in HIV infection at the stage of severe immunodeficiency and belongs to HIV-associated diseases.
The *microscopic picture* of the tumor does not depend on the clinical form. The tumor is represented by vascular cavities, lined endothelial cells and filled erythrocytes and bundles of elongated fibroblast-like cells, characteristic hemorrhage, hemosiderosis.

Tumors from bone tissue

Osteoma is a benign, slow-growing bone tumor.
Macroscopically, nodular, round or oval tumor on a broad basis, a broad-based tumor projecting over the endostal surfaces of the cortical layer. Subperiosteal osteoma most commonly occurs on the bones of the skull, for example, in the paranasal sinuses or facial bones.
Microscopically: is a combination of fibrous and lamellar bones, often determined in the cortical layer and contains systems that resemble the central (gavers) channels.
Osteosarcoma (osteogenic sarcoma) is a very malignant, most common primary bone tumor characterized by osteoid production. 3/4 of the tumors occur in male or young children (10-20 years).
Localization: long bones (area of the knee, metaphysis of the femur or tibia). Osteosarcoma can also occur in different bones in the elderly on the background of bone pathology (Paget's disease, bone irradiation, etc.).
Microscopically: a tumor is made of atypical osteoblastic type cells with a large number of mitoses and primitive bone.
The prognosis is poor.

Cartilage tumors

Chondroma is a benign tumor of hyaline cartilage.
Macroscopically: a dense tumor, in the incision looks like hyaline cartilage, can reach significant sizes.
Microscopically: Built from disorderly placed mature cells of hyaline cartilage, which are located in the underlying substance.
Chondrosarcoma. Feature - the production of tumor cartilage. Occurs 2 times less often than osteosarcoma. Tumors affect men twice as often as women.

Macroscopically: a large tumor is made up of nodes formed by a grayish-white, partially translucent, shiny tissue.
Microscopically: Hypercellularity is noted, chondrocytes contain swollen vesicle nuclei and small nucleoli. Characteristic focal mineralization of the matrix, cartilage may undergo endocrine ossification.

Tumors of melanin-forming tissue

The source of tumors in this group are melanocytes - cells of neuroectodermal origin, which are located in:
• basal layer of epidermis,
• hair follicles,
• Some mucous membranes covered with stratified squamous epithelium,
• pia mater,
• retina and iris.
Melanocytes contain melanin, which has a dark brown (black) color. It can be detected by the Argentafine reaction (by Fontana-Mason) and the DOPA reaction.
With melanocytes can be associated with such pigmentary skin formation as:
1. *Freckles* - focal hyperpigmentation associated with increased melanin synthesis by melanocytes under the influence of insolation.
2. *Lentigo* - pigment spots associated with melanocyte hyperplasia in the epidermis.
3. *Melanocytic (nevus-cellular) nevus*.
4. *Melanoma* - a malignant tumor from melanocytes
Nevus is a congenital or acquired pigment formation (more often it appears at the age of 2-6 years, tends to spontaneous regression with age), which occupies an intermediate position between malformation and benign melanocytic tumors.
Macroscopically:
• pigmented - flat, plaque, papillomatous;
• not permanently pigmented - domed, on the stem.
Microscopically distinguish:
1) junction nevus,
2) compound nevus,
3) intradermal,
4) epithelioid nevus (intracellular),
5) balloon-cell nevus,
6) halo-nevus,
7) giant pigmented nevus,
8) involution nevus (fibrous papule of the nose),
9) blue nevus,
10) cellular blue nevus.
Junction nevus. Nests of nevus cells are found on the border of epidermis and dermis. The nests are round or oval. Their cytoplasm is homogeneous, slightly granular. The nevus cells are localized in the area of reticular layer apices. *Compound nevus*. Together with the nevus cells located on the border of dermis and epidermis, there are nests of nevus cells in derma itself.
Intradermal nevus. Nevus cells are located only in derma. Some of them can be found on the border between derma and epidermis. They resemble nests. The nevus cells look like compact mass. The cells in mature nevi may be

polynuclear. Macroscopically they have papillomatous appearance and may contain hairs.

Epithelioid nevus can often appear on the face, especially in children. It looks like flat or ball-like node. The surface of the skin is smooth, sometimes papillomatous changes are observed. Microscopically it looks like compound nevus with borderline changes.

Sometimes marked acanthosis is present. The amount of melanin is small, it may also be absent. The cells have light basophilic cytoplasm and hyperchromic nuclei. Epithelioid cells with large foamy light cytoplasm may be present. Mitoses are not numerous. Uni- or polynuclear cells resemble Touton's cells. There are a lot of vessels.

Blue nevus. Macroscopically this looks like bluish or bluish-brown or bluish-gray sport, its shape is round or oval, it does not elevate over the surface of the skin. Microscopic examination reveals stretched melanocytes. ***Melanoma*** - a malignant tumor of melanocytes, with nodal or superficial growth form, early hematogenous and lymphogenous metastases in almost all organs.

The pigmented formations with a high probability of developing melanoma include:

1. *Gatchinson's freckle (Lentigo maligna)* is a pigmentation that occurs more often on the skin of the elderly.

Microscopically characterized by proliferation of atypical melanocytes in the basal layers of the epidermis, atrophy of the epidermis, elastosis of the upper layers of the dermis. It is believed that the Hutchinson's freckle is a malignant form - melanoma in situ.

2. *Dysplastic nevi*: characteristic hereditary syndrome, rare. usually numerous, more than 1 cm in diameter, are localized in closed areas of the body. The proliferation of atypical melanocytes is determined microscopically.

Pathological anatomy of melanoma.

Localization: in any area of skin, eye, oral cavity, meninges.

Macroscopically: tumor flat or slightly elevated, domed, pigmented (except for amelanotic forms). It can reach significant sizes, the surface is uneven, easily injured, bleeds.

Microscopically: large polymorphic cells of cubic or polygonal shape. Groups of cells are separated by layers of connective tissue. Pathological mitoses, giant multinucleated cells are present. Cells contain different amounts of pigment.

Clinical and morphological classification of melanoma:

Malignant lentigo-melanoma - occurs on areas of skin that are insoluble from previous Lentigo maligna. Invasive growth in the dermis of atypical, polymorphic, often spindly melanocytes; has a low degree of malignancy.

Superficially disseminated melanoma is the most common variant with typical localization at the extremities and trunk; has the appearance of a spot or plaque of pink-brown or dark brown color without clear boundaries.

Microscopically: a non-invasive tumor, represented by monomorphic atypical melanocytes forming nests of pagetoid cells.

Nodular melanoma - begins with the vertical phase of growth. Has the worst prognosis. Occurs at any area of the skin, gives early hematogenous and

lymphogenous metastases, having the appearance of multiple tumor nodes of dark brown (black) color with clear borders.
Macroscopically, the tumor looks like a blue-black plaque or pigmented node (black, brown, brown), often with an ulcer.
Microscopically: polymorphic (spindle-shaped, lamellar and irregularly shaped, often multinucleated) cells containing granules of black-brown pigment - melanin; irregular nuclei with coarse chromatin and large nuclei, numerous mitoses. The tumor infiltrates the dermis and surrounding fat cells. Intraepidermal spread of the tumor at its edges is not pronounced.
Acral lentigo-melanoma - is more common in dark-skinned people. Typical localization - palms and soles, mucous-dermal areas of the mouth, nose, anus.
Microscopically: intraepidermal proliferation of large, chimeric forms of melanocytes containing a large amount of pigment, and their invasion into the dermis; papillary layer of the dermis enlarged, there is an inflammatory infiltrate.
The prognosis of melanoma is often unfavorable and is determined by the stage of the tumor, the level of invasion, the size of the tumor.

Tumors of the nervous system, brain membranes, peripheral nerves

General classification:

1. Tumors of the central nervous system:
• neuroectodermal
• neuronal
• low-differentiated
• embryonic
• meningo-vascular
2. Tumors of the autonomic nervous system;
3. Tumors of the peripheral nervous system.

Features of tumors of the central nervous system

• More often tumors are localized in the brain; spinal cord tumors are less common.
• Benign intracranial tumors can cause compression of vital parts of the brain (clinically malignant).
• Primary malignant tumors of the CNS metastasize rarely, mainly within the CNS by the current of the cerebrospinal fluid.

The most common CNS tumors

1. Tumors of neuroectodermal origin:
A. Astrocytic tumors:
• astrocytoma;
• anaplastic (malignant) astrocytoma;
B. Oligodendroglial tumors:
• oligodendroglioma;
• anaplastic (malignant) oligodendroglioma.
C. Tumors of the ependyma and choroidal epithelium:
• ependymoma;
• anaplastic (malignant) ependymoma;
• choroidal papilloma;
• choroidal carcinoma.
D. Neuronal tumors:

• ganglionic neuroma
• ganglioneuroblastoma
E. Embryonic and low-differentiated tumors:
• meduloblastoma;
• glioblastoma
2. Meningo-vascular tumors
• meningioma;
• anaplastic (malignant) meningioma.

Astrocytoma is a benign, most common tumor of neuro-ectodermal origin, which occurs mainly at a young age.

Macroscopically: the tumor may have diffuse or nodular growth, 5-10 cm in diameter, may not be clearly separated from the surrounding tissues, sometimes contains cysts, grows slowly.

Microscopically distinguish three types:

1. Fibrillar astrocytoma - a small number of astrocytic cells and a large number of parallel glial fiber bundles.

2. Protoplasmic astrocytoma - the predominance of cells of the type of astrocytes with processes of different sizes and forms intertwined.

3. Mixed (fibrillar-protoplasmic) astrocytoma is rare and is characterized by a uniform number of astrocytes and glial fibers.

Glioblastoma - the most common malignant neuroectodermal tumor, among all CNS tumors, ranks second after astrocytoma in frequency. Most common at the age of 40-60 years.

Macroscopically: localized in the white matter of the brain, has no clear boundaries, its variegated appearance due to the presence of foci of necrosis, hemorrhage.

Microscopically: sharply expressed cellular polymorphism; there are giant cells with hyperchromic ugly nuclei (multiform glioblastoma); cytoplasm of light, granular. In a stroma many vessels, sites of a necrosis, hemorrhages.

Ependymoma. All variants of this neoplasm develop from the epithelial lining of the ventricular system.

Localization: most often ependymoma occurs in children or young people. It affects the IV ventricle, sometimes other ventricles or the spinal cord, where it grows intramedullary.

Microscopically: Tumor cells usually have clear signs of epithelial elements. They are characterized by orientation around small blood vessels in the form of perivascular pseudocysts. The socket structures are separated by a light fibrillar zone from the vessels.

Anaplastic ependymoma is a malignant variant of ependymoma (malignant ependymoma). It has pronounced cellular atypism. In adults it may be similar to glioblastoma and in children it may be like medulloblastoma. It grows rapidly, infiltrating surrounding tissues and giving metastases to the CSF.

Meduloblastoma is a fairly rare and very malignant tumor that grows in the worm or hemispheres of the cerebellum in children 2-7 years old, usually in boys.

Macroscopically: a soft grayish-pink knot consisting of a jelly-like or semi-liquid translucent tissue; may enter the cavity of the IV ventricle. Typical are germination in the soft meninges and spread in the subarachnoid space.

Microscopically: a tumor is composed of a large number of closely spaced, somewhat elongated cells, which often form pseudosets (small fence-like structures that do not have a cavity at the center). If a tumor develops in a child in the cerebral hemispheres, it is often called a tumor with primitive neuroectoderm.

Meningioma is the most common benign tumor originating from the soft meninges.

Macroscopically: looks like a dense node associated with the brain membranes.

Microscopically: nesting clusters of adjacent to each other endothelial-like, subject to calcification, formation of psamomic bodies.

Tumors of the autonomic (autonomic) nervous system

Source	Tumors	
	Benign	**Malignant**
Simpatogonii		Sympathoblastoma
Ganglioneuroblast		Ganglioneuroblastoma
Ganglioneurocyte	Ganglioneuroma	
Cells of non-chromaffin paraganglia	Benign non-chromaffin paraganglioma (hemodectoma)	Malignant non-chromaffin paraganglioma (hemodectoma)

Tumors of the peripheral nervous system

Source	Tumors	
	Benign	**Malignant**
Lemocyte (Schwann cell)	Neuriloma (Schwannoma) Neurofibromatosis (Recklinghausen's disease)	Malignant nevrylemoma (neurogenic sarcoma)

Neurilemoma (Schwannoma) is a tumor that develops from the membranes of the nerves.

Macroscopically, it has clear contours, a dense, whitish, nerve-bound capsule.

Microscopically: the tumor is made of spindle-shaped cells with rod-shaped nuclei; cells form **rhythmic**, or **"fence-like" structures**;, and non-core fibrous areas form **Verokai bodies**.

Macropreparations

Fibrolipoma: in the dermis, the node is yellow in color, lobular structure, with clear borders, no destruction in the center of the node.

Thigh sarcoma: Tumor tissue is represented by radially spaced fibers, resembling fish meat, without clear boundaries, with a variegated appearance due to foci of necrosis and hemorrhage, areas of tumor and reactive bone formation.

Osteosarcoma of the upper jaw: a section of bone is replaced by a tumor with fuzzy borders (infiltrating growth), with its destruction. On the incision, the tumor tissue looks like "fish meat", grayish-white with a pink tint.

Metastases of melanoma into the liver. In the tissue of the liver there are multiple nodes of dark brown color, with a diameter of 1-5 mm to 3-5 cm with clear borders.

Glioblastoma of the brain: The tumor is localized in the white matter of the brain, has a loose texture and grayish color with areas of destruction.

Meduloblastoma of the cerebellum: grayish-pink, soft node, is a semi-liquid, translucent mass, germinating in the soft meninges.

Neurinoma: 2 cm in diameter, soft-elastic, pinkish-white, homogeneous with a clear border (in the capsule), connected to the nerve.

Micropreparations

Leiomyoma of the uterus body(staining with hematoxylin and eosin): The tumor is represented by chaotically located bundles of smooth muscle cells of various sizes with unevenly expressed connective tissue (tissue atypism). Tumor myocytes are monomorphic, with no signs of cellular atypia, mitoses (typical) are single.
Polymorphocellular sarcoma (staining with hematoxylin and eosin): The parenchyma of the tumor is represented by complexes of cells, of various sizes and shapes, with hyperchromic nuclei. There are giant multi-nuclear cells, a large number of figures of pathological mitoses (tissue and cellular atypism). The stroma is poorly developed and is represented by thin bundles of collagen fibers.
Capillary hemangioma (staining with hematoxylin and eosin): The tumor is represented by branched capillary vessels. The vessels are located in a loose stroma. Most blood vessels contain elements of blood.
Cavernous hemangioma of the liver (staining with hematoxylin and eosin): The tumor consists of large vascular thin-walled cavities (caverns) lined with endothelial cells. The cavities are filled with blood clots.
Melanoma (staining with hematoxylin and eosin): The tumor consists of malformed cells with polymorphism, in
the cytoplasm of most of which brown pigment (melanin) is determined.
Astrocytoma (staining with hematoxylin and eosin): The tumor is consist of cells similar to astrocytes, the processes of which are intertwined with each other, forming a dense mesh.
Glyoblastoma (staining with hematoxylin and eosin): The tumor is constructed of cells of different shapes, size and shape of the nuclei. There is a large number of mitoses (cellular polymorphism). The tumor contains a large number of blood vessels.
Neurilemoma (Schwannoma) (staining with hematoxylin and eosin): The tumor is constructed of spindle-shaped cells with rodshaped nuclei. Cells and fibers of the tumor form rhythmic structures (nuclear palisades, bodies of Verokai).

Questions for self-control

1. General characteristics of tumors originating from mesenchyma, their classification.
2. Morphological characteristics of benign and malignant tumors of connective tissue.
3. Morphological characteristics of benign and malignant tumors of muscle tissue.
4. Morphological characteristics of benign and malignant bone tumors.
5. Morphological characteristics of benign and malignant tumors of adipose tissue.
6. Morphological characteristics of benign and malignant tumors from blood and lymphatic vessels.
7. Morphological characterization of benign and malignant cartilage tumors.
8. Nevi, varieties, morphological characteristics.
9. Melanoma, clinical and morphological forms.
10. Classification of tumors from nerve tissue and brain membranes.
11. Neuroectodermal tumors, their histological structure.
12. Meningo-vascular tumors, their histological structure.
13. Tumors of the autonomic and peripheral nervous system.

Examples of tests

A 65-year-old man suddenly lost vision in one eye due to the retinal detachment. The patient underwent enucleation. Histological examination of the removed eye retina and choroid revealed clusters of atypical cells with marked polymorphism of cells and nuclei, with a moderate number of mitoses including the pathological ones. The cell cytoplasm and intercellular medium contained brown pigment resulting in positive DOPA reaction. Perls' reaction was negative. What is the most likely diagnosis?

A. Melanoma
B. Pigmented mole
C. Hemorrhage
D. Cysticercosis
E. Wilson's disease

Autopsy of a 5-year-old child revealed in the area of vermis of cerebellum a soft greyish-pink node 2 cm in diameter with blurred margins and areas of haemorrhage. Histologically this tumour consisted of atypical monomorphous small round cells with large polymorphous nuclei. What tumour is it?

A. Medulloblastoma
B. Meningioma
C. Glioblastoma
D. Astrocytoma
E. Oligodendroglioma

A 50 year old patient underwent resection of tumour of large intestine wall. Microscopically it presents itself as fascicles of divergent collagen fibers of different thickness and form and some monomorphous fusiform cells that are irregularly distributed among the fibers. Cellular atypia is not evident. What tumour is it?

A. Hard fibroma
B. Fibromyoma
C. Soft fibroma
D. Desmoma
E. Fibrosarcoma

Examination of a 55 year old woman revealed under the skin of submandibular area a movable slowly growing pasty formation with distinct borders 1,0x0,7 cm large. Histological examination revealed lipocytes that form segments of diffrent forms and sizes separated from each other by thin layers of connective tissue with vessels. What is the most probable diagnosis?

A. Lipoma
B. Fibroma
C. Angioma
D. Liposarcoma
E. Fibrosarcoma

Examination of the anterior abdominal wall of a pregnant woman revealed a tumour-like formation that arose on the spot of a tumour that was removed two years ago. The neoplasm was well-defined, dense, 2x1 cm large. Histological examination revealed that the tumour was composed of differentiated connective tissue with prevailing collagen fibres. What tumour might be suspected?

A. Desmoid

B. Lipoma
C. Fibrosarcoma
D. Hibernoma
E. Leiomyoma

TUMORS OF HAEMATOPOIETIC TISSUE.
TUMORS OF LYMPHOID TISSUE.

Hemoblastoses - tumors from lymphoid and hematopoietic tissues.

Groups of hemoblastoses:

1. Leukemia - a systemic tumor of hematopoietic tissue with obligatory bone marrow damage.
2. Lymphomas are regional tumors of lymphatic tissue.

Etiological factors of leukemia:

1. Ionizing radiation
2. Chemicals
3. Viruses
4. Congenital genetic factors

Stages of leukemia morphogenesis:

1. The action of leukemic factors that cause activation of cellular oncogenes.
2. Malignant transformation of hematopoietic cells.
3. Reproduction of leukemic cells.
4. Progression of the disease (blast crisis).

Classification of leukemias:

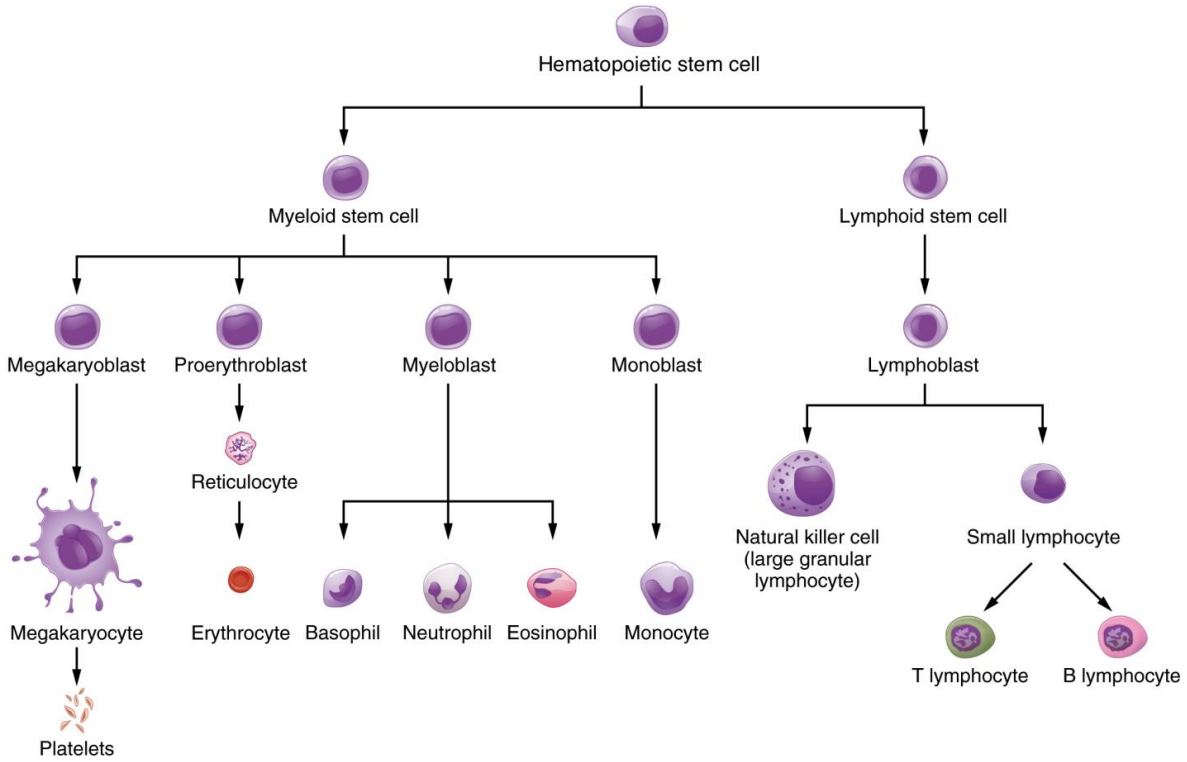
1. Depending on the histo- (cyto-) genesis of leukemia cells
2. Depending on the degree of differentiation of leukemic cells and the nature of the course:

• Acute leukemias
• Chronic leukemias

3. Depending on the number of leukocytes (including tumor cells) in the blood:

1) leukemic (tens and hundreds thousand leukosis cells per 1 microl);
2) subleukemic (not more that 15.000 — 25.000 per 1 microl);
3) leukopenic (leukocyte count is reduced but leukosis cells can be found);
4) aleukemic (leukosiscells in the blood are absent)

Scheme of hematopoiesis



Acute leukemia - leukemia, the morphological substrate of which are undifferentiated or low-differentiated (blast) leukemic cells (according to the scheme up to 4 classes inclusive). Characterized by rapid malignant course.

Histo- (cyto-) genetic forms of acute leukemia:

• undifferentiated;
• myeloblastic;
• lymphoblastic;
• plasmoblastic;
• monoblastic (myelomonoblastic);
• erythromyeloblastic (di Guglielmo);
• megakaryoblast.

Clinical and morphological signs of acute leukemia:

• Reproduction of low-differentiated (blast) tumor cells in bone marrow.
• Leukemic failure (*hiatus leucemicus*) - it is sharp increase of blast count and single mature elements while transitional forms are absent.
• Development of leukemic infiltrates in different organs with their moderate increase.
• Severe anemia, thrombocytopenia and other changes in the blood.
• A pronounced hemorrhagic syndrome
• Prone tendency to develop ulcerative-necrotic changes of mucous membranes and palatine tonsils
• Severe degenerative (necrotic) changes in parenchymal organs
• Fast attachment of infectious complications. ***Acute myeloid (non-lymphoblastic) leukemias*** are found in all age groups and mainly in adults.

Macroscopically: the bone marrow becomes red or grayish, sometimes acquiring a yellowish-greenish tinge (**pioid bone marrow**).The spleen, liver and lymph nodes are enlarged slightly. Infiltration of blast cells of kidneys, lungs (leukemic pneumonitis), brain membranes (neuroleukemia), mucous membrane of the gastrointestinal tract is observed. It causes necrosis and ulcers in the mouth, tonsils, throat, stomach.

Microscopically: myeloblasts displace normal cells from the bone marrow. Infiltration of the spleen, liver, kidneys, mucous membranes, rarely lymph nodes and skin with myeloblasts.

Classification of acute myeloid leukemia by WHO:

• acute myelogenous leukemia with recurrent cytogenetic translocations;
• acute promyelocytic leukemia and its variants;
• acute myelogenous leukemia with abnormal eosinophilic granulocytes of bone marrow;
• acute myelogenous leukemia with anomalies 11q23 (MLL);
• acute myelogenous leukemia with multilinear dysplasia.

French-American-British classification of myeloid (non-lymphoblastic) leukemia (FAB):

Takes into account the direction and degree of differentiation of cells based on their markers and karyotypes:

Type M0 - undifferentiated myeloblastic leukemia.

Type M1 - less than 10% of cells differentiated with the appearance in their cytoplasm of azurophilic granules, positive reaction of granules with myeloperoxidase or sudan black. Most cells have large rounded nuclei that contain up to four nuclei.
Type M2 - existing two-bladed or bud-shaped nuclei, azurophilic Auer sticks. Part of the tumor cells differentiates in the direction of abnormal myelocytes, myelocytes and granulocytes.
Type M3 - In most cellular elements, many azurophilic granules react with myeloperoxidase. Part of the cells contain bundles of Auer sticks and resemble myelocytes.
Type M4 has two populations: myeloblasts and monoblasts.
Type M5 is the complete predominance of monoblasts in the tumor population.
Type M6 - the presence of myeloblasts and primitive erythroblasts with multiple or segmented nuclei. Erythroblasts can account for up to 30% of all punctate cells having nuclei.
Type M7 - acute megakaryoblastic leukemia.
Acute lymphoblastic leukemias are rapidly progressing tumors of immature lymphocytes (lymphoblasts) that are more common in children and young adults.
Macroscopically: bone marrow of spongy and tubular bones *crimson-red, juicy*.
The spleen is red, juicy, its picture is erased. Significantly enlarged lymph nodes (mediastinum, mesenteric), their incision is white-pink, juicy. The same appearance has a thymus, which sometimes reaches a giant size. Lymphoid infiltration of the thymus (Sternberg tumor) can extend beyond the thymus and germinate anterior mediastinum tissue, squeezing the chest organs. Characteristic lesion of the CNS (neuroleukemia).
Microscopically: leukemic infiltration is pronounced in bone marrow, spleen, lymph nodes, lymphatic apparatus of the gastrointestinal tract, kidneys and thymus. Bone marrow aspirate is devoid of fat and consists of blasts. The normal elements of hematopoiesis are supplanted.

French–American–British (FAB) classification non-lymphoblastic leukemia:

L1 - small, monomorphic cells with rounded nuclei that contain barely visible nucleoli, sometimes splitting and serrated nuclei.
L2 - large cells of different sizes with one or two nuclei in irregular nuclei.
L3 - large and relatively monomorphic cells with basophilic and vacuolated cytoplasm.

Chronic leukemias

Chronic leukemia - leukemia, the morphological substrate of which are cells that differentiate (according to scheme 5 class) - "cytar" leukemia. Characterized by long-phasic course.
Classification of chronic leukemia:
Myelocyte origin:
1) chronic myeloid;
2) chronic erythromyelosis;
3) erythremia;
4) true polycythemia (Wakes-Osler syndrome).
Lymphocytic origin:

1) chronic lymphocytic leukemia;
2) skin lymphomatosis (Cesari disease);
3) paraproteinemic leukemia:
a) multiple myeloma;
b) primary macroglobulinemia (Waldenstrom's disease);
c) heavy chain disease (Franklin's disease).
Monocyte origin:
1) chronic monocytic leukemia;
2) histiocytosis (histiocytosis X).

Stages of chronic leukemia and their clinical and morphological features.

Stage 1 (monoclonal, benign) - lasts for many years:
• multiplication in bone marrow of differentiated tumor (leukemia) cells;
• appearance of differentiating cells in the blood;
• leukemic infiltrates in different organs with a significant increase in their size;
• moderate anemia, thrombocytopenia (other changes in blood or lack thereof).
Stage 2 - blast crisis (polyclonal, malignant) - the appearance of a large number of blast cells in the bone marrow, spleen, lymph nodes, quickly leads to death.

General changes in chronic leukemia:

• rapid growth of blast cell forms in bone marrow and peripheral blood with the development of " hiatus leucemicus ";
• increase in the degree of leukemic infiltration in other organs due to blast forms;
• increased anemia, thrombocytopenia and other changes in peripheral blood;
• appearance and increase of the expressed hemorrhagic syndrome;
• ulcerative-necrotic changes of mucous membranes and palatine tonsils;
• development of dystrophic (necrotic) changes of parenchymal organs;
• attachment of secondary infectious complications.
Chronic myeloid (granulocyte) leukemia can be at any age, the peak incidence is 30-40 years.
The main diagnostic features of chronic myelogenous leukemia:
• presence of Ph-chromosome (Philadelphia chromosome);
• a large number of myelocytes;
• increase in the absolute number of bone marrow proliferating elements;
• low concentration of alkaline phosphatase in neutrophils.
Macroscopically: blood is gray-red, anemic organs. The bone marrow of flat bones, epiphyses, and diaphysis of tubular bones is replaced by a juicy gray-pink or greenish tissue (pioid bone marrow). The spleen is dense, the surface of the incision is speckled, with zones of infarctions, the mass can exceed 3 kg, sometimes there are spontaneous ruptures of the spleen causing bleeding. Lymph nodes enlarged slightly, soft, gray-red in color. The weight of the liver reaches 5-6 kg, its surface is smooth, the tissue in the section is gray-brown.
Microscopically: In bone marrow infiltrates consist of granulocyte precursor cells (promyelocytes, myelocytes and megakaryocytes). Lymphatic follicles of the spleen are replaced by a massive outgrowth of leukemic cells. In the liver, there is a marked infiltration of leukemia cells in the course of sinusoidal capillaries, much less in the portal tracts and capsules. Hepatocytes in a state of fatty dystrophy, sometimes observed hemosiderosis of the liver. Leukemic infiltrates are also found in the tonsils,

lymphatic follicles, intestines, kidneys, skin, sometimes the brain and its membranes (neuroleukemia). In the lumen of the vessels leukemic blood clots are formed. Occlusion of the microcirculatory bed by leukemic cell aggregates leads to hemorrhagic infarction of brain tissue, which can be the cause of death.

Chronic lymphocytic leukemia occurs more often at the age of 50-60 years, rarely in people younger than 40 years. It accounts for 50% of all leukemias in humans after 60 years.

Macroscopically: bone marrow of flat and tubular bones of ***red color***, in diaphysis of tubular bones among red bone marrow - areas of yellow color. The lymph nodes are enlarged, forming huge soft or dense packets. On the section they are juicy, white-pink, homogeneous. Enlarged tonsils, lymphatic follicles of the intestine also consist of juicy white-pink tissue. The spleen reaches a large size, fleshy consistency, red in section. The liver is enlarged, dense, light brown in section. Often small gray-white knots are visible on the surface and in the section. The kidneys are enlarged, dense, gray-brown.

Microscopically: in severe cases, all myeloid bone marrow tissue is diffusely displaced by leukemic lymphocytic infiltrate, only small islands of myeloid hematopoiesis are preserved. White blood cells are represented by mature monomorphic small lymphocytes with dark round nuclei and a small amount of cytoplasm. Tumor lymphocytes are not stable and can be easily destroyed by mechanical action, so characteristic spots with an irregular outline can be seen at the site of destroyed cells (*Botkin-Klein-Gumprecht shadow*). In lymph nodes there is a loss of their architectonics: instead of a clear structure - solid masses of lymphocytes. Often, lymphocytes infiltrate the capsule of the lymph nodes and surrounding tissue. In the spleen, the leukemic lymphocytic infiltrate fills primarily the follicles, they become large and coalesce. Then there is the growth of lymphocytes in the red pulp, vessel walls, trabeculae and spleen capsules. In the liver, lymphocytic infiltration occurs mainly in the course of the capsule and portal tracts. Hepatocytes in a state of protein or fatty dystrophy. Leukemic infiltration in the kidneys is pronounced with impaired histostructure. Leukemic lymphocytic infiltration is also found in the mediastinum, mesentery, myocardium, serosa and mucous membranes.

Causes of death in leukemia patients:

• infectious complications;
• hemorrhagic syndrome (more often brain hemorrhage, intestinal profuse bleeding);
• disease progression with the development of a blast crisis;
• ulcerative-necrotic changes with their complications;
• complications from cytostatic treatment (myelosclerosis, etc.).

Multiple myeloma (Rustitsky-Kahler's disease, or generalized plasmacytoma) is a disease that belongs to a group of paraproteinemic hemoblastoses, which are tumors of the B-lymphocyte system responsible for humoral immunity.

Morphological forms:

1) solitary myeloma (single node);
2) diffuse form;
3) diffuse-nodal form;
4) multiple-nodular form.

In 25% of cases myeloma cells are detected in the blood. With a significant number of them distinguish a special form - plasma cell leukemia.

Etiology and pathogenesis. The pathogenic effect of myeloma on the body is:

• pathological proteins, paraproteins, which produce a sharp blood viscosity, are produced by tumor plasma cells;

• bone destruction and related hypercalcemia and hyperphosphatemia;

• paraprotein infiltration by renal interstitium with development of nephrosclerosis and uremia.

Clinical and morphological manifestations.

• 90-100 g / l hyperproteinemia, sometimes up to 200 g / l;

• hypercoagulation syndrome with thrombosis and thromboembolism;

• the appearance of a ***specific paraprotein in the urine*** - a ***Bence-Jones protein***;

• "sinus resorption" of the bone (radiographically "symptom of a hole") - the formation of ***smooth-walled, "stamped" defects of flat bones*** due to the growth of myeloma cells with osteolysis with insufficient bone formation;

• fatty bone marrow is replaced by tumor cells, making it look red;

• myeloma infiltration of internal organs;

• "myeloma kidney" - the kidneys are wrinkled and have a hilly surface.

Microscopically: in the bone marrow, the growth of tumor cells like plasma cells, the resorption of bone beams due to the activation of osteoclasts by tumor cells.

Focal infiltrates from such cells can occur in almost all organs. First of all, there may be signs of amyloidosis in the kidneys as well as in other organs (paraproteins play the role of a protein component of amyloid).

Causes of death: uremia, acute pneumonia, heart failure, paraproteinemic coma, pulmonary artery thromboembolism, myocardial infarction, ischemic stroke, intestinal gangrene.

Lymphomas are regional tumors of hematopoietic tissue with generalization.

Classification of lymphoma:

By origin:

• *B-cell origin*

- small cells;
- centrocyte;
- immunoblastic;
- Plasmolymphocytic

• *T-cell origin*:

- small cells;
- from lymphocytes with twisted nuclei;
- immunoblastic;
- mushroom-shaped mycosis;
- Cesari disease

• *unclassified lymphomas*.

Lymphogranulomatosis (Hodgkin's disease) is a chronic recurrent, sometimes with acute course lymphoma, with predominant lymph node lesions.

Primary localization of the lesion in lymphogranulomatosis:

• typical: cervical, mediastinal, retroperitoneal lymph nodes;

• rare: inguinal, axillary lymph nodes, spleen, liver, lungs, skin, etc.

Stages of progression of lymphogranulomatosis:

• Isolated lymphogranulomatosis - lesions of one group of lymph nodes

• Generalized lymphogranulomatosis - lesions of several groups of lymph nodes, metastasis of the tumor to other organs.

Morphological changes in tumor tissue in lymphogranulomatosis:

Tumor cells that proliferate in lymphogranulomatosis:

- **Large Hodgkin's** mononuclear **cells;**
- **Small Hodgkin's** mononuclear **cells;**
- **Reed-Sternberg cells**(multinucleated)
- Lacunar cells
- "Popcorn" cells

Cells of non-tumoral nature that accumulate in lymphogranulomatosis: lymphocytes, eosinophilic leukocytes, neutrophilic leukocytes, plasma cells, fibroblasts, etc.

Changes in the tumor tissue and the affected organs: foci of necrosis, sclerosis, ***"porphyritic" spleen*** - spleen of varied appearance due to the presence of tumor growth in it, as well as necrosis and sclerosis.

Clinico-morphological classification of lymphogranulomatosis (by Lux).

Options for lymphogranulomatosis with favorable course:

• variant with predominance of lymphoid tissue (lymphogistiocytic) - proliferation of mature lymphocytes and histiocytes,

• nodular sclerosis - the spread of fibrous tissue in the lymph node.

Options for lymphogranulomatosis with malignant course:

• mixed-cell variant - proliferation of atypical reticular cells, cells of Reed-Sternberg, accumulation of lymphocytes, eosinophils, plasmocytes;

• variant with inhibition of lymphoid tissue - lymphoid tissue is displaced by atypical reticular cells.

Macropreparations

Red bone marrow in acute leukemia: red bone marrow is juicy, similar to "raspberry jelly".

Skull bones in myeloma: multiple, rounded, up to 2 cm in size ("stamped") foci of destruction of the spongy substance of the flat bone of the skull vault.

Spleen in chronic myeloid leukemia: the spleen is significantly enlarged in size (splenomegaly, mass increased to several kilograms), in the section has a juicy appearance, dark red, with yellowish-white and reddish-brown dense foci under the capsule (ischemic infarcts of different prescription).

Micropreparations

Leukemic infiltration of liver in acute leukemia (staining with hematoxylin and eosin): Small monomorphic cells form significant infiltrates in the periportal connective tissue and along the sinusoidal capillaries.

Lymphogranulomatosis (staining with hematoxylin and eosin): The typical structure of the lymph node is changed due to the proliferation of lymphocytes, histiocytes, and reticular cells. Single-core giant cells (large Hodgkin cells) and multinuclear Rid-Berezovsky-Sternberg cells are determined.

Questions for self-control

1. Definition, etiology, pathogenesis of leukemia.
2. The concept of acute and chronic leukemia.

3. Classification and morphological characteristics of certain types of acute leukemias, causes of death.
4. Classification and morphological characteristics of certain types of chronic leukemia, causes of death.
5. Definition, etiology, pathogenesis of lymphoma.
6. Classification and morphological characterization of certain non-Hodgkin's lymphoma species.
7. Etiology, classification and pathogenesis of Hodgkin's disease.
8. Morphological characteristics and differential diagnosis of individual species of Hodgkin's lymphoma.

Examples of tests

Autopsy of a body revealed bone marrow hyperplasia of tubular and flat bones (pyoid marrow), splenomegaly (6 kg) and hepatomegaly (5 kg), enlargement of all lymph node groups. What disease are the identified changes typical of?

A. Chronic myelogenous leukemia
B. Chronic lymphocytic leukemia
C. Multiple myeloma
D. Polycythemia vera
E. Hodgkin’s disease

During hystological analysis of the lymph node situated in the posterior neck triangle of an 18-year-old patient a morphologist detected a cluster of cells including the following: isolated multinucleate Reed-Sternberg cells, large and small Hodgkin’s cells and numerous lymphocytes, isolated plasma cells, eosinophils. What disease has developed in the patient?

A. Lymphogranulomatosis
B. Nodular lymphoma
C. Burkitt’s lymphoma
D. Lymphocytic lymphoma
E. Chronic lymphocytic leukemia

Examination of a 66 year old patient revealed a lytic tumour in the locus of pathological rib fracture. Histologically this tumour consists of atypical plasmoblasts. Further examination revealed osteoporosis in the bones of vertebral column and pelvis. These changes are typical for:

A. Myelomatosis
B. Tuberculous osteomyelitis
C. Ewing’s osteosarcoma
D. Neuroblastoma
E. Metastatic lung cancer

A patient has a cluster of matted together dense lymph nodes on his neck. Histological examination of a removed lymph node revealed proliferation of reticular cells, presense of Reed-Sternberg cells. What disease is meant?

A. Lymphogranulomatosis
B. Lymphoblastic leukosis
C. Myeloblastic leukosis
D. Myelocytic leukosis
E. Lymphocytic leukosis

Microscopical examination of an enlarged cervical lymph node revealed blurring of its structure, absence of lymphoid follicles; all the microscopic fields showed cells with roundish nuclei and thin limbus of basophil cytoplasm. It is known from the clinical data that other groups of lymph nodes are also enlarged as well as spleen and liver. What disease might be suspected?

A. Lymphoid leukosis
B. Lymphogranulomatosis
C. Lymphosarcoma
D. Myeloid leukosis
E. Multiple myeloma

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Informational resources

1. Universities websites and electronic Internet resources.
2. Testing center - base of licensed test tasks "Krok-1"
3. Elements: Science News http //elementy.ru/.
4. http://library.med.utah.edu/WebPath/webpath.html
5. http://www.webpathology.com/
6. https://www.geisingermedicallabs.com/lab/resources.shtml.