MINISTRY OF HEALTH PROTECTION OF UKRAINE
ODESSA NATIONAL MEDICAL UNIVERSITY

Faculty of **medicine**

Department **of general and clinical pathophysiology**

I APPROVE

Vice-rector for scientific and pedagogical work

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MANUAL TO LECTURES
FROM EDUCATIONAL DISCIPLINE

Faculty of Medicine, course 3

Educational discipline - " **pathophysiology"**

Approved:
At the meeting of the Department of *General and Clinical Pathological Physiology named after V.V. Podvysotsky* Odesa National Medical University

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LECTURES

Lecture No. 1

Introductory lecture. Pathological physiology as a fundamental and educational discipline. The place of pathological physiology in the system of medical knowledge. Concept of etiology and pathogenesis. Typical responses of cells to damage. Causes of cell damage, their general mechanisms. Typical disorders of peripheral blood circulation and microcirculation: classification, etiology and pathogenesis.

Goal: To form an understanding of the definition of pathophysiology as a fundamental science, to define the subject and tasks of pathophysiology; characterize such concepts of general nosology as health, disease, pathological process, typical pathological process, pathological reaction, pathological condition, etiology, pathogenesis; outline the main concepts of etiology: causative factors, risk factors, conditions of occurrence and development of the disease; determine the essence of pathological, adaptive , local, general, specific and non-specific mechanisms. Define the typical types, mechanisms and mediators of cell damage, causes of occurrence and methods of experimental modeling; to separate the main links in the pathogenesis of cell damage, both actually pathological and compensatory-adaptive ; determine the place of typical types of cell damage, their etiopathogenesis in the development of the disease. Acquaint applicants with the concept and classification of microcirculation disorders .

Basic concepts: Pathophysiology, Nosology, Health, Health, Pathological reaction, Pathological process, Pathological condition, Typical pathological processes, General etiology, Cell damage, types of damage. Microcirculation disorders, arterial hyperemia , venous hyperemia , embolism, stasis, ischemia.

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

"Pathophysiology" is the science of the vital activity of a sick organism ("pathology" from the Greek . Pathos - disease, suffering + 1oroc - teaching, science; "physiology" (from the Greek . Phusis - nature + 1oroc).

Pathological physiology studies the main regularities of the occurrence, development and outcome of the disease. The ultimate goal of pathophysiology is to reveal the laws by which the disease develops.

Nosology forms the basic concepts and categories of pathology, creates classifications and nomenclature of diseases , studies the social aspects of the disease.

Basic concepts of general nosology:

Health is a state of complete physical, mental and social well-being, and not just the absence of disease or physical defects (WHO definition, 1946). This is, first of all, the state of the organism, in which the correspondence of structure and

function, as well as the ability of regulatory systems to maintain the constancy of the internal environment (homeostasis), is noted.

The norm is a state of optimal life activity and development of the organism.

A disease is a violation of the normal vital activity of an organism when it is affected by harmful agents, as a result of which its adaptive capabilities are reduced (MM Zaiko).

Classification of diseases is a certain system of distribution of diseases and pathological conditions into classes, groups and other headings according to established criteria.

1. Etiological principle - hereditary and acquired, infectious and non-infectious , etc.

2. Anatomical and topographic principle - cardiovascular diseases, respiratory diseases, kidney diseases , etc.

3. By age and gender - children's diseases, women's diseases, diseases of old age.

4. Pathogenetic principle - allergic diseases, inflammatory diseases, metabolic diseases , etc.

5. Depending on the state of structural and functional disorders - organic and functional diseases.

6. According to the clinical course - acute and chronic, subacute .

7. Depending on the methods that are mainly used to treat the disease - therapeutic and surgical.

A pathological reaction is an inadequate and biologically inappropriate response of the body to the action of ordinary or excessive stimuli. Examples: various types of pathological reflexes, allergy, a short-term increase in blood pressure after nervous tension or a decrease in blood sugar due to the introduction of large doses of insulin , etc.

A pathological process is a sequence of reactions that naturally occur in the body to the harmful effect of a pathogenetic factor . Examples of pathological processes are inflammation of lung tissue in pneumonia, hypoxia in obliterating endarteritis , inflammation of the heart muscle during myocardial infarction, fever during typhoid fever , etc.

A pathological condition is a set of pathological changes in the body that arise as a result of the development of a pathological process. In the narrow sense of the word, it is a persistent deviation from the norm that has a negative biological meaning. Examples of pathological conditions are a stump after amputation of a limb, cicatricial tissue changes after a thermal burn, atrophy of the alveolar processes of the jaw in connection with the removal or loss of teeth, an acquired defect of the valve apparatus hearts

Typical pathological processes are such processes that have the same laws of development regardless of the cause, localization, species of animals and individual characteristics of the organism. Examples: inflammation, tumor growth, local circulatory disorders, hypoxia, starvation, fever.

General etiology (Greek . Aitia - cause, logos - science, teaching) - teaching about the causes and conditions of disease occurrence and the principles of etiotropic prevention and therapy.

The cause of the disease should be considered the pathogenic factor without which it cannot occur under any conditions. *Conditions* for the occurrence of the

disease are factors that reliably increase the probability of the occurrence of the disease. Example: the cause of ARVI is a virus, the conditions are hypothermia, fatigue, reduced immunity.

A risk factor is a general name for factors that are not the direct cause of a certain disease, but increase the likelihood of its occurrence.

Classification of etiological factors.

- physical - mechanical action, ionizing radiation, high and low temperature, electric current, etc.;
- chemical - inorganic and organic compounds of natural and artificial origin;
- rickettsia , bacteria, protozoa, etc.
- psychogenic - negative emotions, etc.

The main scientific directions of general etiology:

Monocausalism is the course of pathology, which recognizes the absolute supremacy of the cause in the occurrence of the disease, and claims that the disease has only one single cause.

Conditionalism is a direction that does not recognize the determining role of a cause in the occurrence of a disease. Representatives of this direction believe that the disease occurs as a result of the influence of many equivalent conditions.

Constitutionalism . Representatives of this school of thought claim that the decisive importance in the occurrence of the disease belongs not to the pathogenic factors of the external environment, but to the organism itself, in particular, its heredity and constitution.

Psychosomatic direction. Representatives of this direction believe that the basis of the development of most diseases lies in the violation of the mental sphere of a person.

General pathogenesis (pathos - disease, suffering; genesis - origin , birth) - the doctrine of the general mechanisms of development, course and consequences of the disease and the principles of pathogenetic prevention and therapy.

The relationship between the cause of the disease and its pathogenesis.

1. The etiological factor plays the role of a trigger and includes the process of disease development. For the further course of pathogenesis, the continued existence of the cause is not mandatory (for example, radiation sickness, mechanical trauma, thermal injuries).

2. Parallel existence of the cause and pathogenesis. The mechanism of disease development functions as long as the causative factor operates. Most infectious diseases can serve as an example of this type of interaction between the cause and the mechanism of the disease.

3. Persistence of the etiological factor . Disease-causing agents stay in the body longer than the pathogenesis itself. At the same time, the properties of the etiological factor may change under the influence of the organism. An example is bacteremia after infectious diseases.

Adaptation is the adaptation of the organism and its structures to the changing conditions of the external environment. Adaptation ensures preservation of homeostasis and prevents damage under the influence of normal environmental factors.

Compensation is a state that develops as a result of the implementation of compensatory reactions and processes aimed at restoring disturbed homeostasis due to the influence of pathogenic factors.

The second section of general pathological physiology is the study of typical pathological processes. The section contains data on the processes underlying many diseases, namely: inflammation, tumor growth, fever, hypoxia, typical metabolic disorders, starvation.

The second section of pathological physiology - *private pathophysiology* - examines disorders in individual organs or systems: blood circulation, breathing, endocrine, nervous systems , etc.

Research methods, significance of the experiment in pathophysiology

Pathophysiology is an experimental science. Therefore, its main method is an experiment on living objects. A pathophysiological experiment differs from a physiological one by modeling a human disease on laboratory animals. Currently, it is possible to reproduce such pathological processes on animals as traumatic shock, diabetes, atherosclerosis, myocardial infarction, kidney inflammation, arterial hypertension , etc. Meanwhile, we must not forget that the human body is much more complex than even the most highly organized animals and is under the constant influence of social factors, which is why it is almost impossible to get the full extent of human diseases on animals. It is possible to reproduce only some pathogenetically important links, symptoms and syndromes of a human disease. Physiological, electrophysiological, biophysical, biochemical, hematological, morphological, immunological, mathematical research methods are used in the experiment. Pathophysiological experiment, in contrast to clinical observation, has a number of beneficial advantages. These benefits include the ability to:

1. Clarification of the causal factors of the disease;
2. Observations from the pre-disease period and the earliest stage of the disease to the result;
3. Research of incurable forms of the disease;
4. Conducting experimental therapy.

All these possibilities are sharply limited in clinical conditions. All experiments can be acute and chronic. An acute experiment is needed to study the effects of blood loss. Tumor development is studied in a chronic experiment. Conducting the experiment involves humane treatment of animals (using anesthesia). It is unacceptable to conduct an experiment that will cause suffering to the animal.

Typical disorders of peripheral blood circulation and microcirculation: classification, etiology and pathogenesis.

Arterial hyperemia - an increase in blood filling of an organ or a tissue area due to an increase in arterial blood flow.

Reasons:

- physical (temperature, UV radiation);
- chemical (turpentine , mustard powder);
- biological (toxins);
- psychogenic (emotions).

Species:

- ***physiological*** (develops in connection with the increased need of tissue for oxygen and nutrients): *working* (functional) - caused by the metabolic needs of an organ or tissue in connection with an increase in their functioning. For example, hyperemia in the muscle during physical work, hyperemia of the pancreas and intestinal wall at the time of digestion, hyperemia of the endocrine gland during secretion, hyperemia of the salivary glands. An increase in the contractile activity of

the myocardium leads to an increase in coronary blood flow, activation of the brain is accompanied by an increase in its blood supply. *Reactive* (postischemic) arterial hyperemia is observed after a temporary cessation of blood flow (temporary ischemia) and has a protective and adaptive nature (removal of the tourniquet).

- ***pathological*** - develops during pathological processes, such as allergy, fever, inflammation.

The leading link of pathogenesis: dilation of arterioles and increase in arterial blood flow.

Mechanism of arterial expansion:

- **neurogenic:** decrease in the tone of vasoconstrictors (neuroparalytic), increase in the tone of vasodilators due to acetylcholine (neurotonic);

- **humoral** (myoparalytic) - expansion of blood vessels with the help of BAV: histamine , bradykinin , lactic acid, excess carbon dioxide, nitric oxide, adenosine, hypoxia, some prostaglandins , etc.

Manifestations arterial hyperemia:

- reddening of a tissue area due to an increase in the number of functioning capillaries and arterialization of venous blood;

- local increase in temperature (increased arterial blood flow and increased redox processes in the tissue;

- increase in tissue turgor (dilation of blood vessels, increase in blood supply);

- dilation of arterioles, increase in blood flow rate, increase in intracapillary pressure, increase in the number of functioning capillaries.

Consequences: - *positive* : improvement of delivery of oxygen and nutrients to the body , strengthening of metabolic processes and function of the body ; - *negative* : rupture of a vessel with hemorrhage in the presence of pathology, generalization of infection, progression of tumor growth and metastasis.

Venous hyperemia - increased blood supply to an organ or tissue area due to obstruction of venous blood outflow.

Reasons:

- vein thrombosis;

- compression of veins from the outside by a tumor, enlarged uterus during pregnancy, scar, exudate, tourniquet;

- violation of general hemodynamics in right ventricular heart failure;

- constitutional insufficiency of the valve apparatus of veins.

The leading link of pathogenesis: obstruction of the outflow of venous blood.

Mechanism of development: circulatory hypoxia → cell damage → cell death → sclerosis; local intoxication due to the accumulation of lactic acid, carbon dioxide → metabolic acidosis

Manifestations venous hyperemia:

- cyanosis of a tissue area due to increase in the blood of reconstituted hemoglobin ;

- local decrease in temperature (reduction of regenerative processes in the tissue, increase in heat transfer);

- increase in organ volume (increased blood supply, edema);

- expansion of veins and capillaries, slowing of blood flow;

- increase in fluid filtration, decrease in its reabsorption, difficulty in lymphatic outflow .

Consequences: - *positive* : slowing down the development of the local infectious process, facilitating the migration of leukocytes to the focus of inflammation; *negative* - atrophy of parenchymal elements, growth of connective tissue and development of sclerosis.

Ischemia - decrease in blood supply to an organ or tissue area due to a decrease in arterial blood flow.

Reasons:

- compression of arteries from the outside,
- arterial thrombosis and embolism,
- angiospasm of arteries,
- atherosclerotic damage to the inner lining of arteries.

The leading link of pathogenesis: decrease in arterial blood flow.

Mechanism of development: Violation of energy metabolism: ↓ O_2 → violation of oxidative phosphorylation in mitochondria → ↓ ATP → violation of contractile and secretory functions of cells, violation of active transport of substances → necrosis, increased biosynthesis of connective tissue components → sclerosis.

Manifestations of ischemia:

- paleness of the tissue area at the expense of decrease in blood supply and the number of functioning capillaries;
- local decrease in temperature (decrease in flow of warm arterial blood, decrease in redox processes in the tissue);
- pain or paresthesias (irritation of nerve endings by products of metabolism (H^+, K^+);
- organ size reduction (reduction in blood supply);
- reduction of intravascular pressure, slowing of blood flow, reduction of the number of functioning capillaries, reduction of fluid filtration, reduction of lymph outflow .

Consequences of ischemia: restoration of blood circulation in collateral vessels, impaired nutrition and tissue death (necrosis).

Stasis - stoppage of blood flow in the vessels of the microcirculatory channel.

Species:

- ischemic due to cessation of arterial blood flow;
- venous in connection with termination outflow of venous blood;
- capillary (true) - intracapillary aggregation of erythrocytes.

Pathogenesis of erythrocyte aggregation in capillary stasis: etiological factors → damage to capillary walls → increase in their permeability → filtration of fluid and albumins into the surrounding tissues → increase in the level of high molecular weight proteins (globulins and fibrinogen) in the blood → adsorption of proteins on erythrocyte membranes → changes in the surface potential of erythrocyte membranes → aggregation of erythrocytes. Etiological factors → damage to erythrocyte membranes → changes in physicochemical properties of membranes (decreased ability to deform) → changes in surface potential of erythrocyte membranes → aggregation.

Consequences stasis: restoration of blood circulation (reversible stasis), necrosis (irreversible stasis).

Thrombosis - intravital deposition of a clot of stabilized fibrin and formed blood elements on the inner surface of blood vessels with partial or complete obturation of their lumen.

Mechanisms formation and structure blood clots depend on the characteristics of the blood flow in the vessel. Basically *arterial thrombosis* - thrombus formation in the arterial system with a high blood flow rate, - the activation of vascular and platelet (primary) hemostasis lies in the basis *venous thrombosis* - formation of blood clots in the venous system, which is characterized by a low blood flow rate, - activation of coagulation (plasma) hemostasis.

Virchow's triad :

1. Damage to the endothelium: death of endotheliocytes ; violation of their function - endothelial dysfunction; death of endotheliocytes → exposure of the basement membrane → unmasking of collagen → ↑ adhesion of platelets; endotheliocytes release Willebrand factor , which forms "bridges" between collagen and platelets.

2. Violation current of blood - when changing current of blood from laminar to turbulent formative elements of the blood acquire opportunities contact with the endothelium.

3. Increase viscosity of blood

Embolism - movement by blood flow (lymph) and clogging of blood vessels by foreign bodies (embolomas).

Embolism of endogenous origin:

and) thromboembolism ;

b) tissue - pieces of tissue in case of injuries or tumors when they disintegrate;

c) fat - droplets of fat in case of fractures of tubular bones or damage adipose tissue during liposuction ;

d) amniotic fluid embolism - getting into the amniotic fluid water during childbirth into the damaged vessels of the uterus.

Embolism of exogenous origin:

a) air - air bubbles entering from the environment environment in large veins (superior cava, jugular, subclavian), in which blood pressure may be lower than atmospheric;

b) gas - gas bubbles that form in the blood during a rapid decrease in barometric pressure, for example, during the rapid ascent of divers from the area of high pressure to normal; when depressurizing the aircraft cabin at high altitudes (transition from normal to low atmospheric pressure);

c) foreign bodies - in case of gunshot wounds.

General material and bulk-methodological support of the lecture:

Questions for self-control:

1. General organization of the pathophysiology course
2. Definition of pathological physiology (pathophysiology) as a subject.
3. Development of pathophysiology as an independent science
4. Goals and objectives of our subject
5. General information about pathogenic factors (endogenous and exogenous)
6. Types of cellular reactions (cellular response) to damage and development pathologies.

Lecture No. 2

Topic: Inflammation. Stages of inflammation, primary and secondary alteration. Mediators of inflammation, their classification. Changes in blood circulation in the focus of inflammation, the importance of inflammation for the body

Purpose In the pathogenesis of inflammation, the processes of primary and secondary alteration, i.e. tissue damage as a result of the action of phlogogenic agent and those factors released from damaged cells. The main manifestations of alteration are metabolic and physicochemical disturbances in the focus of inflammation. Knowledge of these changes and the reasons for their occurrence is a necessary condition for forming a holistic view of the pathogenesis of the inflammatory process and understanding the mechanisms of the development of cardinal signs of inflammation.

Acquaint students with vascular phenomena in the focus of inflammation (disorders of microcirculation, exudation and emigration of leukocytes), show the reactions of the vessels of the microcirculatory bed, changes in the permeability of the walls of microvessels ; acquaint applicants with the phenomena of leukocyte emigration, its mechanisms, chemotaxis factors, cytopemsis phenomena ; characterize the phenomenon of phagocytosis, "respiratory explosion", types of phagocytosis, stages and mechanisms.

Acquaint applicants with the contribution of scientists (I.I. Mechnikov, O.M. Chernukh , M.O. Yasinovskyi) to the development and detailed study of microcirculation changes in the inflammation zone, leukocyte emigration phenomena and their main function - phagocytosis; on the example of the staged development of the inflammatory process in the focus, show significant compensatory capabilities of the body in response to environmental factors; at the same time show the relationship between the organism and the environment that surrounds it.

1. **Basic concepts: Inflammation,** Alteration, Exudation, **Proliferation** , emigration of leukocytes, **Mediators of inflammation,** reflex spasm, arterial hyperemia, venous hyperemia, stasis,

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

INFLAMMATION

Inflammation is a typical pathological process that occurs when tissues are damaged and is characterized by a violation of blood circulation, a change in blood and connective tissue in the form of alteration, exudation and proliferation. The whole body reacts to this, mostly local, process to one degree or another, and above all such systems as immune, endocrine and nervous.

Emerging in the early stages of evolution, this process gradually changed its character, became more complicated , but two sides could always be found in it. One is an injury with a threat to the organ and even to the whole body, the second is the stimulation of protective mechanisms that help the body in the fight for survival. So, inflammation in the history of the animal world was formed as a dual process, in which there are and always are elements of protection and elements of damage that require the intervention of a doctor.

The main signs of inflammation. Inflammation has always been known to doctors. A description of its signs can be found in ancient books. Celsus and Galen reduced all the variety of these signs to five cardinal ones: tumor , rubor , calor , dolor , functio laesa _ Although centuries have passed since the time of Celsus and Galen , scientists are still busy today trying to better understand how and why swelling occurs at the site of inflammation, how the mechanisms of redness and heat occur, why pain occurs, and how, ultimately, the inflammatory function of the organ is disturbed .

EXPERIMENTAL REPRODUCTION OF INFLAMMATION

Inflammation is an important problem and subject of study in all branches of medicine. The difference lies only in research methods. For example, a medical doctor observes the course of lung inflammation (pneumonia) at the patient's bedside, a pathologist - during an autopsy, a pathophysiologist - in an experiment on animals. Student of Virkhov Kongheim (1867) first studied blood circulation in the mesentery during inflammation in an experiment on a frog, while establishing all its stages from hyperemia to stasis. Kongheim also described the process of emigration of leukocytes through the vascular wall. His experimental model is widely used even now in practical classes with students (Kongheim's experiment) and in scientific research. The experiments of I.I. Mechnikov played a special role in the studied inflammation . He considered inflammation from an evolutionary perspective. I.I. Mechnikov was the first to study inflammation in phylogeny, that is, in animals at different stages of evolutionary development. On the transparent starfish larva , a representative of invertebrates , he discovered the phenomenon of phatocytosis and gave it the main role in the dynamics of inflammation. On the basis of these observations, a theory of inflammation was built, which entered science under the name of comparative pathological, or evolutionary. Subsequently, pathologists began to widely use the evolutionary principle in experimental modeling, based on the fact that pathological phenomena in lower animals, representing the simplest and most primitive conditions, open the way to understanding complex pathological processes (I.I. Mechnikov , 1892).

Today, many biologically active substances - mediators of inflammation - have been identified and their mechanism of action has been studied in detail.

With the help of electron microscopy, ultracentrifugation and other methods, information about biological membranes was obtained, which contributed to the disclosure of the mechanism of inflammatory edema, the passage of leukocytes through the vascular wall, their accumulation in the center of inflammation, etc.

The experiment is also important because with its help, many anti-inflammatory drugs were studied in detail and introduced into the clinic.

ETIOLOGY

Any damaging agent, which in terms of strength and duration of action outweighs the adaptive capabilities of the tissue, can cause inflammation. All phlogogenic factors are usually divided into external (exogenous) and internal (endogenous). External ones include microorganisms (bacteria, viruses, fungi); animal organisms (protozoa, worms, insects); chemicals (acids, alkalis); mechanical (foreign bodies, pressure, reserve) and thermal (cold, heat) effects, ionizing and ultraviolet radiation.

Internal factors include those that arise in the body itself as a result of another disease. For example, inflammation can occur as a reaction to a tumor, gallstones or urinary stones , a thrombus formed in blood vessels. The cause of inflammation can be antigen-antibody complexes, if they are fixed in some organism.

STAGES OF INFLAMMATION

In classical pathology, it is customary to divide inflammation into three stages:

1) alterations , 2) exudations, 3) proliferations. This division persists even today. However, new facts have shown that the named stages are heterogeneous, each of them has different phases and sub-stages in terms of time and content . In connection with this, there was a need to distinguish substages A and B in the first and third stages of inflammation.

I. Alteration stage: A. Primary alteration. B. Secondary alteration

II. Stage exodus with emigration.

Sh. Stage of proliferation and reparation: A. Proliferation . B. Termination of inflammation.

PATHOGENESIS

Among the many factors of inflammation, several main ones can be singled out, which determine the beginning of the process, its development and end: 1) damage due to the action of an inflammatory agent (primary alteration); 2) emission from cells and formation of biologically active substances - mediators of inflammation, release and activation of lysosomal enzymes, their influence on biological macromolecules (secondary alteration); 3) violation of microcirculation, increased permeability of the vessel wall, exudation; 4) cell reproduction (proliferation); 5) recovery in the center of inflammation. Stage I. Primary alteration. Inflammation always begins with tissue damage. After exposure to a damaging factor, structural and metabolic changes occur in the cells, the nature of which depends on the strength of the damage, on the cells (degree of maturity), etc. Some cells rot, others remain viable, and others are even activated. The latter play a special role in the subsequent stages of inflammation. Secondary alteration. If the primary alteration is the result of the direct action of the inflammatory agent, then the secondary alteration does not depend on it and can continue even when this agent is no longer present (for example, with ionizing radiation). The causative factor is the initiator of the process, and then the inflammation proceeds according to the laws that are characteristic of tissues, organs, and the organism as a whole.

The action of the inflammatory agent affects primarily cell membranes, including lysosomes . This has important implications. Enzymes in lysosomes are inactive. When lysosomes are damaged , enzymes are activated and increase the effect of the inflammatory agent. It can be said that the primary alteration is an injury caused by a party, the secondary alteration is a self-inflicted injury .

It should be noted. That secondary alteration carries not only damage and destruction. Some cells really die, and others not only survive, but also begin to produce biologically active substances, involving new cells in the inflammation process both in the area of inflammation and outside it.

INFLAMMATION MEDIATORS

Inflammatory mediators are biologically active substances that are synthesized in cells or body fluids and have a direct effect on the inflammatory process. Cellular mediators were discussed above. Humoral mediators of inflammation are synthesized in blood plasma and tissue fluid due to the action of primary enzymes. The main reason for the appearance (or increase in the amount) of these substances is alteration. As a result of cell damage, lysosomal enzymes are released and activated, which, in turn, activate other enzymes, including those contained in blood plasma, resulting in biochemical reactions. At first, they have a chaotic character ("metabolic fire"), and the products of decomposition have no physiological significance and are often toxic, but gradually this process reveals a certain biological meaning. Proteolytic enzymes do not cleave proteins to the end (limited proteolysis), as a result of which specific substances are formed that cause a certain pathophysiological effect. It turned out that some of them affect mainly vessels, increasing the permeability of their walls, others - on the migration of leukocytes, and the third - on cell reproduction. V. Meniken was the first to see a certain "order", regularity in inflammation . In the inflammatory exudate, he identified and distinguished chemical substances and compared with them some components of inflammation: hyperemia, leukocytosis, chemotaxis. Since then, much has changed in the actual material, but the direction (chemistry of inflammation) has remained quite fruitful. Histamine is contained in the granules of tissue basophils in a complex with heparin and chymase in an inactive form. In a free state, it causes the expansion of small vessels (capillaries, venules), increasing the permeability of their walls. In small doses, histamine expands arterioles, in large doses, it narrows venules . The release of histamine occurs together with the release of all or part of the granules of tissue basophils during their degranulation . This can be facilitated by the influence of heat, ionizing and ultraviolet radiation, solutions of salts, acids, proteins, synthetic polymers and monomers, surface-active substances. Degranulation is always observed during immune reactions, that is, when an antigen interacts with an antibody on the surface of tissue basophils. The second cellular mediator is serotonin. In humans, it is found in thrombocytes , chromaffin cells of the intestinal mucosa , as well as in some nervous structures. Serotonin released during the destruction of cells causes an increase in the permeability of the vessel wall. Tissue basophils also produce heparin, the role of which in inflammation is that it prevents the formation of fibrin on the inner membrane of capillaries, also causing an increase in the permeability of their wall.

Lymphokines are substances of a protein nature that are formed in lymphocytes and also belong to mediators of inflammation. More than ten different lymphokines have been described . In inflammation, three of them are most important: a factor that inhibits the migration of macrophages; factor that activates microphages; chemotaxis factor. In blood cells (leukocytes, platelets, etc.), another group of substances is formed, which play an important role in the dynamics of inflammation. These are prostaglandins . The source of their formation is phospholipids of cell membranes. Violation of the strictly ordered structure of phospholipids in the membrane makes them available for the action of phospholipase A2, as a result of which arachidonic acid is split off. It starts a cascade of chemical reactions that take place in two directions. If the cyclooxygenase enzyme acts on arachidonic acid , prostaglandins (PGE2 SHT2, PG02) or prostacyclin (PGI2) are formed as a result , and when lipoxygenase is primarily active , leukotrienes are formed . Further conversion of prostaglandins takes place under the influence of thromboxane synthetase , as a result of which thromboxane is formed . A2. The latter causes narrowing of blood vessels, aggregation of platelets, thrombosis, swelling, pain. The second path of biosynthesis of prostaglandins is that under the influence of prostacycline synthetase, prostacyclin (PGI2) is

formed . This process is carried out in endotheliocytes , where the specified enzyme is contained. The effect of prostacyclin is opposite to that of thromboxane : it dilates blood vessels and inhibits platelet aggregation. Therefore, arachidonic acid gives rise to two substances with opposite effects, and the choice of one of the biosynthesis pathways is obviously related to the state of the endothelium. In intact endothelial cells, there is enough prostacyclin synthetase and all PGI2 is converted into prostacyclin . If the endothelium is damaged, this enzyme will not be enough, and therefore part of the prostaglandins is converted to thromboxane A2. The arachidonic cascade is also of interest because free radicals are formed during it, which can damage cell membranes, including lysosomes . Arachidonic acid can be a source of another group of substances that play an important role in inflammation. These are leukotrienes . Lice are formed in leukocytes under the influence of a key enzyme - lipoxygenase . Leukotrienes exhibit chemotaxic and chemokinetic (undirected movement) effects, increase the permeability of the vessel wall, cause the contraction of non-striated muscle fibers, and induce the formation of thromboxanes . Inflammatory mediators also include cyclic nucleotides, which would be more correct to call modulators rather than mediators, since they do not create a complete picture of inflammation, but can only transform it to one degree or another. Cyclic nucleotides determine the effect of other mediators, the release of cell lysosomal enzymes, etc. The oppositely directed effect of cAMP and cGMP was revealed . So, the first suppresses the release of histamine and lysosomal enzymes, and the second, on the contrary, promotes it. Of the humoral mediators of inflammation, tires are the most important - a group of vasoactive polypeptides formed as a result of a cascade of biochemical reactions that begin with the activation of the Hageman factor . Contact with a damaged surface or a change in the internal environment (temperature, pH) lead to the fact that this factor becomes active and acts on prekallikrein , which is contained in the blood plasma, turning it into kallikrein . The latter, in turn, acts on a2-globulins, cleaving from them a polypeptide chain consisting of 9 (bradykinin) or 10 (kalidine) amino acid residues. Blood plasma kinins directly affect the tone and permeability of the capillary wall. In addition, they cause itching and pain typical of inflammation. Mediators of the kallikrein - kinin system during inflammation affect the rheological properties of blood, that is, its ability to be in a liquid and fluid state. Hagemann's active factor initiates the processes of kinin formation , hemocoagulation and fibrinolysis, and the formation of blood clots in the inflammation zone, which are somehow related to the state of the kallikrein-kinin system.

The third humoral mediator of inflammation is complement. It is known that complement is an important protective factor of the body, but at the same time it can cause damage to its own tissues, which occurs during inflammation, especially immune. This is explained by the fact that among the nine components of complement, three are most closely related to the inflammatory process. Thus, the C5 component has the ability to fix on cells sensitized and not sensitized by antibodies and destroy their membranes. Components C3a and C5a, as well as the trimolecular complex C567 cause leukocyte homotaxis . Finally, cells loaded with C36 components become the object of active phagocytosis. Stage P. Inflammation is characterized by a violation of local blood and lymph circulation, primarily microcirculation. It is customary to call microcirculation the movement of blood in the terminal vascular bed (in arterioles, metaarterioles , capillaries and venules), as well as the transport of various substances through the wall of these vessels.

Venous hyperemia is explained by the action of several factors, which can be divided into three groups: factors of the blood, vascular wall, and surrounding tissues. Blood factors include marginal placement of leukocytes, swelling of erythrocytes, exit of the liquid part of

blood into the inflamed tissue and blood thickening, formation of blood clots due to activation of the factor Hageman , reduction of heparin content. The influence of vascular wall factors on venous hyperemia is manifested in the swelling of the endothelium, as a result of which the lumen of small vessels decreases even more. Changed venules lose their elasticity and become more susceptible to compression by the infiltrate. And finally, the manifestation of the tissue factor is that the swollen tissue, compressing the veins and lymphatic vessels, contributes to the development of venous hyperemia.
With the development of a prestatic state, a pendulum-like movement of blood is observed - during systole it moves from arteries to veins, during diastole - in the opposite direction. Finally, the movement of blood can stop completely, and stasis develops. The consequence of stasis can be irreversible changes in blood cells and tissues.
One of the characteristic signs of inflammation is the exudation and migration of leukocytes.
Exudation is the exit of the liquid part of blood, electrolytes, proteins and cells from blood vessels into tissues. The output of leukocytes (emigration) occupies a special place in this process.
Native (exudate) that comes out of blood vessels, permeates inflamed tissue or concentrates in a cavity, for example, in the pericardial cavity, in the anterior chamber of the eye, etc. The main reason for exudation is an increase in the permeability of the histohematal barrier, that is, the wall of vessels, primarily capillaries and venules . Studies have shown that the release of water and substances dissolved in it occurs during the months of contact of endothelial cells. The gaps between them can increase when the vessels expand, and also, as it is thought, when the contractile structures are shortened and the endothelial cells are rounded.
Fluid transport in tissues depends on physical and chemical changes occurring on both sides of the vascular wall. As a result of the release of protein, more and more of it is outside the vessels, which causes an increase in oncotic pressure. At the same time, protein and other large molecules are split into smaller ones. Hyperonkia and hyperosmia create a flow of fluid into the inflamed tissue. This is facilitated by an increase in intravascular hydrostatic pressure due to changes in blood circulation in the center of inflammation. Exudate differs from transudate in that it contains more proteins (more than 2%). If the permeability of the vessel wall is slightly impaired, albumins and globulins usually penetrate into the exudate. In case of a significant violation of permeability, a protein with a large molecular weight (fibrinogen) is released from the plasma into the tissue. During primary and then secondary alteration, the permeability of the vascular wall increases so much that not only proteins, but also cells begin to penetrate through it. This is facilitated by the fact that with venous hyperemia, leukocytes are located along the inner lining of small vessels, more or less firmly attached to the endothelium (the phenomenon of marginal standing of leukocytes). The attachment of leukocytes to the vascular wall is explained by the fact that its inner membrane in case of inflammation is covered with a flaky layer, which includes fibrin, glycosaminoglycans , glycoproteins , etc. In electronograms, this layer has the appearance of a fringe.
Emigration is the exit of leukocytes from the vessel lumen through the vessel wall into the surrounding tissue. This process occurs normally, but in the case of inflammation, it becomes much larger. The essence of emigration is that a sufficient number of cells have accumulated in the center of inflammation; which play a role in the development of inflammation.

The mechanism of emigration has been studied quite well. With the help of a microscope on a living object, it was established that a leukocyte passes its pseudopodia between two endothelial cells, and then the whole body. Electronograms show that leukocytes go beyond the blood vessel at the junction of endothelial cells. This is explained by the fact that endotheliocytes are rounded, increasing the gaps between them. After the release of leukocytes, contacts are restored. Some authors suggest that there is a second way of emigration of leukocytes - transcellular , that is, through the cytoplasm of endothelial cells. However , the existence of this pathway, at least in the norm, has recently been questioned. After penetrating through the layers of the endothelium, the leukocyte must overcome another and, obviously, more significant barrier, namely the basement membrane. It has a thickness of 40-60 nm and consists of collagen fibers and a hemogenic substance rich in glycosaminoglycans . Passing through the balsa membrane, the polymorphonuclear leukocyte attacks it with its enzymes (elastase , collagenase , hyaluronidase). They affect the molecular structure of the basement membrane, increasing its permeability. In addition to enzymes, cationic proteins contained in neutrophil granulocytes also play a role. These proteins affect the colloidal substance of the membrane, temporarily transferring it from a gel to a sol and thereby increasing its permeability to the cell.
neutrophilic granulocytes migrate , then monocytes, and finally, lymphocytes.
The cellular composition of the exudate largely depends on the etiological factor of inflammation. If, for example, inflammation is caused by purulent bacteria (staphylococci, streptococci), neutrophils predominate in the exudate granulocytes, and when it runs on an immune basis (allergy) or caused by parasites (helminths), - eosinophilic granulocytes , in case of chronic inflammation (tuberculosis, syphilis) - mononuclear cells (lymphocytes, monocytes).
In the center of inflammation, there is an active movement of leukocytes to chemical stimuli, which can be products of tissue proteolysis. This phenomenon was described by I.I. Mechnikov and called it chemotaxis. Chemotaxis is important at all stages of emigration of leukocytes, especially during movement in the surrounding vascular space and in the tissue in which there are no vessels (cornea). If the inflammation is caused by an infectious agent, then for chemotaxis the products of the vital activity of microorganisms are of great importance, as well as substances that are formed as a result of the interaction of antigen and antibody.
In the chemotaxis of leukocytes, the complement system is of great importance, primarily the C3 and C5 components. Leukotoxically active complement products C3 and C5 can be formed under the influence of various enzymes: trypsin, thrombin, plasmin. The process of emigration can not only be stimulated, but also suppressed. Inhibitors of chemotaxis are produced by lymphocytes that are activated by an antigen. The mobility of leukocytes will decrease if they are affected by such metabolism inhibitors as colchicine , puromycin , actinomycin B, alcohol.
Some physico-chemical factors are important in the mechanism of leukocyte movement, for example, a decrease in surface tension and protrusion of the cytoplasm towards the stimulus. Positively charged macromolecules can reduce the negative charge of leukocytes and cause electrostatic instability of their membranes. This can lead to the movement of macromolecules (shortening - lengthening) both in the cytolem and in the cytoplasm.
Depending on the nature of the dominant local process (alteration, exudation or proliferation), three types of inflammation are distinguished.
In alternative inflammation, damage, dystrophy, and necrosis prevail. It is observed mainly in parenchymal organs in the case of infectious diseases that occur with pronounced

intoxication (caseous decay of the adrenal glands or lungs in patients with tuberculosis). Exudative inflammation is characterized by a significant disturbance of blood circulation with the phenomena of exudation and emigration of leukocytes. According to the nature of the exudate, serous, purulent, hemorrhagic, fibrinous, and mixed inflammation are distinguished. If the inflammation covers the mucous membrane, for example, of the respiratory tract or the alimentary canal and the exudate contains a lot of mucus, this indicates catarrhal inflammation. Proliferative , or productive, inflammation is characterized by the predominant proliferation of cells of hematogenous and histogenic origin. In the inflammatory zone, cell infiltrates appear, which, depending on the nature of the accumulated cells, are divided into round cells (lymphocytes, histiocytes), plasma cells , eosinophil cells , epithelioid cells , macrophages . During inflammation, cells with a completed development cycle (mature) die, and mesenchymal cells undergo transformation and differentiation , as a result of which new connective tissue is formed. The organ or part of it is penetrated by connective tissue cords. In the later stages of inflammation, it can lead to cirrhosis.

SIGNIFICANCE OF INFLAMMATION FOR THE BODY

The inflammatory process, like any pathological process, is inherently contradictory. It combines the mobilization of the body's defense forces and damage (injury). Having arisen in phylogeny as an adaptive phenomenon, inflammation has preserved this property in higher animals as well. The body protects itself from the influence of foreign and harmful factors by separating the inflammatory center from the whole body. This prevents the spread and generalization of the inflammatory process, concentrating the fight against the harmful agent in one place. The inflammatory cell not only fixes everything contained in it, but also absorbs toxic substances that circulate in the blood. This is explained by the fact that a unique barrier with one-sided permeability is formed around the cell. Initially, it is created as a result of blockage of efferent lymphatic and blood vessels and due to blockade of extravascular tissue transport. In the future, this barrier is formed due to the proliferation of connective tissue cells at the border between normal and affected tissues. The protective role of the inflammatory barrier is clearly demonstrated in an experiment with strychnine, a lethal dose of which, injected into the inflammatory site, does not cause the death of animals.

Unfavorable conditions for microorganisms are created in the center of inflammation. In this, the main role is played by phagocytes and specific antibodies, as well as enzymes and basic proteins. The healing side of inflammation is especially clearly evident in the stage of proliferation and regeneration.

However, all of the above reflects only one (positive) side of inflammation. The second, opposite, is that inflammation always carries an element of destruction. The fight against the "aggressor" in the zone, inflammation is inevitably combined with the death of one's own cells. In some cases, alteration begins to prevail, which leads to the death of tissue or even an entire organ . Exudation can lead to a disorder of tissue nutrition, enzymatic melting of it, hypoxia and general intoxication.

The idea of inflammation as a pathological process, in which the protective and the actual pathological are in unity and struggle, gives the doctor a guide to action.

Lecture No. 3

Topic: Pathophysiology of heat exchange . Hypo and hyperthermia. Fever: etiology and pathogenesis, stages. **Pathophysiology of tissue growth.** General patterns of tumor growth. Carcinogens. Pathogenesis of tumor growth.

- ***Goal*** Acquaint applicants with the mechanisms of thermoregulation, the work of the center—I-II level.
- the applicant must be able to distinguish the stages of compensation and decompensation of overheating and hypothermia - III level.
- To know the stages of fever and their characteristics - level III.

- To provide applicants with the ability to reproduce in an experiment the model of fever III - IV level.

- Definition of tumors, features of tumor tissue.
- Sources and ways of spreading carcinogenic factors, transmission of some tumor-causing viruses from animals and insects (Berkitt's lymphoma).
- The material of the lecture is aimed at the formation of logical and professional thinking in the students, the doctor's responsibility for the state of the body of patients with benign and malignant neoplasms.

2. **Basic concepts: FEVER, Stages of fever,** temperature curve, Pathogenesis, pyrogens, Tumors, Hayflick's limit , atypia, anaplasia,

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

FEVER

Fever is a typical pathophysiological process, which is manifested by an increase in body temperature in response to the action of pyrogenic factors. In evolution, fever arose as a reaction of the body to infection, and therefore, along with fever, there are other signs characteristic of the infectious process. Intoxication and self-overheating create a complex picture in which the phenomena of damage and protection are combined.

Normally, thermoregulation occurs reflexively. On the periphery (skin, internal organs) there are cold and heat receptors that perceive temperature fluctuations of the external and internal environment and from which information is sent to the thermoregulation center located in the hypothalamus. The neurons contained here are themselves sensitive to both heat and cold. The integration of temperature signals and the temperature of the hypothalamus itself forms effector impulses that determine the level of metabolism, the intensity of peripheral blood circulation, tremors, shortness of breath. Fever begins with the fact that this reflex mechanism changes and the temperature is set at the second, higher level.

EXPERIMENTAL STUDY OF FEVER.

The ability to regulate the constancy of body temperature arose quite late in phylogeny: in animals with a well-developed brain. Therefore, fever can occur only in higher homoothermic animals. It is clearly found in primates and especially in humans. Animals that do not have stable homoothermy respond to the action of pathogenic factors only with a weak and atypical febrile reaction.

In the ontogeny of one or another animal species, the ability to respond with a febrile reaction is formed differently depending on the degree of development of the central nervous system before birth. Animals that are born mature (ungulates, guinea pigs, some types of birds) have the ability to maintain a constant **BODY TEMPERATURE** from the first hours of independent life. Newborns in humans and rats do not immediately acquire this ability, thermoregulation develops in them gradually. Premature babies do not have homoothermy and react to the temperature of the external environment like poikilotherms, easily overheat and cool down. Newborn puppies and rabbits in the first two months of life react with a weak and atypical fever. In children aged 3-4 months, pneumonia occurs with a subfebrile body temperature or without an increase in temperature at all. The absence of fever in young children is explained primarily by the fact that their physical thermoregulation has not yet matured, that is, the ability to quickly and effectively limit heat transfer. They do not develop a fever even with increased heat generation, since the vasoconstrictor reaction of the skin has not yet developed.

ETIOLOGY.

There are infectious and non-infectious causes of fever. In the process of evolutionary development, the febrile reaction was formed primarily as a response to the penetration of microorganisms and their toxins into the body. At the same time, it is known that it can also occur when substances that are not related to the infection enter the body, for example, during blood transfusions, the introduction of proteins and lipids for the purpose of parenteral nutrition.

Pyrogenic substances. Pyrogenic (heat-bearing) substances are substances that, entering the body from the outside or forming inside it, cause fever. According to their origin, pyrogenic substances are divided into exogenous (bacterial, non-bacterial) and endogenous (leukocyte), and according to the mechanism of action, they are divided into primary (inductive) and secondary (real). Primary pyrogens, entering the body, do not yet cause fever, but only initiate this process, awakening their own cells to the formation of protein substances (secondary pyrogens), which, in turn, affect thermoregulation mechanisms and lead to fever. So, primary pyrogens are etiological factors, and secondary ones are pathogenetic.

Primary pyrogens enter the body together with infectious agents and are nothing more than bacterial toxins. Endotoxins of gram-negative bacteria have been best studied in this regard . It was established that they are lipopolysaccharides — complex biopolymers in which three parts are distinguished: two polysaccharide and one lipid. The latter (lipoid A) has the ability to cause intoxication and fever. The study of the pyrogenic properties of endotoxin showed that already in the amount of 0.0001 μg per 1

kg of body weight, it can cause fever in a rabbit . Humans, and among animals, dogs and horses are approximately equally sensitive to the pyrogenic effect of endotoxin.

Interest in endotoxin increased when it was noticed that under its influence in animals and humans, the course of many diseases improves, including tumors, syphilis of the brain, etc. In this connection, pyrogens began to be used in the clinic. The difficulty, however, was that such pyrogens, along with fever, also produced intoxication phenomena in the form of hemorrhagic shock, thrombosis, skin lesions of the type of Schwartzman phenomenon , etc. Therefore, such a technology of pyrogen extraction was developed in order to preserve its therapeutic effect and at the same time eliminate the toxic one. In the end it was possible to do it, but only partially.

Gram-negative bacteria became the starting material for the extraction of pyrogens with medicinal properties . The domestic drug pyrogenal is produced from Pseudomonas earuginosa , Swiss pyrexal — from Salmonella abortus equi . In order to cause a fever in a person, it is necessary to enter about 1 μg of pyrogenal per 1 kg of body weight. An increase in temperature occurs 40-90 minutes after parenteral administration and lasts 6-9 hours.

Recently, pyrogens have been produced synthetically. At the same time, it was established that the biological activity of the substance is determined by the lipid part of the macromolecule (lipoid).

Primary pyrogens can be formed in the body itself, regardless of bacteria (fever during a bone fracture, myocardial infarction, blood transfusion). These substances are formed as a result of damage or destruction of own tissues and affect the body in a similar way to primary exogenous, i.e. bacterial, pyrogens.

PATHOGENESIS.

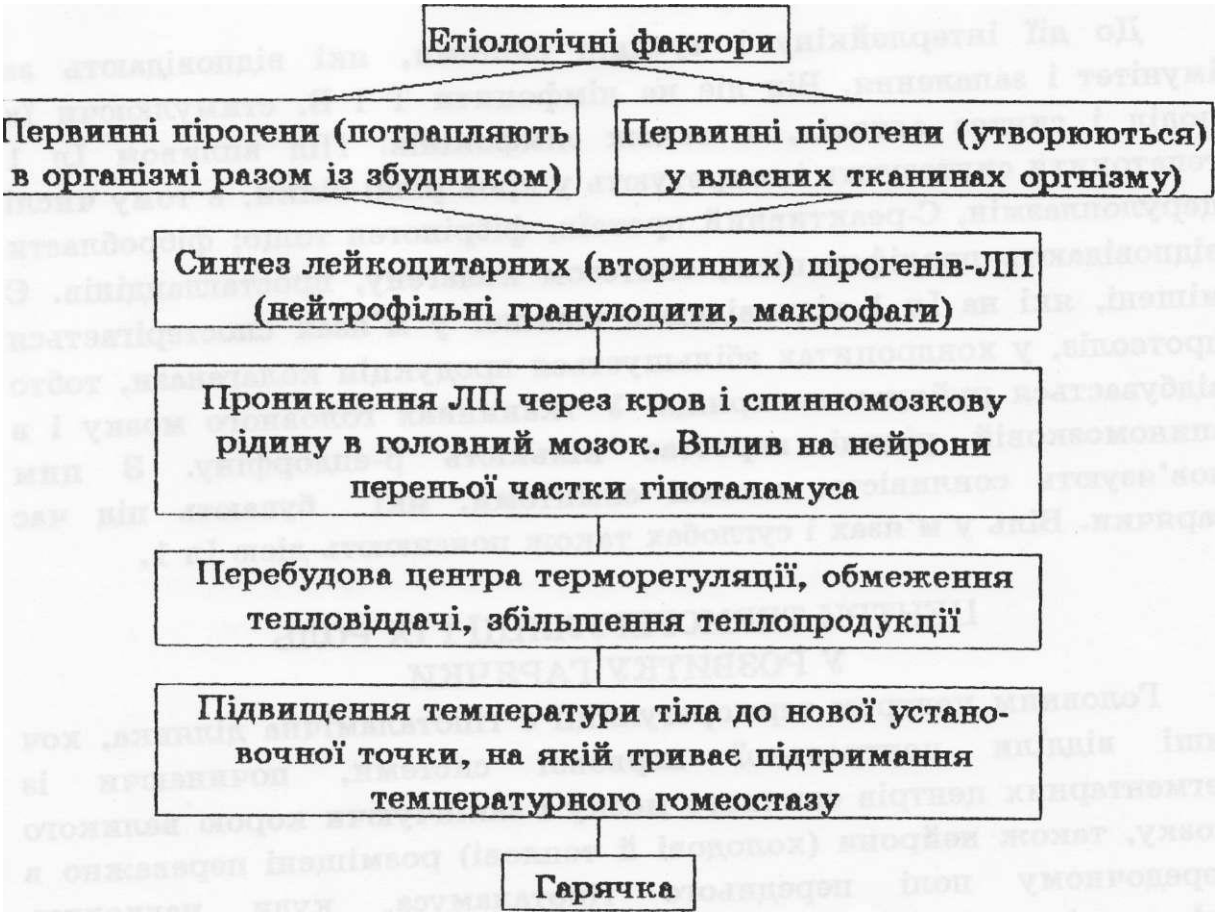
The pathogenesis of fever begins with the fact that secondary pyrogens are formed under the influence of primary pyrogens. This process occurs primarily in macrophages (fixed and free), as well as in neutrophilic granulocytes. The synthesis of secondary pyrogens was shown in experiments in vitro . If a primary pyrogen is added to the cultured leukocytes , then soon a substance appears in the culture fluid, the introduction of which into the body raises the body temperature. When this substance is injected directly into the hypothalamus, where the center of thermoregulation is located, fever occurs even from very small doses.

The synthesis of secondary pyrogens is coded in the leukocyte genome . If formation is blocked with actinomycin D or puramycin , pyrogen synthesis does not occur. Biosynthesis of pyrogens occurs after primary (bacterial) pyrogens act on leukocytes and thereby activate metabolic processes in them. This effect is manifested through receptors on cell membranes or when the toxin enters macrophages by phagocytosis or pinocytosis . This process, obviously, is not strictly specific, since the synthesis of secondary pyrogens can also be induced by other substances, including hormones. So, it is known that in women with a normal menstrual cycle, in the period from ovulation to the first days of menstruation, the body temperature rises by 0.4-0.9 °C. Relative to non-infectious pyrogens, that is, substances that enter the body with sterile material or are formed in organism outside the infectious process (allergy), then the same possibility should be assumed here, i.e. activation of macrophages in the direction of pyrogen synthesis .

Recently, it has been proven that interleukin 1 (IL 1), which is characterized by not only pyrogenic , but also other effects, has the ability to raise body temperature.

Interleukin 1 is a hormone-like protein with a molecular weight of 14,000. It is released by macrophages upon their activation and specifically affects some systems, including the nervous system. Target cells of Il 1, in addition to nerve cells, also include lymphocytes, hepatocytes, fibroblasts, synoviocytes , and myocytes . There is an opinion that there are receptors for Il 1 on the membranes of these cells. Therefore, the release of Il 1 causes not only an increase in body temperature, but also the involvement of other systems in the process, which causes both temperature and non-temperature effects of fever.

Taking into account the above data, the pathogenesis of fever can be shown as follows (Fig . 1).



Together with the causative agent, pyrogens — bacterial toxins — enter the body. They affect macrophages and neutrophil granulocytes, which begin to synthesize Il 1. Il 1 circulating in the blood acts on target cells. Regarding the hypothalamus, where the center of thermoregulation is located, Il 1 does not come into direct contact with the neurons of this center, since it does not penetrate through the blood-brain barrier. However, under its influence, prostaglandins are formed at the level of cerebral arterioles and capillaries Ei and Eg , which pass through the barrier and directly affect the center of thermoregulation. As a result, the set point of this center changes and it maintains the body temperature at a higher level, at which it remains as long as Il 1 synthesis continues.

Fever is a pathological process in which not only the thermoregulation system is involved, but also other systems, primarily the immune system. This is understandable if we consider that fever arose in evolution as a response to infection. The connection

between fever and inflammation also draws attention. It can be said that fever, immunity (allergy) and inflammation are a kind of triad that determines the response to an infectious influence. The connection between these three reactions is so close that they do not exist without each other, and when they occur, one supports the other.

Sensitive systems responsible for immunity and inflammation are also affected by interleukin . It acts on T and B lymphocytes, stimulating their division and synthesis of antibodies, as well as lymphokines . Under the influence of Il 1, hepatocytes synthesize and secrete various proteins into the blood, including ceruloplasmin, C-reactive protein, fibrinogen , etc.; fibroblasts are responsible for proliferation, synthesis of collagen, prostaglandins . There are targets that respond differently to Il 1: proteolysis is observed in muscles, collagenase production increases in chondrocytes , that is, cartilage is destroyed. The amount of (3-endorphin) increases in the tissues of the brain and in the cerebrospinal fluid . Drowsiness, delirious symptoms that occur during fever are associated with this. Pain in muscles and joints is also explained by the effect of Il 1.

THERMOREGULATION CENTERS AND THEIR ROLE IN THE DEVELOPMENT OF FEVER

The main center of thermoregulation is the hypothalamus area, although other departments of the central nervous system, starting from the segmental centers of the spinal cord and ending with the cortex of the cerebrum, as well as neurons (cold and warm) are located mainly in the frontal field of the anterior hypothalamus, which receives information from peripheral (superficial and deep) thermoreceptors. This zone is directly sensitive to temperature fluctuations. The proof of this was the results of research with thermoids — thin tubes that are inserted into a certain center of the brain and pass warm or cold water through them. When passing warm water, there is a reorganization of thermoregulation aimed at removing heat: the rectal temperature decreases. When the brain center is cooled with cold water, the body temperature, on the contrary, rises.

The role of the posterior hypothalamus is that the integration of temperature information and the formation of effector stimuli that control physical and chemical thermoregulation take place here. Destruction of it or the entire hypothalamus makes animals poikilothermic . When the anterior hypothalamus is destroyed, after some time, fever occurs again.

Operations on the central nervous system showed the importance of other departments as well. After cutting the brain above the hypothalamus, the animal retains the capacity for fever. Transection, in which the hypothalamus is separated from the brainstem, deprives the animal of this ability. Finally, when the spinal cord is transected in the thoracic part, the ability to fever is restored after the animal exits the state of spinal shock.

The role of the thermoregulation center is to maintain temperature homeostasis, balancing the processes of heat production and heat transfer. This is possible due to the fact that the thermoregulation center works as a cybernetic device in a precisely set mode and temperature fluctuations (daily) are allowed only within narrow limits from the set point. Therefore, the body of warm-blooded animals is imagined as a biological thermostat, the temperature of which depends on the point at which the thermostat is set, that is, the corresponding center of the brain. This set point can be changed in two cases: under extreme influence (overheating, hypothermia, freezing, hypoxia), when this

mechanism is completely or partially disabled, or under the action of pyrogens, when the setting mechanism is not destroyed, but changes so that the setting point the point moves to a higher level.

The results of subtle electrophysiological studies make it possible to imagine this mechanism as follows. There are three types of neurons in the hypothalamic center of thermoregulation: sensitive to heat, sensitive to cold and "deaf" to temperature fluctuations. It is assumed that the main role is played by the latter. They generate signals of a standard nature, which are a comparison signal for thermosensitive neurons. With any change in body temperature, it returns to a normal level thanks to "deaf" neurons.

There are other explanations of the temperature setting mechanism, according to which the set point is determined by the function of heat-sensitive and cold-sensitive neurons. It was established that they are of two types — with a linear and a non-linear function. Thermosensitive neurons with a linear function are neurons in which the number of depolarizations is directly proportional to the change in body temperature. Thermosensitive neurons with a non-linear function respond disproportionately to changes in body temperature, for example, reducing the increase in the number of depolarizations when the body temperature increases. The set point of temperature homeostasis is formed by neurons with a non-linear function and it is they who are affected by the true pyrogen of leukocytes. Thermosensitive neurons with a non-linear function establish a new, higher, set point of temperature homeostasis. Normal temperature is perceived as low. Then the paths of heat return are blocked, the body temperature rises and remains at that level for some time (during the fever period).

In addition to pyrogens, other substances also play a role in the formation of a febrile reaction. First of all hormones. In people with reduced function of the thyroid gland or pituitary gland, concomitant infectious diseases are accompanied by less severe fever. At the same time, it should be taken into account that thyroxine has a dissociative effect on oxidation and oxidative phosphorylation in tissues.

Glucocorticoids (hydrocortisone) inhibit the development of a febrile reaction, apparently due to the fact that they suppress metabolic processes in leukocytes, including the formation of pyorogens in them .

STAGES OF FEVER, THE RELATIONSHIP BETWEEN HEAT PRODUCTION AND HEAT DISCHARGE.

Three stages are distinguished in the febrile process: increase in temperature (st . incrementi); standing temperature at an elevated level (st . fastigii), lowering the temperature to the initial level (st . decrementi).

Stage of temperature increase. The increase in temperature in this stage reflects the restructuring of thermoregulation: a change in heat production and heat output. At the same time, heat production exceeds heat output. The main importance is the limitation of heat transfer, which is not only more effective in understanding the rate of body heating. And it is more economical for the body, as it does not require additional energy consumption.

Heat transfer decreases due to the narrowing of peripheral vessels and a decrease in blood flow to the tissues, at the same time, sweating is inhibited and evaporation decreases; in animals, there is a contraction of the muscles of the hair follicles and

ruffling of the wool, which increases thermal insulation. The human equivalent of this reaction is goosebumps.

In second place in the increase in body temperature during fever is an increase in heat production due to the activation of metabolism in muscles (contractile thermogenesis) against the background of increased muscle tone and muscle tremors. Muscle tremors are associated with spasm of peripheral vessels. Due to a decrease in blood flow, the temperature of the skin sometimes drops by several degrees. Thermoreceptors are excited, there is a feeling of cold — chills. In response, the thermoregulation center will increase impulses to motor neurons — tremors occur. At the same time, non-contractile thermogenesis increases , that is, the generation of heat in organs such as the liver, lungs, and brain. This is a consequence of the trophic effect of nerves, when enzymes are activated, oxygen consumption and heat generation increase.

Humoral factors can play a role in the imbalance of thermal homeostasis. It is known that some bacterial toxins are able to uncouple oxidation and oxidative phosphorylation and thereby INCREASE the generation of heat. This additional thermogenesis can accelerate the temperature rise in the first stage of fever.

The stage of standing temperature at an elevated level. After the temperature has risen to a certain level, it is kept at this level for some time (days, hours). As the heat transfer increases, the temperature does not rise further. Heat transfer is carried out due to the expansion of peripheral vessels; pale skin becomes hyperemic , hot to the touch. There is a feeling of heat.

Maintaining the temperature at an elevated level is explained by the fact that under the influence of leukocyte pyrogen, the set point of the thermoregulation center changes. At this level, the mechanism of maintaining temperature constancy with aharteric ones is restored oscillations in the morning and evening, the amplitude of which is much larger than normal.

According to the degree of increase in body temperature in the second stage of fever, the following types are distinguished: subfebrile — an increase in temperature up to 38°C; high — 39-41°C; hyperpyretic — over 41 °C.

The new level of temperature, its fluctuations during the day are determined by a number of factors, among which the number of pyrogens and the sensitivity of thermoregulation centers to them will be of decisive importance. In addition, the power of the heat removal system, the accuracy and reliability of functional and trophic innervation, the formation of disconnecting substances and, finally, the presence of a reserve of energy material in the body, primarily fat, are important. Exhausted people can have infectious diseases without fever. It develops quickly in children, in elderly people

— slowly, to a low level.

The stage of lowering the temperature. After the pyrogens cease to act, the thermoregulation center returns to its previous state, the temperature setpoint drops to a normal level. The heat accumulated in the body is removed due to the expansion of skin vessels, profuse sweating and rapid breathing. The decrease in temperature can be gradual, lytic (within several days), or rapid, critical. In the latter case, a very sharp

vasodilatation can occur and, when combined with intoxication, a life-threatening collapse can occur.

TYPES OF TEMPERATURE CURVES.

The temperature curve during fever consists *of* three parts

— rising, standing and falling, however, each of them, like the curve as a whole, can have its own features that give the doctor information about the patient's condition and have differential diagnostic value.

The nature of the temperature curve can be influenced by the characteristics of the pathogen, for example, the cyclical nature of its development in the blood. In this regard, the temperature curve in patients with malaria (febris intermittents). So, with prolonged malaria, fever attacks occur every other day. During an attack, the temperature rises sharply and remains at a high level from 30-60 minutes to 2-3 hours, and then decreases to the initial level and even below it.

The dependence of the temperature curve on the causative agent is also clearly visible on the example of fever with typhoid fever (febris recurring). The typhus spirochete is phagocytosed by macrophages and reproduces in them. As spirochetes accumulate in cells , they break through the barrier of mononuclear phagocytes and enter the blood. This causes another bout of fever, which lasts 6-8 days, after which the temperature drops critically and a period of apyrexia begins , which also lasts 6-8 days. Attacks can be repeated again.

Fever during croup pneumonia has the character of a constant (febris continue). At first, the temperature curve rises sharply, then it seems to reach its maximum and is maintained for 7-9 days, fluctuating within one degree, and then sharply decreases. With sepsis (febris hectica) daily temperature fluctuations reach 2-3 °C

Febrile biorhythms depend not only on the causative agent, but also on the patient's body, on the ability of his immune system to respond to anigenic stimuli.

It should be noted that recently, as a result of the widespread use of antibiotics, temperature curves have largely lost their typicality.

HYPERTHERMIA AND ITS DIFFERENCE FROM FEVER.

Overheating or hyperthermia should be distinguished from fever. Both processes combine only the final result — an increase in body temperature, and their mechanisms are directly opposite. Overheating is not related to the action of a pyrogenic substance. The body temperature rises as a result of either an external influence that limits heat transfer, or a primary malfunction of the thermoregulation center. The first, i.e. overheating of the body as a result of retention of heat in it, is observed in factories with high ambient temperature or in areas with a hot climate. Overheating in these cases is facilitated by the increase in heat production in connection with muscle work.

Compensation for overheating is aimed at overcoming difficulties in allocation and maintaining thermal homeostasis.

Since at an ambient temperature of about 33°C, heat transfer by radiation and convection practically stops, this process is carried out only through the evaporation of sweat and moisture during breathing. However, with high air humidity, this path is also

blocked and all compensatory mechanisms are ineffective. The body temperature rises, but it is not a fever.

The body temperature can rise even without the influence of external factors, as a result of a primary malfunction of the thermoregulation center: in case of pathology of the brain, tumors, injuries, hemorrhages , infections, etc. In the clinic, this phenomenon is known as " hyperthermic syndrome".

CHANGES IN ORGANS AND SYSTEMS DURING FEVER.

In addition to disorders of thermoregulation, other disorders are also observed during fever, primarily metabolism, activity of the cardiovascular and respiratory systems, secretory and excretory functions. A complex of symptoms arises, in which it is necessary to distinguish what depends on pyrogen , what on interleukin 1 and what on the disease itself (pneumonia, heart attack, hepatitis).

The most obvious are changes in the circulatory system. According to Liebermeister's rule , an increase in body temperature by 143 is accompanied by an acceleration of the pulse by 8-10 beats per 1 minute. Since local warming of the pacemaker is accompanied by an acceleration of heart contractions, tachycardia during fever is explained in the same way. In addition, it is important to increase the tone of sympathetic nerves. The stroke and minute volume of the heart increases. In the first stage of fever, blood pressure may rise. There is a narrowing of the vessels of the skin and the expansion of the vessels of the internal organs. In the third stage, with a critical decrease in body temperature, collapse may occur due to a sharp decrease in arterial tone.

Tachycardia during fever does not always occur. With some infectious diseases, the body temperature rises and at the same time bradycardia is observed. An example is typhoid, as well as typhoid — diseases that progress with significant intoxication, when the heart reacts not so much to high temperature, but to the action of toxic substances of exogenous and endogenous origin.

External breathing in the first stage of fever slows down a bit. After reaching the maximum temperature, breathing accelerates, sometimes two or three times. As the depth of breathing decreases, pulmonary ventilation does not undergo significant changes. Acceleration of breathing (tachypnea) is a consequence of brain temperature,

During a fever, ***the digestive system undergoes significant changes — the secretion of saliva decreases (the tongue is dry, coated),*** the amount and acidity of gastric juice increases , and appetite is lost. However, the degree of these phenomena is not the same and largely depends on the nature of the disease. For example, during the flu, these changes are less pronounced than during typhoid fever.

Comparing the action of highly purified bacterial pyrogens with the changes that occur during the natural development of an infectious disease, P.M. Veselkin came to the conclusion that changes in the digestive system occur not so much due to fever, but as a result of starvation, intoxication, and non-thermogenic effects of bacterial toxins.

Fever is accompanied by changes ***in the endocrine system —*** the pituitary-adrenal system is activated, signs of stress are observed. With infectious fever, the release of thyroid hormones increases, which leads to an increase in basic metabolism.

in ***the central nervous system*** . A slow a-rhythm appears on the electroencephalogram, which is characteristic of cerebral cortex inhibition. When

pyrogens are injected, a person may experience insomnia, a feeling of exhaustion, fatigue, and a headache. In infectious diseases, these phenomena are more pronounced. Hallucinations, loss of consciousness, dizziness are possible. Since these phenomena are not so much associated with an increase in temperature, it is obvious that they are associated not so much with an increase in temperature as with intoxication.

The main metabolism during fever is increased, although there is no direct connection between the activation of the metabolism and the increase in temperature. The respiratory coefficient in the first stage of fever approaches unity, which indicates an increase in the oxidation of carbohydrates, and later - fats, especially when carbohydrate reserves are already exhausted. In such cases, oxidation does not occur to the end products and ketone bodies accumulate in the cortex. Acetone is excreted in the urine. If a patient with fever is given a sufficient amount of carbohydrates in an easily digestible form, then these disorders can be stopped.

In some infectious diseases, ***protein metabolism is disturbed.*** The nitrogen balance becomes negative, the urinary excretion of products of nitrogen metabolism, in particular urea, increases, which indicates an increase in the breakdown of proteins. However, this is not always the case . Thus, during the flu, as a rule, it is not disturbed, and at the same time, some infectious diseases that run without fever are characterized by a sharp increase in protein oxidation. This indicates that the cause of the disturbances is not in fever, but in the degree of intoxication, in the development of inflammatory and dystrophic changes in the tissues, finally, in starvation due to loss of appetite and malabsorption in the intestines.

Changes in water and mineral metabolism are characteristic of fever . In the first stage, an increase in diuresis is observed due to an increase in blood pressure and blood flow to the internal organs. In the second stage, as a result of the increased synthesis of aldosterone, sodium and, therefore, water is retained in the tissues. Diuresis decreases. In the third stage, the removal of chlorides, in particular sodium chloride, increases, water leaves the tissues, diuresis and sweating increase.

TUMOR

A tumor is a top pathological process, which is an unregulated, unlimited growth of tissue, unrelated to the general structure of the affected organ and its functions.

A tumor occurs in the body as a result of the transformation of normal cells into tumor cells, in which the regulation of division is disturbed, there is no inhibition of cell division or it is ineffective, which causes the unstoppable proliferation of tumor cells, as well as when self-sustaining stimulation of division occurs in cells.

Tumor tissue is characterized by unlimited growth. This process ends only with the death of the organism. In tissue culture, growth is maintained indefinitely, unlike normal tissue, due to the fact that there is no " Hayflick limit ". The ability of tumor cells to multiply indefinitely is inherited as a dominant feature of somatic heredity and is manifested not only in the body, but also in the culture of tumor tissue, as well as in tumor transplantation.

The tumor grows "by itself", that is, it increases due to the reproduction of a single malignant cell.

Tumor tissue differs from the primary tissue from which it originates in structure, biochemical , physicochemical and other properties. These changes express *anaplasia* - a

return to the embryonic state, as well *metaplasia* - acquiring the properties of another tissue.

Tumor growth can be *expansive* and *infiltrative.* With expansive growth, the surrounding healthy tissue moves as the tumor grows, with infiltrative growth, tumor cells grow between normal cells and through the vascular wall. Getting into the lymph or blood, they are transferred to other organs and can form new growth centers *(metastases).* Expansive growth is characteristic of benign tumors, and infiltrative growth with the formation of metastases is characteristic of malignant tumors.

EXPERIMENTAL TUMOR REPRODUCTION

Despite the fact that the tumor as a disease has been known for a long time, its experimental reproduction has not been successful for a long time. That is why the experimental reproduction of this pathological process began at the beginning of the 20th century. a huge scientific achievement. Experimental tumor models make it possible to study the causes and pathogenesis of the tumor process, to develop new methods of its prevention and treatment of patients.

Methods of experimental modeling are tumor induction, explantation and transplantation Tumor *induction by chemical substances.* In 1775, a surgeon at the London Percival Hospital Pott described an occupational malignant disease - skin cancer of the scrotum in soot sweepers. However, despite the obvious connection between cancer of soot shakers and contamination of the skin with soot and tar, attempts to reproduce the hook tumor in an experiment were unsuccessful for a long time. In 1915, Japanese scientists Ita Kawa and Yamagiwa were able to induce tumors in animals for the first time. For six months, they lubricated the skin of rabbits with coal tar,! only then did the animals develop skin cancer. Later, carcinogenic substances were isolated in their pure form, the carcinogenicity of substances in their pure form was established, and the carcinogenicity of substances belonging to different classes of chemical compounds was established . *Tumor induction by viruses.* In 1908, Ellerman and Bunt modeled leukemia in chickens for the first time using a cell-free filtrate from leukemic leukocytes. It is obtained by filtering the extract of crushed tumor tissue through porcelain filters. In 1910 Raus , using a cell-free filtrate obtained from a chicken sarcoma, caused the development of sarcoma in healthy chickens. This was the first evidence of the viral etiology of leukemia and tumors.

However, in the following decades, it was not possible to detect tumor-causing viruses in mammals, except for Shoup's papilloma and Bittner's milk factor . IPope discovered warty growths on the skin (papillomas) in some rabbits , which were successfully transplanted into healthy animals with the help of cell-free filtrate. The milk factor was discovered by Bittner (1936). There are lines of mice highly cancerous (with a high incidence of breast cancer) and low cancerous . However, if newborn mice are taken from the female of the high cancer line after their first feeding and given to the male of the low cancer line for feeding , the incidence of cancer in them will decrease dramatically. Conversely, when a female with a high cancer line feeds mice from a female with a low cancer , the frequency of tumors in

them will increase significantly. Bittgner proved that there are high levels of cancer in the milk mice is a factor that causes mammary gland cancer in the offspring. But cause acellular the filter failed to cause cancer in adult mice . Only in 1950, L. Gross , after many unsuccessful attempts to induce leukemia in adult mice , first introduced cell-free filtrate from leukemic blood cells to newborn mice and induced leukemia in them. Therefore, direct evidence of the viral etiology of tumors in mammals was obtained, and 40 years of failures after the discovery of Raus are explained by the resistance of the body of adult mammals to viruses in which oncogenes have now been discovered .

Tumor induction by physical factors. It is possible to reproduce the tumor with the help of an inosizing agent radiation , including X-ray , radioactive isotopes, and ultraviolet radiation.

Tumor explantation is the growth of a tumor in a tissue culture by an organism. This method was successfully applied by O. D. Timofeevsky . A tissue culture taken directly from an animal or human tumor is called primary. In addition, the laboratories have a large number of stamps of tumor cells, which are constantly pasteurized and whose properties are well studied, which allows experiments to be carried out on the same material. Tissue culture makes it possible to induce a tumor outside the body with chemical carcinogens and oncogenic viruses. This method is especially valuable because it is possible to study the induction of tumors and tumor-causing viruses on the tissues of the human body. Passivated or induced tumor cells in tissue culture, when implanted in a healthy animal, grow in its body and form a malignant tumor.

Tumor transplantation. For the first time in 1876, M.O. Novinsky successfully transplanted a tumor of an adult dog into puppies. In fact, this study marked the beginning of experimental oncology. The method of transplantation is widely used even today. There are strains of pasteurized tumors with well-studied properties: Ehrlich's ascites carcinoma in mice , chicken Raus's sarcoma , Jensen's sarcoma in rats, Jaun -Pierce carcinoma in rabbits , etc. Allogeneic tumor transplantation (i.e., tumor transplantation into non-inbred animals of the same species) is successful. whereas the same transplantation of normal tissues without immunosuppression fails. The reasons for successful transplantation of allogeneic tumors are antigenic simplification of tumors, as well as their immunosuppressive effect. The injection of a small amount of tumor cells (400,000) leads to the suppression of the immune system and the growth of the tumor (remember that 1 ml of blood contains 5 ml of erythrocytes). Only the injection of an even smaller number of tumor cells can lead to immunization and subsequent rejection of tumor transplantation.

ETIOLOGY

The causes of tumor development are various factors capable of causing the transformation of a normal cell into a tumor. They are called carcinogenic or blastomogenic . Chemical, physical and biological factors, different in nature and in the way they affect the body, but the same in their ability to disrupt the regulation of cell division, form one etiological group.

Carcinogenic factors have the following properties.

1. Mutagenic action - the ability to directly and indirectly affect the genome of a cell , which leads to mutations. Chemical substances (hydrocarbons, nitrosamines , etc.), physical

(ionizing radiation) and biological (viruses) factors have this property. Viruses can cause tumors also through an epigenomic pathway. The site of interaction of chemical carcinogens with nucleic acids is obviously guanine. The ability to penetrate through external and internal barriers. Thus, upon contact with the skin, tumor development is caused only by those potential chemical carcinogens that penetrate through the keratinized epidermis . Since biological membranes consist of lipoproteins, fast-dissolving substances, which include carcinogenic hydrocarbons, penetrate primarily through them.

2. The dosed effect of carcinogenic factors, which provides a slight damage to the cell, which enables it to survive. In this regard, the dose and toxicity of the carcinogenic factor are important for achieving a carcinogenic effect . A small increase in the dose leads to an increase in the number of tumors, the number of animal diseases and a shortening of the tumor development period. A further increase in the dose is accompanied by the predominance of the toxic effect and the death of the animals before a tumor is formed. Reducing the dose of the carcinogen made it possible to establish: 1) there are no subthreshold carcinogenic doses (in experiments, the carcinogenicity of very small doses is revealed, but at the same time, the duration of the appearance of new tumors is prolonged); 2) the action of carcinogens is irreversible; 3) carcinogens are characterized by the effect of summation and calculation, a similar dependence is observed under the action of ionizing radiation: large doses cause radiation and tissue death, and only relatively small doses create conditions for the emergence of tumors.

The action of viruses during an abortive course, and not in the case of an acute infection (cell death), most often causes carcinogenesis. The probability of carcinogenesis increases with the duration of exposure to the carcinogenic factor .

3. In organs and tissues with different characteristics of permeability and metal metabolism , conditions can be created that are favorable for the manifestation of carcinogenicity of some factors and unfavorable for others. This can explain the existence of organotropic carcinogens.

4. Carcinogens inhibit tissue respiration and immune response.

Enhanced tumor formation under the influence of several carcinogenic factors (syncarcinogenesis). Sometimes factors that are not carcinogenic themselves can increase the effect of carcinogens. Such a phenomenon is called cocarcinogenesis , and the factors that cause it are called cocarcinogens . *Chemical carcinogens.* After 15 years of Christmas experiences Yamapva and Ishikawa in 1930. Cook, Hewitt and Haiger obtained 50 g of chemically pure 3,4- benzpyrene from 2 tons of coal tar , which turned out to be an active carcinogen 1, 2, 5, 6- dibenzanthracene (DBA). Since then, the study of chemically pure carcinogenic substances began. The carcinogenicity of many compounds belonging to different classes was established .

Polycyclic and aromatic hydrocarbons (surfactants). These include 3,4-benzigyrene, DBA and 9,10-dimethyl-1,2-benzanthracene (DMBA). An active carcinogen - methylcholanthrene was obtained by processing bile acids . The synthesis of this carcinogen first suggested the possible carcinogenicity of some biological products produced by the body itself, which was later confirmed.

Carcinogenic surfactants mostly show a local carcinogenic effect: injected under the skin,

they cause sarcoma, applied to the skin - cancer. In the case of introduction, which ensures the spread of the carcinogen in the body, surfactants cause the formation of tumors in those organs where they accumulate: when secreted with milk, tumors of the mammary glands are formed, with urine - tumors of the kidneys and renal pelvis, with sebaceous glands of the skin - skin tumors.

Some surfactants are very strong carcinogens: 0.2 - 0.5 mg of DMBA when injected subcutaneously into mice caused the development of tumors in almost all animals. A more active carcinogen is 20-methylcholanterene.

Using the methods of quantum organic chemistry, Pulman determined the density of the electron cloud in the molecular structures of surfactants. It turned out that when any derivative of anthracene or phenenthrene has carcinogenic activity, an increased density of the electron cloud is observed near a certain radical in the same place of the main cyclic structure, which reaches 1-2 e. This zone in the hydrocarbon molecule was called the K-region (from the German Krebs - cancer). Further, it was theoretically calculated in which derivatives of the anthracene series the electron density in the K region has a value corresponding to carcinogenicity . Experimentally, this calculation was confirmed mainly for the anthracene and phenanthrene series.

Carcinogenic surfactants are very common in the human environment because they are often products of incomplete combustion. Surfactants are formed at a temperature of 400-600 °C (the burning temperature of tobacco in a cigarette), are contained in smoke and tobacco resin, in burnt oil in exhaust gases, in smoked products, as well as *in* petroleum bitumen and asphalt. In the rats that were on the asphalt highway during the experiment , lung tumors developed in most cases compared to those that were on the field road.

During long-term follow-up of people who smoke, it was found that the incidence of cancer of the lungs and upper respiratory tract in them is proportional to the number of cigarettes smoked with a latent period of 10 years. It is several tens of times higher in smokers compared to non-smokers.

Carcinogenic *aminoazo compounds* and *amines* have pronounced organotropy . Dimethylaminoazobenzene (DAB) experimentally causes liver cancer in 80% of cases, regardless of how it entered the body. A similar bottom is caused by orthoaminoazotoluene . B- Naphthylamine causes bladder cancer in humans and animals. The organotropy of carcinogenic substances is explained by the formation of active compounds from less active precursors in the affected organ . The carcinogenicity of β- naphthylamine is manifested in the action of its metalbolites - 2-aminonaphthol-i and *2*- naphthyloxyamine .

nitrosamines - was discovered . A feature of these substances is also organotropy , which can change due to relatively small rearrangements in the molecule. Thus, diethylnitrosamine mainly causes cancer of the liver and esophagus, methylnitrosourea - brain tumors, phymethylnitrosourea - tumors of the brain and peripheral nervous system.

Nitrosamines are formed in the human stomach from non-carcinogenic precursors (nitrites and amines) in the presence of hydrochloric (hydrochloric) acid. Nitrates, such as sodium nitrate, and amines (amino acids, amidopyrine), entering the body with food, form nitrosamines , causing 80-100% of experimental animals to develop tumors.

Recently, many *carcinogens of biological origin have been discovered.* They are produced

in the body, occur in the composition of food and among substances used in medicine and in production. *Aspergillus fungus flavum* synthesizes aflatoxin - a substance that has pronounced carcinogenic properties. The doses of aflatoxin that cause the development of liver tumors are very small - lower than the doses of azo dyes such as DAB. In the rainy summer, the entire crop of groundnuts (peanuts) is infected with a fungus that produces aflatic acid . The fungus also parasitizes corn, rice, eggs, powdered milk. Aspergillus is even more common mdulaiis , which produces carcinogenic Sterigmatocystin .

Since the mechanism of carcinogenesis is associated with disruption of the regulation of cell division, it can be assumed that substances or factors that stimulate cell division under normal conditions are capable of disrupting its regulation under pathological conditions . This applies primarily to *hormones.* Gonadotropic hormones of the pituitary gland cause the proliferation of follicle cells in the ovary. Estrogens , produced by these cells according to the principle of feedback, inhibit the production of follicles . After the transplantation of the ovary into the spleen with the simultaneous removal of the second ovary, the transplanted ovary is constantly subjected to intensive stimulation with folitrosh , which causes the development of a tumor in it in 80% of cases. This indicates that own hormones, if they are formed in larger quantities and attack the target organ more than usual, can cause the formation of a tumor in it.

We will prove that the cause of the development of spontaneous tumors found in animals are *tumorigenic viruses,* and mainly those that contain RNA.

The classification of oncogenic viruses takes into account the following characteristics: the type of nucleic acid that is part of the virus (RNA or DNA), the place and method of reproduction of the virus in the cell, *the form.* There are four groups of viruses.

1. RNA - including spiral-shaped viruses that multiply in the cytoplasm, mice and chicken leukemia viruses, Rous sarcoma, Bittner's milk virus , etc.
2. RNA - contained viruses of polyhedral form.
3. Viruses of both of these groups, which contain RNA, are called oncornaviruses (oncogenic, containing RNA), or retroviruses (in connection with the transmission of information in the reverse direction - from RNA to DNA). DNA - contained viruses of polyhedral shape. Reproduce in cell nuclei. These include rabbit papilloma viruses , polyomas , human warts, and monkey vacuolating virus - SV40. The properties of these viruses are so typical for the entire group that they are united under the general name of raroua , which comes from the initial letters of the names of tumors and functional changes (papilloma , polypoma , vacuolisation).
4. Large DNA- containing viruses. They multiply in the cytoplasm, forming characteristic cellular inclusions. This group includes Shawpa fibroma virus, Yaba virus , and molluscum contagiosum virus. All of them are very similar to the smallpox virus and infect mostly benign tumors.

Of great interest is the polyoma virus , studied in detail by Stuart and Eddy . This virus contains a single DNA molecule in the form of a double ring or a double linear molecule. It can cause about 27 types of tumors in various tissues in seven species of mammals (mice , rats, rabbits , hamsters, etc.). When you introduce the virus to newborn animals, the morbidity reaches 100%. With age, sensitivity to the virus decreases: if the virus is injected

into mice after 14 days, tumors do not develop. Viral DNA capable of inducing tumors can be isolated from the blood of infected animals.

Among the tumors that form in humans and are caused, apparently, by a virus, Burkigt's lymphoma , which affects the submandibular lymph nodes in children, is of interest. It is common in lowland areas of Africa. Such an epidemiological feature is usually associated with the presence in the zone of some carrier of infection, in this case, apparently, one of the mosquito species .

The connection of viruses with the occurrence and development of some common human tumors has been established : herpes virus and cervical cancer; hepatitis B virus and hepatocellular carcinoma (liver cancer that originates from hepatocytes); adenoviruses and tumors of the epithelium of the upper respiratory tract, with which the Epistein-Barr virus (nasopharyngeal tumors), previously identified as the causative agent of Burkitt's B-cell lymphoma, was also associated . For the first time, a retrovirus (onco - RNA C-type) was isolated from leukemic cells of people suffering from a form of T- lymphocytic leukemia - human lymphoma. The virus is called HTLV (from the English Human T. Lymphoma vims). This T-cell leukemia is an infectious disease of people, infection occurs during blood transfusion . There is a clear connection between oncogenic DNA- containing papilloma viruses and tumors of human genital organs.

R. Huebner and D. Todaro experimentally proved that oncornaviruses in DNA form are in the chromosomes of normal cells. However, they do not show their effect, possibly due to the function of cell repressor genes that suppress the viral genome. In the event of, for example, chemical carcinogens , this inactive DNA (provirus) begins to function as part of the cell's genome , causing the transformation of a normal cell into a tumor cell.

Physical carcinogens. Physical factors such as inducing and ultraviolet radiation, possibly thermal energy, ultrasound have *a carcinogenic effect.* In addition, physical factors can play the role of syn or cocarcinogens .

The carcinogenic effect of ultraviolet radiation was observed in an experiment with animals. Daily exposure of laboratory rats to the bright sun for five hours led to the development of skin tumors in many animals after 10 months. Often, the tumor occurs under the influence of X-ray radiation and after the introduction of radionuclides into the body . Occupational tumor diseases caused by exposure to ionizing radiation are observed in humans: cancer in radiologists, lung cancer in miners who work in mines with radioactive ores.

of the atomic explosions in Hiroshima and Nagisaki were tragic . Among 1B thousand residents In Hiroshima , who were near the epicenter of the explosion and remained alive, the incidence of leukemia increased significantly.

carcinogenic factors with other chemical and biological factors is of interest . It was found that the simultaneous action of ionizing radiation and chemical carcinogens in low doses leads to an extremely strong induction of tumors, disproportionate to the doses of these factors, which result in tumor development only in a small number of cases when acting separately.

The carcinogenic role of long-term mechanical impact on tissue has also been established. In 1948, B. Oppenheimer , E. Oppenheimer and Stone found that rats whose kidneys were

wrapped in cellophane to create renal hypertension developed sarcoma. Implantation of plastic plates showed that near plates measuring 0.5x0.5 cm and more, malignant connective tissue tumors were induced , while the administration of powder from this plastic did not cause the formation of tumors. Apparently, metal or plastic plates prevent the completion of the proliferative stage of inflammation, which leads to an excessive accumulation of proliferative inducers that cause tumor formation.

PATHOGENESIS.

Three stages are distinguished in the pathogenesis of tumor growth: transformation of a normal cell into a tumor (initiation), promotion ("incitement") and tumor progression.

Transformation consists in the acquisition by the incoming normal cell of the ability to multiply indefinitely and pass this ability on to daughter cells as an inheritance. Transformation can occur, apparently, in two ways - mutational and epigenomic . Both ways constitute a mechanism of disruption of the regulation of cell division. Therefore, understanding the mechanisms of carcinogenesis is directly related to the central problem of modern cell biology - the essence of cell division and regulation of this process.

The leading biochemical process that ensures cell division is DNA replication of the entire cell genome in phase 8 of the mitotic cycle. This process is carried out by a multi-enzyme complex and begins with the appearance of a special initiator of cell division in the cell in the G1 phase. The initiation of cell division and the start of DNA reduplication depends on protein synthesis in the G1 phase. Cycloheximide, an inhibitor of protein synthesis introduced during this period, blocks the beginning of DNA synthesis, and introduced later does not affect the reduplication that has begun.

The appearance of the initiator in the cell and the start of cell division are the result of the depression of the gene encoding this initiator. Therefore, ensuring the reiulation of the function of the gene - the initiator of cell division makes it possible to regulate the reproduction of this cell. The limitation of a normal cell in the number and speed of division is explained by the fact that each cell has its own division regulation system consisting of special regulatory genes.

By hypothesis Hughes , the gene regulation of division is carried out in each cell by a system that consists of three regulatory genes. The repressor 1 gene encodes repressor 1, which stops the function of the gene - the initiator of cell division. In turn, gene- repressor 1 is under the control of gene- repressor 2. Gene- repressor encodes repressor 2, which stops the function of gene- repressor 1. At the same time, the synthesis of repressor 1 stops and the gene-initiator of cell division is activated. An initiator of cell division appears, capable of turning on the DNA reduplication mechanism of the genome . However, under normal conditions, this does not happen, because the components of the initiator of cell division are able to repress the repressor gene 2. Therefore, the regulatory system has a feedback loop that ensures its autonomy and thanks to which the regulation is normally set to prevent cell division.

For cell reproduction, presence in the genome is required factor that prevents the repression of the gene- repressor 2 by the component of the initiator of cell division or the

repression of the gene-initiator of cell division by the repressor 1. If this factor is not present, the system of regulatory genes turns off the gene-initiator. Cell reproduction stops. The essence of carcinogenesis can be imagined on the basis of Hughes' scheme of cell division regulation .

Mutational carcinogenesis. Suppose that a mutagenic factor caused a disruption in the repressor 1 gene and an active repressor 1 cannot be synthesized. In this case, the cell division initiator gene is inhibited and DNA replication begins. Cells formed as a result of division do not have the repressor 1 gene, as a result of which the cells continue to replicate DNA, and during division, a family of cells is formed, capable of unlimited uncontrolled division. Obviously, these are tumor cells.

Similarly, mutations in other genes of this regulatory system can also lead to unlimited cell proliferation, for example, a mutation in the gene that encodes the initiator of cell division, as a result of which it becomes inaccessible to the inhibitory effect of repressor gene 1.

Along with the mutational one, the following is possible *epigenomic carcinogenesis, which is* characterized by the acquisition of tumor properties by a normal cell due to the influence on the cell genome of factors that do not belong to the genome of a given cell and do not cause a mutation, but create a persistent violation of the normal regulation of the genome , which leads to unlimited growth.

Epigenomic influence, which is transmitted from generation to generation, can be formed, for example, under the influence of a virus that infects the original cell and enters each newly formed cell during mitosis. Suppose that among the small number of genes in the viral genome there is a gene (oncogene Hübener and Todaro), which carries the code for the cellular repressor gene 2. The vios repressor gene 2, however, does not have a code through which the initiator of cell division produced in the cell would inhibit its function, as is the case with a normal cellular repressor gene 2. In this case, there is no feedback with the viral gene. In the cell, repressor 2 will be synthesized on the non-repressed viral gene- repressor 2, which is capable of turning off the work of the normal gene- repressor 1, as a result of which the synthesis of the initiator of cell division is inhibited and the cell begins to divide. The resulting cells contain a viral genome that enters them during mitosis from the original cell and supports the disruption of regulation of cell division and subsequent generations of cells. There is evidence that oncogenes of polygenic viruses are indeed identical with cellular growth factors. Moreover, a cell division repressor gene called Rb was found in the cells of the retina, and the hereditary defect or inhibition of which leads to the development of a malignant tumor of the retina - retinoblastoma in a child .

Mutational and epigenomic mechanisms of carcinogenesis may be related. The cell has special regulatory genes that repress the genome of the tumor-causing virus. So, a mutation can happen to a cell's repressor gene, as a result of which an oncogene is activated of a tumor-causing virus that has gotten out of control, and an epigenetic transformation of the cell takes place. Thus, chemical and physical factors can not by themselves cause transformation, but contribute to the activation of viral carcinogenesis.

The role of viruses in carcinogenesis. In 1945, L.O. Zilber proposed a plausible genetic theory of the emergence of tumors, according to which the mechanism of tumor transformation consists in the fact that the genome of the virus penetrates the genome of the

cell. Then Huebner and Todaro showed that oncogenic C-type viruses are found in healthy tissues of animals of various species and are transmitted vertically, that is, through the zygote. However, a tumor is not formed, probably because in the process of evolution, the body has developed genes that repress the viral genome.

To embed the genome into the genome of the cell of oncornaviruses has the meaning of "reverse transfer of genetic information". M.S. Gershenzon (1960) and Temin (1964) showed that the transmission of hereditary information is possible not only from DNA to RNA, but also in the reverse direction. A special enzyme was discovered that carried out the synthesis of complementary DNA using RNA as a matrix . The enzyme was named tranecryptase , or RNA-dependent DNA polymerase . In RNA- containing viral reverse transcriptase was detected in tumor-causing viruses , and DNA coigs of these viruses were found in cell genomes . So, the idea of prevention and treatment of patients with tumors caused by oncornaviruses , inhibition of reverse transcriptase , arose .

In the genome tumor-causing viruses have oncogenes that cause the transformation of normal cells into tumor cells. These oncogenes were captured by viruses in the genome of previously infected cells, in which these normal genes took part in the regulation of cell division. Viruses, taking into their genome normal cellular genes - division regulators, disrupt the regulatory regions of these genes, therefore, viral oncogenes are not subject to normal regulatory relationships in the cell.

In order to distinguish viral oncogenes , proto-oncogenes , as well as proteins synthesized on these genes, the following notation system is used: V - viral oncogene ; C - cellular proto-oncogene ; if the product of the oncogene is a simple protein, it is assigned p, and if it is in a phosphorylated state - pp ; if it is a complex protein consisting of two or more polypeptides, - P; further denote the molecular weight of abbreviations in kilodaltons and in the exponent, write the three-letter name of oncogenesis (v=pp60 ^{src} protein - the product of the oncogene from the Rous sarcoma virus in a phosphorylated form, 60 kD).

The mechanism of normal induction of cell division can be imagined as follows. The extracellular growth factor binds to a specific receptor on the cell membrane. From the receptor, the signal is transmitted by the conductor molecule, which penetrates through the membrane into the cell, where it activates the intracellular part of the receptor; from the latter, the signal is transmitted to the cell nucleus, where specialized molecules, which are activated, activate the work of some genes and suppress other genes. It turned out that all the above-mentioned types of molecules, which normally turn on the mechanisms of cell division, are used as oncogenes by viruses . 1. *Growth factors.* Oncogene sis is the gene that encodes the b-chain of TGF. Unlike normal TGF, which is activated by binding to a receptor on the cell membrane, the product of the viral oncogene is already produced in an active state and does not need to bind to a cell receptor for activation. 2. *Cell membrane receptors.* Analogues of cell membrane receptors are the products of viral oncogenes src of the Rous sarcoma virus , egBV of AEV viruses, which cause sarcoma and cancer in birds. It turned out that EGBV is an analogue of the cell receptor for epidermal growth factor (EGF), its intracellular part, and by its action - protein tyrosine by a kinase (attaches phosphate groups to tyrosine residues of proteins, due to which the functional activity of phosphorylated proteins changes dramatically). Unlike a normal receptor, the product of the viral oncogene

is produced in the actin state and mimics the effect of EGFR for the cell. 3. *Signal transmitters.* Examples of viral oncogenes that encode analogues of signal transmitters in cells are gas and RKS. 4. *Cytoplasmic and nuclear proteins.* Products of oncogenes v- myc , v- myb of viruses that cause myeloid leukemia in birds, v- tjs of the osseosarcoma virus in mice were found in cell nuclei ; very common oncogenic inducer P ^{53} . The products of many oncogenes of DNA- containing viruses are detected in the nuclei of transformed cells: the EIA product is a transcription regulator in the nucleus and cytoplasm; the large T-virus protein SA40 - initiates DNA synthesis in the nucleus, affects transcription, stabilizes the P 53 inducer

According to the biochemical activity of the synthesis products, viral oncogenes and their corresponding cellular proto-oncogenes can be divided into the following groups. 1 . *Tyrosinated protein kinases :* yes , fgr , fps , ros , fins , erbB , ser , abL . 2. *Serine-threonine protein kinases* (phosphorylate proteins by amino acid radicals of erin and threonine): mos , mil , raf . 3. *Family ras oncogenes derived* from yeast growth factors. They are activators of adenylate cyclase and guanylate cyclase , 4. *Division indicators* that act through nuclear proteins: myc , myb , fos . *5 Analogues of growth factors:* sis (similar to TFR). Oncogene tus can play the role of a promoter , that is, a gene that activates the work of a nearby gene. It turned out that when the oncogene tus is included in the genome of the breast cancer virus in lactating women mice that received such a virus intensively form a tumor of the mammary gland, but when the oncogene tus joins the genes that control the production of immunoglobulins , then the mice develop lymphocytic leukemia .

Along with the mechanisms of induction, a fundamentally different mechanism of oncogenesis was discovered , which is associated with the loss of the repressor of cell division. Such a repressor gene Rb is present in the cells of the retina, and its hereditary defect leads to the obligatory development of retinoblastoma in a child. The Rb gene is found in humans on the 13th chromosome in the H38 fragment of band 13 q 14.1 and is linked to the esterase D gene. It turned out that retinoblastoma can be induced by carcinogenic factors in a healthy organism that has the Rb gene , if the carcinogen causes the termination of the gene's function Rb and binding of its products.

How are oncogenes and tumorigenicity of viruses formed? 1. Changes in the structure of proto-oncogenes , leading to their deregulation, occur when these proto-oncogenes are not fully captured by viruses, when the proto-oncogene is detached from its own regulatory sites or the regulatory sites of other cellular genes. The difference between viral oncogenes and proto-oncogenes is that proto-oncogenes in the cell genome are represented by two genes - an intron and an exon , while only exons are found in viral genomes proto-oncogenes , that is, there is a loss of an essential regulatory part of cellular genes.

It also turned out that viral reverse transcriptase makes mistakes when reading the genome . A point mutation in the oncogene of a virus that caused a benign tumor turns the virus into an inducer of malignant tumors. Point mutations in oncogenes of viruses significantly affect various aspects of oncogenesis .

2. A special mechanism of increasing oncogenicity is virus superinfection of cells previously infected with a weak strain of an oncogenic virus. Genetic information can be exchanged between viruses, and a defective virus can get a missing gene or a booster for its

activity. Superinfection can lead to the multiplication of a weak oncogenic virus or the activation of the function of its genes.

It is assumed that the transformation (initiation) is a multi-stage process, however, the first link is immortalization , that is, acquiring the ability to multiply infinitely, as shown by the Hughes scheme .

Between the beginning of the action of the transforming agent and the development of a clinically pronounced tumor, there is a latent period that can last for years in a person. The existence of the latent period is due to the need to turn off the repressor , which can last for years in a person. The existence of the latent period is due to the need to turn off the repressor , which suppresses the activity of the viral genome (in the case of viral carcinogenesis); the predominance at the beginning of tumor growth of tumor cell types that grow slowly; the need to promote hidden transformed cells.

Promotion (activation) is the second stage in the mechanism of carcinogenesis. Transformed cells can remain in the tissue for a long time in an inactive form. The additional effect of a carcinogenic factor, which itself does not cause transformation, but stimulates cells to multiply, leads to the fact that tumor cells, which are in a latent state, begin to divide, forming a tumor node.

Most carcinogens are complete, that is, those that cause both transformation and activation. However, experimentally, carcinogenesis can be transformed into a two-step process, when transformation and promotion can be studied separately. After all Berenblum-Mottram applied methylcholanthrene to the skin of mice in a dose of 25 μg, which was insufficient to reproduce the tumor during the animal's lifetime. Then they lubricated the same area of the skin with croton oil, which never causes tumors. However, in the conditions of this experiment, it activated the division of cells transformed by the carcinogen. Tumors began to form in the animal .

The existence of latent ("sleeping") transformed cells can also be detected in Fisher's experiment. 50 tumor cells of Walker's carcinoma were injected into a rat's vein . This dose is not sufficient to indicate a tumor, and for many months after injection, tumors did not develop in rats. However, if these rats are dissected several times in the abdominal cavity and touch the liver, they will develop Walker's carcinoma in the liver .

Not all substances that cause inflammation are activators of carcinogenesis. Thus, dilute solutions of mustard and cantharidin , which cause only weak skin irritation, showed an active anticarcinogenic effect under the conditions of the Berenblum - Mattram experiment .

Progression is the third stage of the mechanism of carcinogenesis. Progression refers to stable qualitative changes in tumor properties in the process of growth , mainly in the direction of malignancy, which occur under the influence of several factors.

1. As a rule, not one cell, but several, is involved in primary carcinogenesis, which causes the formation of several cell sublines in the tumor . In a cyst that grows in minimal conditions (nutrition, blood supply, innervation), the most viable cells are constantly being selected. Certain cells gain an advantage. During the growth of tumor tissue in the body, hormonal regulation changes, it is possible to produce antibodies against cells that are in any subline . As a result, over time, one of the sublines of tumor cells, which was initially a minority, gains an advantage.

2. A change in the genotype and phenotype of cells leading to progression may be associated with the continued effect of the carcinogenic factor on the gene of tumor cells .
3. Spontaneous mutations of tumor cells in case of a decrease in the activity of reparative enzymes.
4. Acquisition of new properties by tumor cells associated with superinfection tumorigenic and non-tumorigenic viruses, facilitated in tumor cells.

From a practical point of view, it is important that progression in most cases leads to acceleration of tumor growth. Due to the heterogeneity of tumor cells , the selection of drug-resistant cells during chemotherapy is observed.

FEATURES OF TUMOR TISSUE

In the process of carcinogenesis and progression, cells lose their differentiation, returning as if to an embryonic state. This phenomenon is called *anaplasia.* Signs of anaplasia are in the biochemical processes of tumor cells (biochemical anaplasia), in their physicochemical state (physicochemical anaplasia), in their structure and function (morphological and functional anaplasia). It also happens *metaplasm* - transformation into new cellular forms.

In the process of transformation, a complex of changes occurs in the cell along with a violation of the regulation of cell division.

1. Cells begin to synthesize new growth factors, different in tumors both from different tissues and from one. However, in all cases, growth factors, the induction of which begins with cells when they are transformed into tumors, belong to two groups.

A. Growth factors that act on the producer cells themselves and support their reproduction: glycoprotein P52, insulin-like growth factors - IGFR-1 and IGFR-2, an analogue of platelet growth factor (TGF), oncogene $p28^{sis}$, v- ras and other oncogenes and proto-oncogenes . In cells that have undergone carcinogenesis, it is established *autocrine secretion* of these growth factors, i.e. cells keep them in themselves and this supports continuous reproduction. A small part of the secreted growth factors affects the neighboring cells of the same tissue.

B. Growth factors intended for cells of a different type, primarily for cells of the stroma and vessels. With the help of these growth factors, the tumor tissue forces other cells to grow into the tumor node. For fibroblasts, the mentioned TGF or its viral analogue $p28^{s,s\ is\ produced}$, as well as a special growth factor that stimulates the synthesis of collagen by fibroblasts - CSSFs (from the English Collagen synthesis-stimulating growth factor). For blood vessels, tumor cells produce the growth stimulator angiogenin , which exhibits activity in extremely small doses, insulin-like and other growth factors.

The production of growth factors for cells of a different type is named *paracrine* .

2. Synthesis and expression of receptors, primarily for growth factors, such as v- erbB for epidermal growth factor (EGF), increases dramatically in tumor cells.
3. There is a synthesis of enzymes that destroy the components of connective tissue and blood vessels, which leads to the migration of tumor cells and metastasis. This includes plasminogen activator - a very active enzyme that not only acts directly on the substrate, but also activates other enzymes; type IV collagenase (namely, the basement membrane of blood vessels consists of type IV collagen), other collagenases .

4. Cytoskeleton , microtubules included in it undergo significant changes in tumor cells . Cytoskeleton proteins - vinculin and others are phosphorylated , as a result of which the function of these proteins changes, the number of intercellular contacts in tumor cells sharply decreases, which facilitates metastasis. Contact inhibition of cell division disappears.

5. The ability of tumor cells to form factors whose action is opposite to the action of plasminogen activator , collagenosis, is revealed . These are factors that indicate the synthesis of collagens of various types, including IV, synthesis of other ingredients of interstitial tissue and vascular network. In addition, tumor cells contain their own enzymes that synthesize components of interstitial tissue.

With the help of factors of this group, tumor metastases are fixed and grow *in* other organs.

Biochemical features of tumor tissue.

Biochemical features of tumor tissue are based on *fusions of genetic regulation of cells.* As a result of the repression of some genes, the synthesis of related enzymes, structural proteins and others stops; derepression of other genes leads to the appearance of new types of proteins and isozymes in the cell. As a rule, the production of enzymes and proteins that enable the cell to perform a specialized function is repressed, and those enzymes that ensure cell division are activated through depression.

Carcinogenic factors are potentially able to perform not only the breakdown of the regulation of cell division, but also the disruption of the function of other structural and regulatory genes. Therefore, in a tumor cell, there is a sudden depression of the synthesis of substances, such as hormones, which are not normally produced in this tissue. Thus, the synthesis of corticotropin or gonadotropin can be detected in primary lung carcinoma , and thyroxine *in kidney tumors.* For the same reason, the production of an enzyme may be lost in tumors or a new one may be formed. It is characteristic, however, that different tumors approach each other according to the complex of enzymes that are included in their composition, and this complex is the smaller, **what** greater dedifferentiation of cells.

The most important biochemical feature of a tumor cell is *the activation of nucleic acid synthesis. The set of DNA* polymerases changes in tumor cells compared to normal cells . Among the three types of ***DNA*** polymerases in tumors, the amount of DNA polymerase 3, which uses native DNA as a matrix, decreases, and the amount of DNA polymerase 2, which is able to build DNA not only on a native , but also on a denatured matrix, increases.

Protein synthesis changes qualitatively and quantitatively in tumor cells. The proteins whose synthesis in tumor cells increases sharply include the proteins of the mitotic apparatus, including the large-molecule spindle protein. Normally, the content of proteins in the mitotic apparatus is up to 11% of their number in the cell, and in a tumor their number increases to 30%.

Protein metabolism changes. The ability of tumor cells to peraminate and deaminate amino acids decreases, sometimes some enzymes involved in the exchange of amino acids are not formed. In most tumors, uptake of amino acids from the blood and protein synthesis increases. Protein catabolism is reduced to such an extent that even in an organism that is starving, the tumor protein does not participate *in* the general exchange. Moreover, the radiological method proved that when the tissues of a starving body lose amino acids, the

tumor "appropriates" them . All this made it possible to characterize the tumor as a "nitrogen trap". Due to the loss of enzymes, the ability to synthesize some essential amino acids, such as L-asparagine, may be lost.

Carbohydrate exchange and energy production occupy a special place in the biochemistry of tumors. In tumors, the rate of glycolysis often increases significantly, intensive glycolysis is not specific a feature of tumors. However, when comparing the activity of glycolysis enzymes in the tumor and in the primary tissue, an increase in the activity of the main glycolysis enzymes - hexokinase , phosphofructokinase , and pyruvate kinase - is observed . Aerobic glycolysis occurs in tumors, that is, the breakdown of carbohydrates into shruvate and its transformation into lactic acid in the presence of oxygen - *the negative Pasteur effect. At the same time, inhibition of the conversion* of taruvate to lactic acid in the presence of oxygen and a decrease in the intensity of glycolysis is observed in most normal tissues . Warburg formulated the hypothesis that the cause of malignant transformation of cells are factors that prevent cells from obtaining energy from oxidation, as a result of which cells are forced to switch to glycolysis. Today, increased glycolysis should be considered not as a cause of tumor formation , but as a consequence of carcinogenesis, complex restructuring of synthesis and regulation of enzyme function.

The tumor intensively captures glucose from the blood. Even with an increase in the blood glucose content to 16.7 mmol/l (300 mg%), the blood flowing from the tumor does not contain glucose (V.S. Shapot). This ability of the tumor is associated with a change in the activity of transferases hexose : the activity of regulated glucokinase decreases and hexokinase , which is less sensitive to hormonal glucokinase , is sharply activated and hexokinase , which is less sensitive to hormonal regulation, is sharply activated. The energy that tumor cells receive from glycolysis is sufficient to ensure the synthesis of nucleic acids and cell division.

Oxidation (tissue respiration) also changes in tumors. Basically, there is a tendency to decrease respiration in proportion to the degree of cell differentiation. At the same time, the Crabtree effect is observed - inhibition of oxidation during glucose loading, which may be the result of a "struggle" between the tumor's powerful glycolytic enzyme system and its oxidizing enzymes for inorganic phosphate, other substrates and coenzymes.

Antigenic features of the tumor.

According to its antigenic composition, the tumor tissue differs from the normal tissue from which it originates. Thus, antigens specific to embryonic tissues (tumor -embryonic antigens) can be detected in tumors. G. _ *And .* Ablev showed this on the example of hepatoma , in which he discovered the protein afetoprotein . Based on the presence of this protein in the blood, it is possible to diagnose a liver tumor before its clinical signs appear. In tumors of viral origin, virus-induced agents appear that are specific for this virus and are the same in different tumors and in different individuals .

Random agents arise in induced tumors due to mutations. If several primary tumors arise in the body under the influence of one carcinogen, then they can produce different random antigens as well as different enzyme complexes.

of tumor cells in the body does not necessarily lead to the development of a tumor process. Tumor cell clones fall under the control of immunocompetent tissue, and as a result of

immune reactions, the clone with any antigenic differences is eliminated. Therefore, the growth of tumor tissue is observed due to the ability of tumor cells to avoid immunological control.

The mechanisms that make it possible to avoid immunological control are as follows.

1. Tumor progression is accompanied by the loss of part of the antigens that are present in a normal cell - the so-called antigenic simplification, which can contribute to the survival of tumor cells and reach such a degree when tissue-specific antigens are completely lost , to which every organism of a certain species has tolerance. 2. The appearance of fetal antigens in the tumor tissue does not cause an immune reaction due to the fact that there is immunological tolerance to these agents. 3. Masking of tumor antigens. So, chorioepithelioma cells have a neutral polysaccharide capsule. 4. In some tumors, antigenic determinants have been found that preemptively stimulate T- suppressors , which lead to inhibition of the immune response against the tumor. 5. Carcinogenic factors can cause immunodepression. 6. Overloading of the immune system and suppression of the immune response by tumor tissue after reaching a certain mass.

However, despite all mechanisms of tumor avoidance from immunological surveillance, transformed cells are destroyed in the body and the clinical manifestation of the tumor occurs much less often than cell transformation.

Mechanisms* immune *protection of the body against tumors. To combat the tumor in the body, there are mechanisms that are divided into adaptive and non-adaptive. *Adaptive mechanisms* are classical immune reactions that take place. T- and B-lymphocytes against tumor cells, if there are antigens on these cells. The appearance of new tumor antigens can be caused by several factors: 1) mutation under the influence of carcinogens; 2) tumor induction by viruses (viral antigens); 3) depression of genes that lead to the appearance in tumor cells of a enzyme , hormone or germ antigen unusual for the original tissue; 4) a change in antigens of the main histocompatibility complex (MHC) due to mutations or disruption of gene regulation. Lymphocytes can participate in the immune response, both limited by MHC antigens and unrestricted, while the consequences depend on the quantity and quality of expressed MHC antigens. If in the process of carcinogenesis, histocompatibility antigens of class i (HYA-A, HYA-B, HYA-C) change in tumor cells , such cells will be recognized and destroyed by T- killers without a previous immune reaction. The same will happen in the case of changes in antigens of her class (HLA-B). But in this case, antigens that are not part of MHC will not be recognized on tumor cells, since T- helpers have antigenic restriction and recognize antigens only on cells that have the same class II antigens (HLA-D) as T- helpers . If class II antigens on tumor cells and immunocytes are the same and there are no additional antigenic marks, the possibility of an immune attack and activation of adaptive immunity mechanisms is blocked. Class III histocompatibility antigens (complement components) are required for activation of B-killers .

To *non-adaptive (* carried out without the participation of antibodies) defense *mechanisms* against tumors include: 1) natural killers (NK); 2) tumor necrosis factor (TNF) of lymphocytes, which destroys cells and vessels of tumors and whose effect is enhanced by interferon V; 3) lymphoid toxin (LT) of lymphocytes; 4) cytotoxic factor of natural killers

(TNFK); 5) lysosomal enzymes of leukocytes. In addition, non-adaptive mechanisms are involved in adaptive through Fc -fragments of immunoglobulins and complement activation.

Physico-chemical features of tumor tissue. The change in the physicochemical properties of tumor cells is mostly the result of biochemical remodeling of the tumor tissue. Intensive glycolysis leads to the accumulation of lactic acid. When loaded with carbohydrates, pP in tumor tissue can decrease to 6.4. The tumor has an increased content of water, and sometimes some electrolytes, in particular potassium salts. The content of calcium and magnesium is reduced, the K/ Ca ratio is increased. Due to hydration and an increase in the content of hydrogen ions, as well as some electrolytes, the electrical conductivity of the tumor tissue is increased. At the same time, the viscosity of colloids is reduced. There is an increase in the negative charge of tumor cells, the value of which approaches the value of the charge of lymphocytes. It was suggested that due to the similarity of charges, lymphocytes are less able to control tumor tissue than normal ones, so they do not attack tumor mutants. An increase in the negative charge of tumor cells occurs due to an increase in the number of electronegative neuraminic acid radicals in the outer membrane of cells.

The degree of physicochemical anaplasia corresponds to the degree of dedifferentiation and growth rate.

Functional features of tumor tissue. *Functional anaplasia* is manifested in the impact of functions that cells were able to perform before grasformation . For example, in a hepatoma , the synthesis of bile pigments ceases, in significantly dedifferentiated tumors that grow rapidly, primary specific functions are lost. Partially differentiated tumors, which have retained the ability to carry out some processes specific to the primary tissue, lose control over them. Thus, an uncontrolled synthesis of adrenaline is observed in a tumor of the medulla of the adrenal glands (pheochromocytoma). Genital tumors may partially retain sensitivity to hormonal regulation. Along with dedifferentiation and a decrease in control efficiency, a process unusual for the primary tissue can occur in tumor cells, for example, the synthesis of glycosaminoglycans or hormones, in particular, glucocorticoids by a lung tumor.

Tumor malignancy. The ability of tumor cells for unlimited uncontrolled reproduction does not yet determine the inevitability of the death of the organism in the event of tumor growth, since surgical removal of the tumor node provides a complete cure. However, this may be hindered by the malignancy of the tumor, which is characterized by *infiltrative (invasive) growth and the ability to metastasize.*

Malignant tumors are also characterized by *tissue anaplasia , which is more pronounced than in benign tumors* , and the ability to perform general deep exhaustion of the body - *cachexia* _ Benign tumors can become malignant.

Infiltrative growth and formation of metastases are associated with disruption of intercellular connections in the tumor tissue . In tumors and tumor cell cultures, there is a decrease or absence of contact inhibition. When in tissue culture, normal cells of two adjacent areas, multiplying in the direction of growth, touch each other, tissue growth and cell division in this area stops. Tumor cells in such cases continue to grow, forming multilayered areas. The lack of contact inhibition makes it possible to explain the ability of

malignant tumors to infiltrative growth, that is, to sprout into healthy tissue. The basis of normal contact inhibition is obviously the influence of membranes on the regulation of cell division. This mechanism is lost in tumor cells.

Metastasis consists of the following stages: detachment of tumor cells from neighboring cells; movement into the tissues, melting at the same time of the components of the connective tissue and the vessel wall; transfer with blood or lymph; attachment to the vessel wall in a new place; induction of the growth of connective tissue and blood vessels in the newly formed tumor tissue. Among the mechanisms and factors that cause metastasis at its various stages, the main ones can be singled out.

1. Termination of intercellular contacts, changes in membrane receptors and acquisition of motility are largely associated with changes in cytoskeleton proteins , in particular with their phosphorylation protein kinases , which are a significant number of products of oncogenes and growth factors. There is also a change in the regulation of genes that encode cytoskeletal proteins and membrane receptors.
2. In cells that are transformed, the synthesis of plasminogen activator takes place - an enzyme that intensively destroys the components of the main substance of connective tissue and the vascular wall, and also activates enzymes of other biologically active systems, in particular ischasminogen . In tumor cells, collagenases are formed , which destroy collagen of various types, including IV, which consists of the basement membrane of blood vessels. Tumor cells that do not have plasminogen produce a factor that attracts monocytes, whose enzymes thin the matrix and create an opportunity for tumor cells to metastasize. . Similarly, tumor cells attract tissue basophils, whose enzymes, in particular, serine protease and metalloproteinase , also contribute to the splitting of magrix , and heparin enhances the effect of anpogenin and the ingrowth of blood vessels into the tumor tissue.
3. There are cathepsins both embedded in the membrane of tumor cells and free in the intercellular fluid of tumor tissue.
4. Tumor cells have a set of factors that activate the synthesis of collagen, glycoproteins and other components of the main substance in connective tissue cells and the reproduction of these cells, ingrowth into the tumor node.
5. Tumor cells secrete angiogenin and other vascular growth factors, which provides blood supply to the tumor tissue.
6. In the membranes of tumor cells, unlike normal ones, the radicals of neuromic acid, glycoproteins , α-D- glucopyranoside and N-acetyl-D- galactosamine remain open. Protein concanavalin A, as well as lectins . thanks to the presence of open radicals, tumor cells agglutinate . If tumor cells are treated with cleaved concanavalin A, which blocks open radicals in membranes without causing agglutination, they grow for a while in the same way as normal cells. All this gives reason to assume that the disruption of tumor cell membranes and the appearance of free radicals in them prevent the formation of tight contacts between tumor cells and contribute to infiltrative growth and the formation of metastases. One of the reasons for the discovery of radicals in tumors and disruption of membranes is an increase in sialtrasferase , which transfers glycoprotein radicals .

with normal ones in tissue culture, the former divide and grow like normal ones. Obviously, tumor cells lose the ability to amplify the inhibition signals to other cells, but they are able

to perceive the inhibition signals sent by normal cells to a certain extent. In the cancerous node, conditions are created for the overload of tumor cells and the invasive grow them

The impact of the tumor on the body. Depending on the localization of the tumor and its metastases, various pathological processes in the body may occur. Thus, tumors of the organs of the digestive system cause severe disorders of digestion and nutrition. Stomach cancer is accompanied by suppression of the secretory function of this organ . As a result, insufficient intake and assimilation of food, at the same time, starvation of the body develops.

In addition to direct damage to organs by a tumor and its metastases, there are other ways of impact of malignant tumors on the body, for example, toxic substances that cause metabolic disorders, which often leads to deep exhaustion of the body - cancer cachexia.

In the case of a tumor process, the activity of catalase, an enzyme that catalyzes the reaction of decomposition of hydrogen peroxide, is reduced in the body. While studying the causes of this phenomenon, Nakahara and Fukuora isolated a fraction from a human tumor, which, when administered to mice, caused a decrease in the level of catalase in the liver . This substance was called toxohormone . Subsequently, a highly active crystalline polypeptide with a molecular weight of 4,000 was isolated . decrease in iron content in the blood, which is affected by toxohormone 200-500 times more than catalase activity, development of anemia due to inhibition of erythropoiesis ; hypertrophy of the adrenal glands and involution of the thymus gland; enlargement of the spleen and liver.

Underoxidized metabolic products enter the body from the tumor . In a neutralized state, they are excreted by the kidneys. Normally, the ratio of the amount of carbon and nitrogen (C/N) in urine is 0.7, with a tumor process - 0.9 and higher. This indicates an increased excretion with urine under-oxidized products (disokeidative carbonuria).

Part of the enzymes of the tumor passes into the adjacent tissues as a result of increased permeability of cell membranes, as well as necrosis of the tumor tissue. At the same time, the enzymes synthesized by the tumor are detected in the blood or other body fluids, and other enzymes in the blood of patients with osteogenic sarcoma increase by 20-40 times; an increase in its activity is also observed in the process of hepatoma growth . An increase in the content of acid phosphatase in the blood is observed in tumors of the prostate gland, and an increase in the activity of glucose phosphagisomerase in patients with breast cancer. With various tumors, the content of aldolose , some isoforms in the blood increases lactate dehydrogenase , the activity of cholinesterase and ribonuclease decreases . It should be noted that changes in blood enzymes are not always specific for one or another type of tumor. Special changes in the body are observed in tumors in which there is an uncontrolled synthesis of hormones or other biologically active substances. In the case of Zollinger-Ellison syndrome, an intensive synthesis of gastrin (a hormone of the mucous membrane) is observed in the tumor of the pancreas stomach , an active stimulator of gastric juice secretion). The synthesis of gastrin , which is not peculiar to the pancreas, is a consequence of the abnormal function of the corresponding gene, which functions without control, out of connection with the natural mechanisms of regulation of the synthesis of gastric gastrin . Continuous stimulation of gastric secretion by tumor hormone leads to the development of gastric ulcer .

Similarly in pheochromocytoma adrenaline is secreted , which causes the development of hypertension.

The role of the organism as a whole in the tumor process The organism affects the tumor process at all stages. With regard to carcinogenesis, the processes that occur in the body can have a double meaning; or induce or inhibit the occurrence of tumors.

Known precancerous conditions are diseases in which the frequency of tumor development increases significantly, for example cervical cancer in patients with erosion of its mucous membrane .

Hereditary properties of the body determine the peculiarities of the reaction to carcinogenic factors and the occurrence of tumors. For example, breeding inbred lines of animals resistant to the effects of carcinogens. Species, sex, tissue and other features of the body determine the variants of metabolism and action of chemical carcinogens, as well as differences in immune reactions against tumor-causing viruses and mutant clones of tumor cells. As a result, some types of organisms are insensitive to the outpouring of a tumor-causing virus, while in others this virus causes tumor development. Stomach cancer is more common in men , and genital cancer in women.

Hormonal regulation has a significant impact on the tumor process. Hormones can act as carcinogens and induce tumor development or facilitate its progression. Growing tumors are often particularly sensitive to hormonal regulation. Thus, the growth of various tumors is inhibited under the influence of insulin, somatotrochle deficiency , increases with hypofunction of the thyroid gland, and also as a result of the influence of some sex hormones. As a result of the variability of changes in tumor cells, different reactions to hyper- or hyposecretion of hormones are observed. While the development of many tumors is inhibited with hypersecretion of insulin, insulin-dependent carcinoma of the mammary gland was observed experimentally , which was induced by DMBA. Without insulin, this tumor cannot grow.

The tissue of malignant tumors is not innervated in most cases . Nerve endings are located in the stroma - normal connective tissue. However, even here the innervation is insufficient.

Since the activity of the nervous system is related to endocrine regulation, its disruption can lead to changes in hormonal regulation , which causes the development of tumors.

In connection with the accumulation of factors about the participation of the nervous system in organogenesis and its trophic influence on the type of structure of innervated tissue, for example, muscle, it can be assumed that in some cases, the disruption of the functions of the nervous system is connected, directly or indirectly, with the processes of carcinogenesis and tumor progression. The influence of the mediator of the sympathetic nervous system, adrenaline, on the regulation of tissue mitotic activity is of particular importance. The number of mitoses in the tissue is under the control of repressor hormones - keylons , which are produced in dividing cells. The more dividing cells in this tissue, the higher the concentration of keylons , the stronger the mitotic activity of the remaining cells is inhibited. It is assumed that in this way a constant number of cells is maintained in the body. Considering the role of the nervous system in the regulation of cell division 1, therefore in the mechanisms of carcinogenesis, it is important that the activity of keylons is found in combination with adrenaline. In tumor tissue, this mechanism of regulation of cell

division is disrupted.

However, the body has means of protection against carcinogenic factors. This is primarily a function of organs and systems that capture, disinfect and remove carcinogens, protect cells and macromolecules from the effects of peroxides and radiolysis products; immune system and phaocytosis . In addition, there are special protection mechanisms:

a system of reparative enzymes, which eliminates gene disorders and restores their normal structure after mutation (endonucleases); cellular inhibitors of nucleic acid synthesis (interferon); obviously, genes that repress the viral genome, etc.

Treatment of patients with tumors. Natural killers are not cytotoxic to all cells. S.A. Rosenberg and colleagues used lymphokine - gransgene to stimulate autogenous lymphocytes interleukin 2 (1l 2), synthesized by micro-organisms into which the gene for this lymphokine was introduced . il 2 was added to blood lymphocytes of patients with inoperable forms of various tumors with metastases. Under the influence of Il 2, lymphocytes multiply, their function is activated. Then each patient was injected with his own activated lymphocytes (1.8 - 18.4* U^{10} cells) together with Il 2. The combined administration of activated autogenous lymphocytes and lymphokine led to the regression of tumors, including metastases, in 11 out of 25 patients. One melanoma patient was completely cured, including the disappearance of bone metastases.

At the same time, the authors discovered a new subpopulation of lymphocytes, which they called lymphokine-activated killers (LPK), applied to which with the help of Il 2 causes effective cytotoxic activity against tumors resistant to natural killers under normal conditions. The effectiveness of treatment has been proven in different countries on many hundreds of inoperable patients.

The second method was applied by the group of T. Takvorian in leukemia: bone marrow was taken from patients, monoclonal antibodies were obtained against leukemic cells (patients whose leukemic cells expressed antigen B1 were selected), the bone marrow was cleaned of leukemic cells with the help of antibodies, the patient was irradiated with a burning dose of inositol radiation and injected each with his own bone marrow. Result: in 34 patients out of 45, remission was observed without maintenance therapy, which lasted about 52 months, on average - 11 months. In addition to immunological methods, with the help of which the complete cure of individual tumor patients with disrupted metastases was achieved for the first time, other methods of pathogenetic treatment aimed at blocking the action of oncogenes , restoring the regulation of the reproduction of transformative cells and preventing the formation of metastases are being searched for.

Lecture No. 4

Topic: Allergy and immunity. Etiology of allergies, classification of allergic reactions. Mechanisms of development.

Purpose :

- get acquainted with the modern definition of an immunopathological state and

reaction, when one's own cells and extracellular structures are destroyed, which affects the development of hypersensitivity , that is, allergies.

- get acquainted with the contribution of domestic scientists - O. Bogomolets, 1.1. Mechnikova , V.V. Pidvysotskyi, AM Bezredka in the study of this problem; be able to explain to the patient the need for timely treatment and preventive recovery.

3. **Basic concepts:** Allergy, allergens, anaphylactic shock, serum sickness, nodular periarteritis , Artus phenomenon , post-streptococcal glomerulonephritis , vasculitis , systemic lupus erythematosus, rheumatoid arthritis.

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

Allergy is an immune reaction (a qualitatively altered immune response) accompanied by damage to the body's own tissues.

The causes of allergies are **allergens.**

Classification of allergens : exoallergens and endoallergens .

Exoallergens :

1) infectious: a) bacterial, b) viruses, c) fungi,

2) pollen of flowering plants, fluff of poplar, dandelion, ambrosia, cotton,

3) household - detergents, household and library dust, as a product of the vital activity of a house mite, specific for a particular apartment,

4) food products - especially for children - cow's milk, chicken eggs, chocolate, citrus fruits, strawberries, fish, crabs, lobsters, cereals,

5) medicines - especially therapeutic serums, antibiotics, vitamins,

6) products of chemical synthesis.

Endoallergens :

a) natural (primary): lens and retina of the eye, tissues of the nervous system, thyroid gland, male gonads,

b) acquired (secondary), induced from own tissues under the influence of external influences: infectious, non-infectious (cold, burns, radiation).

Classification of allergic reactions:

1. According to the reaction time after repeated exposure to the allergen (according to Cook):

- Allergic reactions of the immediate type (hypersensitivity of the immediate type) - I, II, III - develop 15-20 minutes after repeated exposure to the allergen.

- Allergic reactions of the delayed type (hypersensitivity of the delayed type) - IV - develop 24-48 hours after repeated exposure to the allergen.

2. According to pathogenesis (according to Coombs and Jell):

- I. Anaphylactic;
- II. Cytotoxic;
- III. Immunocomplex ;
- IV Hypersensitivity of delayed type.

General pathogenesis of allergic reactions:

I. Immunological stage

1. Formation of antibodies or sensitized T-lymphocytes upon initial contact with an allergen (sensitization);

2. Formation of complexes allergen + antibody (type I, II, III) or allergen + sensitized T-lymphocyte (type IV) upon repeated contact with the allergen.

II. Pathochemical stage. It is characterized by the release, activation, synthesis of biologically active substances - allergy mediators.

III. Pathophysiological stage (stage of clinical manifestations). It is characterized by structural and functional changes in organs and tissues:

- vasomotor reactions (local and systemic), leading to changes in blood pressure, peripheral blood circulation and microcirculation;
- increased permeability of vessel walls, which leads to the development of edema;
- spastic contractions of the smooth muscles of the bronchioles and intestines, which may manifest as asphyxiation, dyspeptic disorders;
- an imbalance between the factors of coagulation, anticoagulation and fibrinolytic systems of blood, which can lead to both hemorrhagic syndrome and thrombosis;
- irritation of nerve receptors, which leads to the development of a feeling of pain, itching , burning;
- inflammatory reactions accompanied by significant cell infiltration of tissues.

Sensitization - formation of increased sensitivity of the body to this allergen.

It is characterized by the formation of specific antibodies or sensitized T-lymphocytes to a specific allergen. Clinically, sensitization is not manifested. The state of sensitization can be detected with allergy tests.

Distinguish ***active*** (develops 10-14 days after the introduction of the allergen into the body; the immune system of the body is actively involved in the process of formation of specific antibodies or sensitized T-lymphocytes) and ***passive*** sensitization (develops after the introduction of serum containing ready-made antibodies or a cell suspension with sensitized T-lymphocytes; at the same time, the body's own immune system does not participate in the formation of antibodies and sensitized T-lymphocytes).

ALLERGIC REACTION TYPE I (anaphylactic)

Immunological stage: allergen → recognition of allergens by dendritic cell (DC) → reading of information, its processing, isolation of AG determinants and its incorporation into the membrane of DC → activation of T- helpers (Th_0) → formation of Th_2 → B-lymphocytes → transformation of B-lymphocytes into plasma cells → synthesis of antibodies - immunoglobulins Ig E, G4 → fixation of antibodies on the surface of mast cells (antibodies with their end Fc (constant fragment) are fixed on the corresponding receptors of mast cells and basophils; nerve receptors of blood vessels, smooth muscles of intestinal bronchi and blood cells → repeated contact with the allergen → formation of allergen-antibody complexes on the surface of mast cells (Fab (antigen-binging fragment) antibody fragment binds to AG, and 1 molecule of IgE can bind 2 molecules of AG).

There is activation of the cell and transition of the process to **the pathochemical stage** , which includes degranulation mast cells (Fig. 1) and the release of granules from them: histamine , heparin, chemotaxis factors of eosinophils and neutrophils ; formation of leukotrienes and prostaglandins from phospholipids of membranes ; migration of eosinophils, neutrophils to the zone of allergic reaction and their release of secondary mediators: histamines , arylsulfatases , proteases, phospholipases

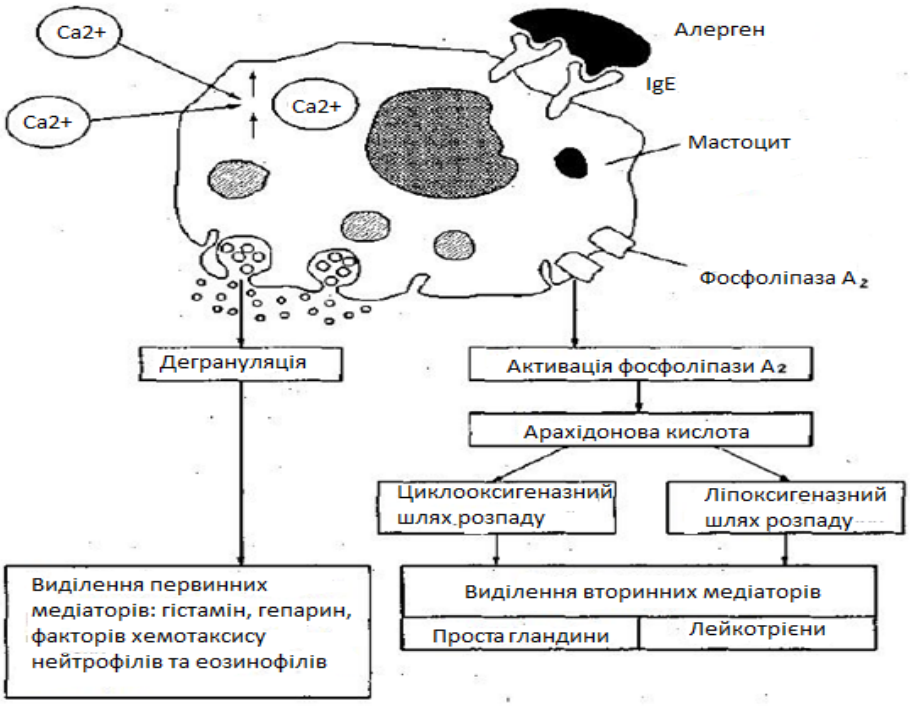


Fig. 1. Isolation of primary and secondary mediators from mast cells .

Pathophysiological stage: spasm of bronchial smooth muscles → bronchospasm ; dilation of blood vessels → arterial hyperemia; increased permeability of the vascular wall → edema; hypersecretion of mucus, irritation of nerve endings → itching, pain. *Clinical forms:* urticaria, pollinosis , Quincke's edema , bronchial asthma, anaphylactic shock.

ANAPHYLACTIC SHOCK

Bronchospasm

Mucus hypersecretion Increase

vascular permeability

Violation of pulmonary ventilation

Expansion of arterioles

Lower blood pressure

Violation of microcirculation

Hypoxia

↓

Dysfunction of the respiratory and cardiovascular centers

↓

Death

TYPE II ALLERGIC REACTION (cytotoxic)

Immunological stage: allergen (changed components of cellular and basal membranes (autoallergens) → recognition of allergens by dendritic cells (DC) → reading of information, its processing, isolation of AG determinants and its incorporation into the DC membrane → activation of T- helpers (Th_0) → formation of Th_2 → B-lymphocytes → transformation of B-lymphocytes into plasma cells → synthesis of Ig $G_{1,2,3;}$ IgM → fixation of antibodies on the surface of target cells → upon repeated contact with an allergen, the formation of an allergen + antibody complex on their surface.

Pathochemical stage: activation of complement components; release of lysosomal enzymes and superoxide radicals (O, OH, H_2O_2) during phagocytosis; granzyme , perforin from NK cells.

Pathophysiological stage. Lysis of target cells, destruction of basement membranes:

1. Complement-dependent cytolysis (activation of individual fragments of complement components): C3a, C5a - chemotaxis of neutrophils and phagocytosis; C5b-C9 - formation of channels in the cell membrane and osmotic cell lysis.

2. Complement-independent cytolysis (the role of opsonins is performed by antibodies (IgG).

3. Antibody-dependent cellular cytotoxicity (NK cells are activated, which have receptors for the Fc fragment of antibodies on their surface).

Clinical forms: hemotransfusion shock, hemolytic disease of newborns, autoimmune thrombocytopenic purpura, autoimmune agranulocytosis, Dressler's syndrome (postinfarction myocarditis), acute rheumatic fever, hyperthyroidism, drug allergy.

ALLERGIC REACTION TYPE III (immune complex)

Immunological stage: allergen (soluble proteins, drugs, therapeutic serums) → recognition of allergens by dendritic cells (DC) → information reading, its

processing, isolation of AG determinants and its incorporation into the DC membrane → activation of T- helpers (Th_0) → formation of Th_2 → B-lymphocytes → transformation of B-lymphocytes into plasma cells → synthesis precipitating antibodies - Ig G; Ig M → upon repeated contact with the allergen, the formation of soluble complexes → fixation of allergen + antibody complexes on the walls of microvessels .

Pathochemical stage: activation of complement components; chemotaxis of granulocytes and macrophages (C3a, C5a); activation of phagocytosis (C3b) and release of lysosomal enzymes and superoxide radicals by phagocytes; activation of mast cells (C3a, C5a), their degranulation and release of histamine , heparin, chemotactic factors; factor selection Hageman in case of damage to the endothelium of vessels by immune complexes; and activation with its help of the kallikrein-kinin system, coagulation, anticoagulation and fibrinolysis systems .

Pathophysiological stage. Circulating immune complexes are deposited in the vessels of kidney glomeruli and cause various types of glomerulonephritis , alveolitis in the lungs , and dermatitis in the skin. In severe cases, inflammation can take on an alterative character with tissue necrosis, partial or complete thrombosis, and hemorrhage . Initially, the focus is dominated by neutrophils , which actively phagocytose immune complexes, releasing lysosomal enzymes and factors that increase permeability and chemotaxis for macrophages. Macrophages accumulate in the focus of inflammation and phagocytose destroyed cells, cleaning the affected area. Inflammation ends with the proliferation of cellular elements.

Clinical forms: serum sickness, nodular periarteritis , Artus phenomenon , poststreptococcal glomerulonephritis , vasculitis , systemic lupus erythematosus, rheumatoid arthritis , etc.

TYPE IV ALLERGIC REACTION (delayed type hypersensitivity)

Immunological stage: allergen → recognition of allergens by a dendritic cell (DC) → reading information, its processing, isolation of AG determinants and its incorporation into the DC membrane → activation of T- helpers (Th_0) → accumulation of $Th_{1\ clones}$ (sensitized T-lymphocytes) . in the cell membrane of which are embedded structures that perform the role of AT, able to connect with the corresponding allergen → upon repeated application of the allergen, T-lymphocytes diffuse from the bloodstream to the site of application and connect with the allergen, which is located on the target cells.

Pathochemical stage: lymphocytes are thrown out lymphokines , NK cells secrete granzyme and perforin .

Pathophysiological stage: the development of foci of allergic exudative inflammation of a dense consistency.

Clinical forms: contact dermatitis, infectious and allergic diseases (tuberculosis, brucellosis, syphilis, fungal diseases); tuberculin reaction; graft rejection reaction.

Hyposensitization - a decrease in the body's sensitivity to an allergen. There is a distinction between specific and non-specific hyposensitization.

Specific hyposensitization is achieved by the introduction of the allergen that caused the allergy (introduction of serum according to the method of A.M. Bezredka

). Specific hyposensitization is effective for type I allergic reactions.

Nonspecific hyposensitization is achieved by changes in the body's reactivity (normalization of the function of the neuroendocrine system: working conditions, rest, nutrition, reflexology , physiotherapy ; administration of drugs (antihistamines , GCS, leukotriene receptor blockers).

Pseudoallergic reactions are a group of reactions that are similar in appearance to allergies, but differ in the absence of an immunological stage. They develop under the action of factors that cause degranulation mast cells and the release of biologically active substances.

Mechanisms of development:

- Histamine : degranulation mast cells , violation of histamine inactivation , increased intake of histamine with food, dysbacteriosis .
- Violation of activation of the complement system : excessive activation of the complement system , deficiency of complement inhibitors .
- Disruption of the metabolism of the arachidonic system: imbalance between prostaglandins and leukotrienes (aspirin use).

- **ALLERGY AND IMMUNITY**

- The basis of immunity in the sense of 1.1. Mechnikova (as immunity to infectious diseases) is a function of the immune system. A higher indicator of immunity under normal conditions is that the repeated entry of the pathogen into the body does not cause disease, but ends with suppression and destruction of microorganisms.
- It should be noted that under natural conditions, a small amount of infectious antigen enters the body, which, however, can cause high virulence in a non-immune organism. If an infectious antigen is administered in doses close to the final dose that causes allergic reactions, instead of immunity, an infectious allergy can be induced. Therefore, allergy also includes infectious allergy, which follows the general patterns of allergic reactions.
- In this regard, the induction of the biochemical stage of allergic reactions by complexes of antibodies with infectious antigens depends on the quantitative ratios and qualitative characteristics of antigens and antibodies, as well as on the body systems involved in the production and inactivation of VAR. On this basis, it can be assumed that the state of specific immunity is determined by such a level of processes in the immunological and biochemical stages that the stage of functional and structural disorders does not develop, but the destruction of the infectious agent is achieved. This level of processes and the state of immunity are established when the decontamination systems completely inactivate the BAR after the pathogen has been destroyed with their help. An allergy develops when, under the influence of the antigen-antibody complex, such a quantity of VARs is formed that the BAR inactivation systems cannot suppress them, and they begin to act not only on the causative agent of the infection, but also on the tissues of the body itself. A secondary alteration develops.

Lecture No. 5

Topic: Pathophysiology of metabolism. Pathophysiology of water-salt exchange: dyshydria , edema. Pathophysiology of metabolism . Peculiarities of disturbance of acid-alkaline balance: acidosis , alkalosis .

Purpose :

- To acquaint the recruiters with the modern definition of damage to the BSO, CLR and integral mechanisms in the event of damage, the acquirer should know the general mechanisms of dysregulation of the BSO, CLR in case of damage and the mechanisms of the development of pathological conditions, which are the main links of the pathogenesis of this process; must be able to determine the role of osmo- and volume regulation in the pathogenesis of BSO disorders, the role of many organs (kidneys) in the pathogenesis of CLR disorders; to distinguish actual pathological manifestations and protective and compensatory reactions in case of violation of BSO and CLR.
- Formation of logical and professional thinking in applicants; emphasized the role of environmental factors in the development of violation of BSO, CLR; provided the assimilation of the winners of the leading importance of domestic clinical and research schools in the development of problems of pathophysiology of VSO and CLR.

Basic concepts: dyshydria , dehydration , hyperhydration , edema, hyperparathyroidism , acidosis, alkalosis, buffer system,

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

DISORDER OF WATER AND MINERAL EXCHANGE.

The water content in the body of an adult is on average 60% of body weight, ranging from 45 (in smooth elderly people) to 70% (in young men). Most of the water (35-40% of body weight) is contained inside the cells (intracellular fluid). Extracellular (extracellular) fluid makes up 15-25% of body weight and is divided into intravascular (5%), intercellular (12-15%) and intracellular (1-3%).

During the day, a person drinks about 1.2 liters of water, about 1 liter enters the body with food, up to 300 ml of water is formed in the process of oxidation of food substances. Under normal water balance, the same amount of water (about 2.5 l) is excreted from the body: by the kidneys (1-1.5 l), through evaporation through the skin (0.5-1 l) and lungs (about 400 ml), as well as with feces (50-200 ml).

Constancy of the volume and osmolality of the extracellular fluid is maintained by - regulatory mechanisms, the main effector organ of which are the kidneys. Irritation of osmoreceptors of the hypothalamic area (in case of increased blood osmolality) and volume receptors of the left atrium (in case of a decrease in blood volume) increases the release of

vasopressin (ADH) by the supervisory and paraventricular nuclei of the hypothalamus. Vasopressin increases the reabsorption of water in the tubules of the nephrons.

Irritation of the receptors of the adduct arteriole of the kidney (in the case of a decrease in renal blood flow, blood loss) and sodium receptors of the dense spot of the juxtaglomerular complex (in the case of sodium deficiency) increases the synthesis and release of renin. Angiotensin, formed under the influence of renin, increases the release of aldosterone by the adrenal glands, which increases sodium reabsorption. The reduced volume of extracellular fluid and angiotensin also stimulate the thirst center located in the lateral part of the hypothalamus.

Antidiuretic and antinatriuretic mechanisms are opposed by diuretic and natriuretic mechanisms , the main factors of which are renomedullary prostaglandins and atrial natriuretic factor (ANF, atrio -peptide). ANF is synthesized in the cells of the left atrium and is a peptide consisting of 28 amino acids. It increases diuresis and natriuresis , relaxes non-striated muscle fibers of blood vessels and lowers blood pressure. The content of ANF in the left atrium and its secretion into the blood increase after excessive consumption of water and salt; due to stretching of the atria; an increase in blood pressure, as well as in the stimulation of α-adrenoceptors and vasopressin receptors.

These mechanisms function constantly and ensure the restoration of the water-electrolyte balance after blood loss and dehydration, in case of an excess of water in the body, as well as changes in the osmotic concentration of the extracellular fluid. However, in a sick organism, these adaptive mechanisms can be "misled" and then they are included in the pathological process as its most important pathogenetic factor (reduction of blood mass in the left atrium and arterial bed in heart failure).

Violations of water and electrolyte exchange are usually divided into dehydration - (dehydration) and water retention in the body (hyperhydration). Depending on changes in osmotic concentration (ratio of water and electrolytes), dehydration and hyperhydration are divided into three types: isoosmolar , hypoosmolar , and hyperosmolar . The normal osmotic concentration of blood and intercellular fluid is about 0.3 osmol /l.

Dehydration

Dehydration (dehydration, hypohydria , exicosis) develops in those cases when the release of water exceeds its intake into the body (negative water balance). The reason may be a violation of water intake in the body (water starvation, swallowing disorder, esophageal atresia, comatose state, etc.) or increased water loss (diarrhea, vomiting, blood loss, polyuria, hyperventilation, increased sweating, loss of fluid with exudate - burn, etc.) , as well as a combination of these violations. In the case of dehydration, primarily sodium ions and extracellular fluid are lost, and in more severe cases, potassium ions and intracellular fluid are lost.

Dehydration leads to serious consequences, which are associated with a decrease in the volume of circulating blood (hypovolemia) and an increase in its viscosity (disruption of blood circulation and microcirculation, collapse).

Impaired blood circulation leads to tissue hypoxia, which primarily affects the central nervous system. This can manifest itself in a clouded consciousness, hallucinations, and the development of a comatose state. The functions of the nervous centers, the rhythm of breathing are also disturbed, and the body temperature rises.

A significant decrease in blood pressure can be accompanied by impaired filtration in the glomeruli of nephrons, oliguria , hyperazotemia , and non-gaseous acidosis. In response, compensatory reactions occur. Thus, hypovolemia and decreased blood flow in the kidneys contribute to hyperproduction of vasopressin and aldosterone. Under the influence of these hormones, the reabsorption of water and sodium in the tubules of the nephrons increases. A

decrease in filtration pressure also leads to a decrease in diuresis. The great importance of the kidneys is evidenced by the fact that a five-fold reduction in diuresis (to the level of the "mandatory amount of urine") does not yet disrupt the excretion of products of nitrogenous metabolism.

is especially difficult for a child's body. This is caused by the high content of extracellular fluid in children , the low concentration capacity of the kidneys, the relatively large surface area of the skin, the high frequency of breathing, and the imperfection of regulatory mechanisms. As a result, children of the first two years of life are dehydrated

(with intestinal toxicosis, hyperventilation, etc.) occurs more often than in adults and is a formidable complication that often leads to death.

Isoosmolar dehydration develops in cases of equivalent loss of water and electrolytes. This is sometimes observed with polyuria, intestinal toxicosis, as well as in the early stages after acute blood loss and is characterized by a decrease in the volume of extrapelvic fluid without a change in its osmolarity .

Hypoosmolar dehydration is observed in the case of preferential excretion of salts, primarily due to the loss of gastric and intestinal secretions (diarrhea, vomiting), as well as increased sweating, if water loss is restored by drinking without salt. A decrease in osmotic pressure in the extracellular environment leads to the transfer of water into the cells, as a result of which hypovolemia , blood thickening and circulatory disorders are particularly pronounced. Dehydration and loss of electrolytes often lead to acid-base disturbances. Thus, dehydration in the case of loss of gastric juice, accompanied by the excretion of chlorides and H^{+} ions , leads to alkalosis. Loss of pancreatic or intestinal juice, which contains more sodium and bicarbonates, on the contrary, causes acidosis.

Hyperosmolar dehydration develops in those cases when the loss of water exceeds the loss of electrolytes (primarily sodium): with hyperventilation , increased secretion of sweat and saliva (sweat and saliva are hypotonic relative to blood), as well as in the case of diarrhea, vomiting, and polyuria, when compensation for water loss its intake into the body is insufficient. The volume of extracellular fluid decreases, while its osmotic concentration increases. A compensatory mechanism comes into effect - increased production of vasopressin, which limits water loss by renal and extrarenal pathways. Sometimes a second compensation mechanism joins: a decrease in the extracellular space, which stimulates the secretion of aldosterone, which leads to sodium retention and an even greater increase in hyperosmolarity .

An increase in the osmotic pressure of the extracellular fluid causes the movement of water from the cells to it. Dehydration of cells causes an unbearable feeling of thirst, increased breakdown of proteins, an increase in body temperature, and sometimes - darkening of consciousness, coma. To restore the water-electrolyte balance in hyperosmolar conditions 5% glucose solution or hypotonic saline solutions should be administered in case of ecchymosis .

Increased removal of water from the body is observed in non-diabetic patients. The pituitary form of the disease is characterized by polyuria - increased urine output (5-10 liters or more) with a low relative density in the absence of glycosuria .

The main factor in pathogenesis is a decrease in the synthesis of vasopressin, which increases the reabsorption of water in the tubules of the nephron . As a result of water loss, the osmotic concentration in the extracellular space increases.

Irritation of osmoreceptors leads to thirst. In the case of insufficient intake of water in the body, dehydration may be insignificant. Dehydration of the body occurs with uncompensated polyuria.

The cause of the development of this form of diabetes insipidus can be a tumor (mostly metastatic), an inflammatory process, sarcoids , or trauma, when the synthesis of vasopressin is disrupted as a result of damage to the neurohypophysis , pituitary stalk, or hypothalamic nuclei .

The second form of the disease is primary polydipsia of psychogenic origin , which is accompanied by secondary polyuria.

The third form of the disease is nephrogenic diabetes insipidus (usually hereditary), which is based on the insufficiency of vasopressin receptors on the contraluminal side of the distal part of the tubules of the nephron . It is characterized by a decrease in the production of cyclic 3',5'-AMP in the epithelium of the tubules and a decrease in the permeability of the tubules to water.

Excessive accumulation of water in the body.

A positive water balance (hyperhydration , hyperhydria) is observed after excessive introduction of water into the body, as well as in the case of impaired excretory function of the kidneys and skin, water exchange between blood and tissues, regulation of water-mineral exchange.

In an experiment on animals hypoosmolar hyperhydration (water poisoning) can be caused by repeated administration of water into the stomach. A single water load in healthy animals usually does not cause serious consequences. Studies have shown that with excessive introduction of water into the blood, even in a volume equal to the mass of the blood, the mass fraction of water in the blood changes little. This is due to the retention of water in the liver, muscles, spleen, and skin, as well as its increased removal from the body. However, in case of violation of the regulation of water exchange, even a small water load can lead to hyperhydration . Hak, experimental water poisoning can be caused by water stress against the background of vasopressin, aldosterone administration or adrenal gland removal. The fact that adrenalectomized animals, which usually die from loss of sodium salts and dehydration, do not tolerate water stress well is explained by a decrease in blood pressure (and, therefore, glomerular filtration) after removal of the adrenal glands.

In case of water poisoning, the amount of water increases and the osmotic pressure decreases in both "compartments", i.e. in the extracellular and intracellular, however, the increased influx of water into the cells due to a violation of the normal ratio between the concentration of sodium and potassium ions on both sides of the cell membrane is of the greatest importance. which is a consequence of a decrease in the level of sodium in the blood plasma.

In the clinic, water poisoning can be observed with reflex anuria, as well as in the second stage of acute kidney failure. Its signs are the lumen of arterioles and the tone of precapillary sphincters (kinins , biogenic amines , metabolic products, etc.). An increase in filtration pressure can also be caused by a sharply negative pressure in the intercellular space. Thus, with a burn, the negative pressure of the intercellular fluid can reach -30 mm Hg . Art. (-4 kPa) due to the evaporation of water from the surface and the change of colloids, which causes the appearance of compressive forces. This mechanism is considered to be the main one in the pathogenesis of edema in skin burns.

Edema intensifies in the event of a decrease in the osmotic pressure gradient between blood and intercellular fluid, which occurs primarily as a result of hypoproteinemia (proteinuria , starvation, liver cirrhosis) due to a decrease in blood oncotic pressure ; accumulation of osmotically active substances (protein ions, metabolic products) in the intercellular space; an increase in the oncotic pressure of the interstitial fluid, which, in turn, increases filtration. Usually, increased filtration by the type of inverse connection leads to a compensatory increase in lymph flow and a decrease in the oncotic pressure of the interstitial fluid due to

the removal of proteins from the lymph (lymph contains an average of 20 g/l of protein). Because of this, the oncotic pressure of the interstitial fluid increases most noticeably when the lymph outflow is blocked . It should be noted that the hydrophilicity of tissue colloids depends on the concentration of NH ions. In particular, the pH shift in the acidic direction causes swelling of parenchymal elements and dehydration of connective tissue; in the alkaline direction - hydration of the connective tissue.

An excess of sodium ions in the intercellular space is observed after excessive intake of sodium chloride and in case of impaired kidney function. However, in the pathogenesis of edema, the active retention of sodium in the body is more important than the excessive amount of sodium chloride, which is the result of the activation of pathologically changed mechanisms of regulation of water and mineral metabolism.

Retention of sodium is one of the strongest adaptive reactions of the body, developed during the evolution of animals and protects them from the severe consequences of blood loss. As soon as blood loss reduces its total volume in the vessels, the pituitary gland, adrenal cortex and kidneys are reflexively activated to retain sodium and water in the body and thereby increase blood mass. This happens not only with bleeding or sodium deficiency, but also when blood pressure drops or the amount of circulating blood decreases for other reasons. Such a situation occurs, for example, in case of decompensation of the heart, when blood stagnation imitates its deficiency, in case of sclerosis of kidney vessels and other pathological conditions. This is how a "regulation error" occurs, which increases swelling.

An important role in the development of edema is played by an increase in the permeability of the vessel wall. Hydrostatic, oncotic , and osmotic pressure affect various processes in the body only under a certain state of vascular wall permeability. The increase in permeability is accompanied by the release of proteins

shooting pain, nausea, vomiting, cramps; coma may result in death.

Hyperos. molar hyperhydration may develop after drinking salt (sea) water. As a result, the osmotic pressure in the extrapellular medium increases and the liquid moves from the cells to the intracellular space. Severe disorders due to dehydration of cells and similar to those caused by hyperosmolar dehydration develop. However, a strict restriction in drinking promotes adaptation to salt water and there may be no serious violations.

Isoosmolar (isotonic) *hyperhydration* is rare . It can be observed for some time after the introduction of excessive amounts of these isotonic solutions.

Water retention, associated with a violation of the regulation of water-mineral metabolism, is observed in the case of a decrease in the production of ANF and thyroid hormones (myxedema); an increase in the production of vasopressin, insulin , which increases the hydrophilicity of tissue colloids, as well as in the case of secondary hyperaldosteronism .

An excessive amount of fluid is usually not retained in the blood, but passes into the tissues, primarily into the extracellular environment, which is expressed in the development of hidden or pronounced edema.

Swelling (oedema) - excessive accumulation of fluid in the intercellular space due to a violation of water exchange between blood and tissues. Accumulation of extracellular fluid in body cavities is called hydrops ; edema of the abdominal cavity - ascites , pleural cavity - hydrothorax , brain ventricles - hydrocephalus , pericardial cavity - hydropericardium . Accumulated non-inflammatory fluid is called transudate .

Edema is a typical pathological process that occurs in many diseases. In the mechanism of the development of edema, a violation of the water balance, microcirculation, lymph flow , a change in hydrostatic and osmotic, especially colloid -osmotic (oncotic) pressure, an increase

in the permeability of the capillary wall, as well as a disorder of the nervous and humoral regulation of water-mineral exchange play a role.

Most often, the cause of increased venous pressure in pathological conditions is defects of the heart valves, which lead to heart failure and stagnation of blood in the veins. Venous pressure also increases with compression and occlusion (thrombosis) of veins, violation of their valve apparatus, during prolonged standing.

However, filtration pressure in capillaries can increase without significant changes in venous pressure. This is observed in case of microcirculation disturbance: expansion of arterioles and narrowing of venules . Such disorders often arise under the influence of humoral factors that regulate

from the blood into the interstitial environment, by lowering the oncotic pressure of the blood plasma and increasing it in the intercellular space. Therefore, an increase in the permeability of the capillary wall is a prerequisite for the development of edema.

of lymph formation is closely related to the degree of capillary wall permeability . Increased lymph formation and accelerated outflow of lymph play a compensatory role in the edema mechanism: not only interstitial fluid, but also filtered protein returns to the blood through the lymphatic vessels. Difficult outflow of lymph, on the contrary, increases the development of edema. It was established that venous stasis, which is accompanied by an increase in pressure in the superior vena cava, causes a reflex spasm of lymphatic vessels. In addition, the interstitial fluid that accumulates in the process of edema compresses the lymphatic vessels, closing the vicious circle, which causes the progression of edema.

Hormonal factors in the regulation of water and mineral metabolism disorders are closely related to neurogenic factors. This relationship is expressed in the pituitary-adrenal mechanism, which plays an important role in the development of various types of edema.

Depending on the causes and the mechanism of occurrence, edema can be distinguished as a result of damage to the heart (insufficiency of blood circulation), kidneys, liver, as well as cachectic , inflammatory, toxic, neurogenic, allergic, lymphogenic , etc.

Edema as a result of damage to the heart (congestive edema) is caused mostly by venous congestion and an increase in venous pressure, which is caused by increased filtration of blood plasma in the capillaries. The hypoxia that develops leads to a violation of trophicity and permeability of the vessel wall. The reflex-renin- adrenal mechanism of water retention is also of great importance .

Edema due to kidney damage. In the pathogenesis of edema in glomerular nephritis , primary importance is given to a decrease in glomerular filtration , which leads to water retention in the body. The reabsorption of sodium in the tubules of the nephrons also increases, in which, obviously, a certain role belongs to secondary hyperaldosteronism , since the antagonist of aldosterone - spironolactone (a synthetic steroid) has a diuretic and natriuretic effect. A certain role in the mechanism of the development of edema in glomerulonephritis is also played by an increase in the permeability of the capillary wall . In the case of nephrotic syndrome , the factor of hypoproteinemia comes to the fore , which is combined with hypovolemia , which stimulates the production of aldosterone.

In the development *of edema due to liver damage,* an important role is played by hypoproteinemia caused by a violation of protein synthesis in the liver. An increase in production or impaired inactivation of aldosterone is of some importance . It plays a decisive role in the development of ascites in liver cirrhosis

difficulty in blood circulation in the liver and an increase in hydrostatic pressure in the portal vein system.

Reasons *cachetnic* , or hungry, *edema* is alimentary dystrophy (starvation), hypotrophy in children, malignant tumors and other debilitating diseases. The most important factor in its pathogenesis is hyperproteinemia , caused by a violation of protein synthesis, and an increase in the thickness of the capillary wall, associated with a violation of trophism.

In the pathogenesis *of inflammatory and toxic edema* (under the influence of poisonous substances , bites of bees and other insects), a primary role is played by the disruption of microcirculation in the site of the lesion and the increase in the permeability of the capillary wall. An important role in the development of these disorders is played by released vasoactive mediators: biogenic amines (histamine , serotonin), kinins (bradykinin , etc.), adenosine phosphoric acids, arachidonic acid derivatives (prostaglandins , leukotrienes), etc.

Neurogepnshi edema develops as a result of a violation of the nervous regulation of water exchange, trophic tissue and blood vessels (angiotrophoneurosis). These include swelling of the extremities in case of hemiplegia and syringomyelia , swelling of the face in case of trigeminal neuralgia and Quincke 's edema . Along with neurogenic factors, an allergic component is also important in the pathogenesis of angioedema . An important role in the origin of neurogenic edema is played by an increase in the permeability of the vessel wall and a violation of metabolism in the affected tissues.

Allergic edema occurs in connection with sensitization of the body and allergic reactions (urticaria, allergic rash, damage to the forehead muscles, etc.). The pathogenesis of allergic edema is in many respects similar to the pathogenesis of inflammatory and neurogenic edema. Along with the release of biologically active substances, the formation of immune complexes plays a role in microcirculation and capillary wall permeability disorders.

Two stages should be distinguished in the development of edema of various origins. In the first stage, excess fluid that enters the interstitial space accumulates mainly in gel-like structures (collagen fibers and the main substance of connective tissue), increasing the mass of painless , fixed, interstitial fluid. When the mass of fixed fluid increases by approximately 30%, and the pressure reaches atmospheric pressure, the second stage begins, characterized by the accumulation of free interstitial fluid . This fluid is able to move in the interstitial space under the influence of gravity and gives the symptom of a pit when pressing on the swollen tissue.

The influence of factors that cause swelling can be compensated to some extent by protective mechanisms, which include the negative pressure of the interstitial fluid - in some places up to -0.8 kPa (-6 mm Hg); under a 20-25 times increase in lymph outflow when the interstitial fluid pressure increases to the atmospheric level (this mechanism can compensate for an - increase in filtration pressure by 0.92 kPa (7 mm Hg)); washout of proteins with increased lymph outflow , capable of reducing the oncotic pressure of the interstitial fluid.

The final indicator of the action of these mechanisms is 2.27 kPa (17 mm Hg). It is believed that edema develops only when this indicator exceeds 2.27 kPa. Thus, for the development of edema under the influence of only an increase in filtration pressure, it is necessary to increase it by at least 2.27 kPa. When combining an increase in filtration and a decrease in oncotic pressure, both factors together must exceed this value.

A condition in which the reserve of protective mechanisms is reduced, and visible edema has not developed, is called preedema.

The consequences of edema depend on its degree and localization. A significant accumulation of fluid causes compression of tissues, disruption of their trophism and functions. Edema of the brain and lungs is especially dangerous. Accumulation of fluid in body cavities disrupts the function of nearby organs (difficulty breathing due to pleural effusion, etc.).

Violation of mineral metabolism.

The mass of mineral substances in the body is about 4% of the body weight. They are contained in a dissolved state in the form of electrolytes in extra- and intracellular environments, in connection with proteins, in the composition of various organic compounds , as well as in the mineral phase of calcified tissues (bones and teeth). A significant part of calcium, phosphorus, sodium and other minerals of the skeleton form a labile fraction that can be mobilized to compensate for disorders of mineral metabolism.

Electrolytes dissolved in body fluids provide constant osmotic pressure of the internal environment, and their ratio largely determines the acid-base state. Therefore, a violation of electrolyte metabolism is closely related to a disorder of water metabolism and acid- base balance.

Violation of sodium, potassium, magnesium metabolism. Sodium is the main cation of the extracellular medium, together with the corresponding anions (primarily SG) it makes up more than 90% of osmotically active substances in it. The concentration of Ia $^{+}$ ions in the extracellular fluid reaches 140 mmol/l, while in the intracellular environment it is only about 20 mmol/l. The total mass of sodium in the human body exceeds 100 g (approximately 0.14% of body weight), and more than a third of it is concentrated in bones. The labile fraction makes up about half of the sodium in calcified tissues and by its mass is 2-3 times greater than the mass of sodium in the intravascular fluid. Under normal conditions, the daily balance of sodium that enters the body with food and drink is 4-5 g. Most of the sodium is excreted from the body with urine (75-95%) and sweat (2-10%).

Disturbance of sodium metabolism is closely related to violation of water balance . A negative balance of sodium is possible in case of increased loss of it with urine, sweat, digestive secretions (diarrhea) or exudate (burn). Of particular importance is the violation of sodium reabsorption in the channels of nephrons, which is observed with insufficient synthesis of aldosterone (Addison's disease), excessive production of ANF in the atria, prostaglandins E $_{2}$ and B (prostacyclin) in the kidneys, as well as under the influence saluretics - carbonic anhydrase inhibitors (diacarb), benzothiadiazine derivatives (dichlothiazid) , etc.

The loss of sodium in the body leads to the release of K $^{+ \text{ ions from the cells}}$, disrupting the activity of the heart, skeletal and non-striated muscles. Muscle adynamia develops, appetite is lost. Sodium deficiency through sodium receptors located in the hypothalamus and kidneys stimulates the biosynthesis and secretion of aldosterone, which retains sodium in the body.

A positive sodium balance develops with excessive salt consumption, impaired sodium excretion by the kidneys (glomerulonephritis , long-term use of glucocorticoids), as well as in the case of excessive production of aldosterone , which increases sodium reabsorption in the tubules of the nephrons, the alimentary canal, salivary and sweat glands. The molecular mechanism of action of aldosterone is associated with the genetic induction of the synthesis of enzymes involved in the transmembrane transfer of ions and K $^{+}$.

An excess of sodium salts in the body contributes to the development of inflammatory processes , water retention, and the development of arterial hypertension.

The content of potassium in the extracellular medium is 4-5 mmol/l, in the intracellular medium - 110-150 mmol/l. The total content of potassium in the body is 4000-6000 mmol (156-235 g). Two-thirds of it falls on muscles and more than 5% - on the skeleton.

The daily balance of potassium is about 110 mmol (up to 4 g). Violation of this balance is closely related to sodium metabolism disorder. Thus, an excess of potassium increases the removal of sodium and water from the body, and its deficiency causes disorders similar to the effect of excess sodium.

A negative balance of potassium can develop as a result of its insufficient intake with food, in the case of its loss with vomiting or diarrhea, long-term therapeutic use of corticotropin and glycocorticoids , as well as hyperaldosteronism .

A negative balance of potassium leads to hypokalemia , which is accompanied by alkalosis, that is, with a deficiency of K^+ ions, excretion of H by the kidneys increases. Hypokalemia can be compensated for a long time due to the transfer of potassium from the cells into the blood. Prolonged hypokalemia causes a decrease in the content of potassium in cells, muscle weakness, a decrease in gastric motility and

intestines, vascular tone, tachycardia. ECG with hypokalemia characterized by an increase in the C)-T interval and a decrease in the amplitude of the T wave .

Retention of potassium in the body can be observed in the case of an excess of it in food, as well as due to a violation of the release of K^+ ions by the kidneys. In the experiment , a significant retention of potassium can be observed in adrenalectomized animals, in the clinic - with hypofunction of the adrenal cortex (Addison's disease) and acidosis.

Retention of potassium in the body can lead to hyperkalemia , which is accompanied by bradycardia and muscle paresis. It is possible to stop the heart in diastole. Hyperkalemia also develops as a result of the release of potassium from cells (tissue breakdown, insulin deficiency, etc.).

Magnesium is the second most concentrated cation in the intracellular medium (13 mmol/l). It is necessary for the action of some enzymes that catalyze the breakdown of carbohydrates, as well as for the action of phosphatases and phosphoferases . The human body contains about 1000 mmol (24 g) of magnesium, half of which is in the bones. The concentration of magnesium in blood plasma is 1 mmol/l.

Hypermagnesemia is possible in case of consumption of food rich in magnesium (green parts of plants, beans, peas, etc.), as a result of acidosis and impaired excretion of magnesium by the kidneys (uremia). At the same time, depression and sleep develop (magnesium narcosis).

Hypomagnesemia is sometimes observed in pancreatitis as a result of impaired absorption of magnesium (formation of insoluble salts with fatty acids). Clinically, like hypocalcemia , it is manifested by tetany.

Violation of the content of chlorides and hydrocarbons. Chlorides. The total chlorine content in the body is about 2400 mmol (85 g). Chlorine is the main anion of the extracellular fluid, where its concentration is 100-105 mmol/l. Disturbance of chloride metabolism usually develops in parallel with a violation of sodium and water balance.

Hydrocarbon (HCO'z) is the second most important anion of the extracellular environment, where its concentration is 25-30 mmol/l (in the intracellular environment - about 10 mmol/l). The content of hydrocarbons changes with disturbances in the acid-base state.

Disorders of calcium and phosphorus metabolism. The content of calcium in the body before the growth of a person is about 20 g per 1 kg of body weight, most of which (more than 98%) is contained in bones and teeth. About 3 L of the body's total phosphorus is also fixed in calcified tissues . The close relationship between calcium and phosphorus metabolism is caused by the fact that they form insoluble compounds of the oxyapatite type [Sayu (P04)b(0H)2], which form the basis of the crystal structure of calcified tissues (bones and hard tissues of teeth).

Disorders of calcium-phosphorus metabolism can be manifested by a disorder in the absorption of calcium and phosphates in the intestines, a violation of calcification of bones and teeth, as well as deposition of phosphorus -calcium salts in soft tissues.

VIOLATION OF THE ACID-BASE STATE.

Constancy of the pH of the internal environment is a necessary condition for the existence of higher organisms. It is provided by a certain ratio of acids and bases (acid-base state - KOS) in biological environments, in case of violation of which (the pH value exceeds 6.8-7.8) the organism dies. Violations of COS are observed in many diseases, aggravate their course and are subject to correction. Depending on the direction of changes in blood pH , the violation of KOS exceeds the normal range (7.35-7.45), acidosis or alkalosis is called compensated. If regulatory mechanisms are insufficient and pH deviations become significant, then such conditions are called decompensated .

According to the mechanism of development, acidosis or alkalosis can be gaseous (respiratory), which is based on disturbances in the exchange and transport of CO2, and non-gaseous, which is the result of the accumulation of non-volatile products of acidic and basic nature in the body .

pH changes in the body is carried out with the help of physicochemical and physiological regulation mechanisms. The buffer systems of the blood are the first to react, along with the dilution of acids and bases by the extracellular fluid. Biological buffer consists of acidic (donor H^+) and basic (acceptor H^+) components, the ratio between which at normal pH is a constant value. Based on this, hydrochloric (hydrochloric) acid, for example, is stronger than carbonic acid, and the SG anion compared to HSO'z has less pronounced basic properties, since it holds hydrogen ions closer to itself more weakly.

The main buffers of the body are: bicarbonate , which is mainly in the blood; phosphate - in kidneys and other tissues; protein and hemoglobin . Depending on where the buffer functions - in a liquid medium or in cells, its composition will include ions and K^+, respectively . Hydrocarbonate buffer does not have a large capacity, but it is the most labile of the buffers. Therefore, the determination of its components as COS indicators (CO2 tension in the blood, which reflects the concentration of carbonic acid, and the content of hydrogen carbonate) is of great diagnostic value. The buffer properties of proteins are related to their ampholyticity . The most capacious buffer is hemoglobin . Its share accounts for up to 75% of the entire buffer capacity of blood. Hemoglobin, as is known, is an ampholyte protein , the buffering properties of which are mostly associated with the existence of its two forms: oxidized and reduced. In the oxidized form, hemoglobin shows its acidic properties (that is, the ability to dissociate with the return of HGH ions) and is 70-80 times stronger than in the reduced form. Instead of donated hydrogen ions, oxidized Hb binds correspondingly more potassium ions with KNSOz , which is contained in erythrocytes. Reduced Hb, acting as a base, on the contrary, attaches hydrogen ions and gives potassium ions. In addition, 10-15% of CO2 from tissues is transported by hemoglobin in the form of an unstable compound of carbhemoglobin . If necessary, it can transport about 30% of CO2.

The main cellular buffers are protein and phosphate. The buffer system is able to neutralize the excess of both acids and bases in the body, converting them into a form convenient for excretion. Since the products of these reactions are also acids and bases, albeit weaker, the pH shift is only softened, but not eliminated. Complete normalization of KOS occurs only with the help of physiological mechanisms that remove acids and bases from the body and restore the normal ratio of buffer system components. This happens mainly due to the respiratory mechanism (the release of volatile products is ensured) and the kidneys (non-volatile substances are removed). The stomach , intestines, and skin play a much smaller role in this . The participation of the lungs in restored pH is manifested by a change in their ventilation, the intensity of which is regulated by $pC0_2$ and blood pH .

The kidneys regulate the content of acids and bases in the body due to three main processes.

1. *Acidogenesis* (secretion of H+ ions by the epithelium of the tubules of the nephron and their removal from the urine by converting basic phosphates into acidic ones, as well as excretion of weak organic acids). The secretion of $H^{+ ions}$ is ensured by the complex work of the epithelium of the tubules of the nephron , where carbonic acid is constantly formed with the participation of carbonic carbonic anhydrase from $C0_2$ and water. It then dissociates into hydrogen ions, which are actively secreted into the tubule lumen, and NSO3 anions . The intensity of the secretion of $H^{+ ions}$ depends on the amount of $C0_2$ in the cells, and therefore, on the $pC0_2$ in the blood. In order to prevent a significant decrease in the pH of urine (below 4.5, the epithelium of the renal tubules) binds free $H^{+ ions}$ in it. If the binding takes place with the help of $HHП0_4$ (the main component of the phosphate buffer), then its transformation into $HH_2П0_4$ leads to some increase in the acidity of urine, but to a lesser extent than free hydrogen ions. The sodium cations released at the same time are reabsorbed and sent to the blood in the composition No. HCO3 . The amount of acid phosphate and weak organic acids (ketone bodies, lactic, citric and other acids) determines the titration acidity of urine.

2. Ammoniogenesis . An increase in ammonogenesis is observed in case of a significant decrease in urine pH . This process consists in the formation of ammonia from glutamine and other amino acids in the epithelium of the tubules of the nephron and the subsequent binding of H+ ions by it. The formed ammonium cation reacts with the anion of a strong acid (usually chlorine). Ammonium salt NH4Cl is excreted in the urine without lowering its pH . Ammonium cation is able to replace a significant amount of sodium cations in urine, which are reabsorbed into the blood instead of secreted ones

hydrogen ions, and this is one of the ways of preserving bicarbonate in the body.

3. Reabsorption of hydrocarbonate. Hydrocarbon, which is filtered in the nephron, is usually not detected in the secondary urine. Passing through the tubules, it gives sodium cation instead of secreted hydrogen ions and turns into carbonic acid, which is split into CO2 and water. At the same time, urine does not change its reaction. The source of formation HCO3 , which gives its $H^{+ ions}$ in exchange for CO2 of the blood in the event of an increase in its elasticity and CO2, which diffuses from the urine. Anion HCO'z , which remained in the cells after splitting off hydrogen ions, joins the reabsorbed cation and, in the form of NNCO3 , replenishes the amount of blood bicarbonate that entered the urine after filtration. As can be seen, in the process of reabsorption of bicarbonate anion HSO'z is not transported, and only the cation Na^+ enters the blood .

Acidosis. Gas acidosis develops in the event of an excess of carbon dioxide in the body due to a violation of its removal by the lungs. The reason for this is most often a decrease in alveolar ventilation (lung disease or suppression of the respiratory center by narcotics, barbiturates). In addition, gas acidosis occurs when inhaling mixtures with a high CO2 content. An excess of CO2 in the blood leads to an increase in the concentration of H2CO3, which is formed in erythrocytes. The ratio of H2CO3/ NaHCO3 becomes greater than 1/19. Compensation in this case will consist in restoring this ratio by reducing the content of carbonic acid and increasing the content of hydrocarbons. The decisive role in the compensation of gas acidosis belongs to the hemoglobin (to a lesser extent protein) buffer and the kidneys.

The excess of $H^{+ ions}$, which are formed in the process of dissociation of carbonic acid, is largely retained in erythrocytes by reduced hemoglobin, which acts as a base. Part of the released HCO^3 anion binds to the $K^{+ cation}$ of hemoglobin, but in larger quantities (partially in exchange for Cl - ions) it enters the plasma, where it combines with sodium ions (from NaCl , proteins, phosphates) . Due to this, the content of hydrocarbonate increases. A certain amount of hydrogen ions in gas acidosis binds to proteins, which in this case behave as bases.

Therefore, most of the excess $C0_2$ in the blood is transformed into hydrocarbonate under the influence of carbonic anhydrase of erythrocytes and hemoglobin buffer (to a lesser extent protein).

The role of the kidneys in compensation of gas acidosis is to increase the secretion of H^+ ions . Urine acidity increases. Ammoniogenesis may be slightly increased.

If acidosis is not eliminated for a long time, pronounced hypercapnia can lead to secondary damage. Thus, spasm of arterioles causes an increase in blood pressure and thus makes it difficult for the heart to work. Spasm of renal vessels reduces the formation of urine. Under the influence of CO2, the vessels of the brain, on the contrary, expand, as a result of which the intracranial pressure increases. A significant concentration of CO2 in the blood increases the excitability of the vagus nerve , and this, in turn, can lead to cardiac arrest, as well as spasm of the bronchioles and increased secretion of mucus in them, which further complicates breathing. Sometimes gaseous acidosis is complicated by non-gaseous acidosis, since breathing disorder usually leads to insufficient oxygen supply to the body and accumulation of hypooxidation of metabolic products in the tissues.

Non-gaseous acidosis is the most threatening form of COS disorders, which occurs most often. It develops in case of accumulation of non-volatile acidic metabolic products in the blood as a result of excessive formation, insufficient excretion or excessive introduction of them into the body (deep hypoxia, diabetes, starvation, severe damage to the liver and kidneys, etc.). The cause of non-gaseous acidosis can also be a significant loss of hydrocarbons in the composition of the alkaline intestinal juice. Non-gaseous acidosis develops most rapidly and severely during oxygen starvation as a result of profound circulatory disorders (cardiac arrest, shock, collapse, etc.). An inevitable complication in such cases is the weakening of CO2 removal from the blood and the addition of gas acidosis.

Neutralization of a high concentration of H^+ ions , which has a compensatory value, occurs primarily by binding them with NaHCO3 - the main component of the bicarbonate buffer. As a result, there is a decrease in the amount of NaHCO3 that reacts, the formation of carbonic acid and the sodium salt of the neutralized acid. At the same time, the ratio between the numerator and the denominator in the formula of the hydrocarbonate buffer changes in the direction of the predominance of the numerator. Restoration of their normal state due to an increase in the concentration of NaHCO3 and a decrease in $H2CO3$ occurs as the compensatory reactions develop further. The lack of bicarbonate in the plasma (this is the main indicator of non-gaseous acidosis) is compensated to a large extent due to the exchange of ions between erythrocytes and plasma: excess carbonic acid reacts with NaC1 with the formation of $KaHCO_3$, H^+, Cl - ions ; chlorine ions pass into erythrocytes. Recovery of hydrocarbonate occurs partly due to the interaction of carbonic acid with the bases of other buffer systems (protein, phosphate), as well as its reabsorption in the kidneys.

The main mechanism for eliminating excess carbonic acid in the body is hyperventilation of the lungs. Being unstable, carbonic acid disintegrates into $C0_2$ and $H_2 0$ under the influence of carbonic anhydrase of erythrocytes . A high concentration of $C0_2$ (as well as a decrease in pH) excites the respiratory center, causing hyperventilation of the lungs. This mechanism, like the bicarbonate buffer, has a decisive role in the compensation of non-gaseous acidosis.

the hydrogen carbonate buffer, protein also plays a role in binding excess hydrogen ions . In part, H^+ ions in exchange for K + move from plasma to erythrocytes and tissue cells, which leads to hyperkalemia . Hydrogen ions penetrate into the bone tissue, exchanging for sodium and calcium ions. The concentration of cations K^+, Ca^{2+} increases in the blood plasma .

A change in the excretory function of the kidneys in non-gaseous acidosis is less important than hyperventilation of the lungs. Since $pC0_2$ in the blood is reduced, the activity of processes dependent on it in the

epithelium of the tubules of the nephron decreases - the secretion of H^{+} ions and the associated reabsorption of bicarbonate. The titration acidity of urine is significantly increased due to the filtration of non-volatile organic acids that cause acidosis (ketone bodies, lactic acid, etc.); the allocation of ammonium salts increases.

Maintenance of acid-base balance can be achieved at the cost of changing the functions of other systems. Thus, a decrease in $pC0_2$ can lead to a respiratory disorder, as well as to a decrease in vascular tone, which causes a decrease in renal blood flow, and therefore, urine formation. Release of K^{+}, Ca^{+} ions from cells and bone tissue in exchange for H^{+} and their subsequent loss with urine can cause heart arrhythmia, inhibition of neuromuscular excitability, decalcification of bones, etc.

Alkalosis. Gas alkalosis develops in the case of a decrease in $pC0_2$ in the blood due to hyperventilation of the lungs. The reasons for this can be inhalation of rarefied air at a height, brain damage, which is accompanied by excitation of the respiratory center, excessive artificial ventilation of the lungs with the help of an apparatus.

Compensatory reactions in gas alkalosis are aimed at reducing the concentration of hydrocarbons in the blood and restoring the content of carbonic acid. This is ensured by proteins, which, in exchange for sodium ions (from NaHCO3), donate their ions to hydrogen. Replenishment of plasma with ions also occurs at the expense of H^{+} ions from blood cells and bone tissue in exchange for K^{+} and Ca^{+} ions. H^{+} ions, which were released from the depot, adding HCO'z in the plasma , replenish the amount of H_2CO_z lost during hyperventilation of the lungs .

However, the kidneys play a decisive role in the compensation of gas alkalosis. Due to the decrease in $pC0_2$ in the kidneys, the secretion of H^{+} ions and the reabsorption of hydrocarbons decrease. Therefore, filtered hydrocarbons are found in significant quantities in secondary urine. The reaction of urine is alkaline, the content of titrated acids and ammonium salts is negligible. The ionic balance in the plasma with the loss of HCO ions is partially restored due to the Cl - ions that came from the cells and contribute to an increase in the chloride content in the plasma.

Lecture No. 6

Topic: Peculiarities of protein, fat, and carbohydrate metabolism disorders: etiology, pathogenesis.

Purpose : To acquaint students with the pathological features of protein, fat and carbohydrate metabolism.

Give etiological, pathological and classification of metabolic disorders.

The material of the lecture is aimed at the formation of logical and professional thinking in the students, the responsibility of the doctor for the condition of the patient's body in the case of metabolic disorders

Basic concepts: Starvation, obesity, atherosclerosis, hypoglycemia, hyperglycemia, diabetes, microcirculation disorders.

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

Pathophysiology of energy and protein metabolism. Etiology and pathogenesis. Starvation.

Define the concept of basic exchange

The level of basic metabolism of an adult depends on age.

Methods of determining the main exchange

In the case of which pathological changes there is an increase and decrease in the basic metabolism.

Starvation. Characteristic. Kinds Stages.

Manifestations and clinical symptoms.

Complication.

Fats are contained in all human tissues, and are the main and mandatory components of human food. The need for fats depends on age, lifestyle, climate and other factors (on average, you need to consume 80-100 g of fats per day).

Lipids include triglycerides , glycerophosphates , cholesterol and its esters, bile acids, fatty acids (unsaturated and saturated) and other compounds. Lipids are part of cell membranes, are the main sources of energy, solvents of vitamins A, D, E, F, participate in the synthesis of steroid hormones, in the creation of protective heat-insulating and water-repellent coatings, play a mechanical role (fixation of the kidneys). Lipids (prostaglandins) are regulators of the functions of various organs in normal and pathological conditions, participate in the transmission of nerve impulses, in the creation of intercellular contacts. Enzyme complexes that are part of lipids play an important role in blood clotting, digestion, and immunological processes. The lack of lipids in the body leads to a violation of these functions. Some lipids enter the body with food, other lipids are synthesized in the body. Some polyunsaturated acids (linoleic , linolenic, etc.) are introduced into the body with vegetable fats, which belong to essential fatty acids, because they are not synthesized in the human body, their function is extremely important. Therefore, the European Association of Experts for the Elimination of Fat Metabolism Disorders recommends limiting only the total consumption of fats, especially of animal origin, and not completely eliminating the consumption of fatty acids and dietary cholesterol. It is also recommended to increase the consumption of products enriched with polyunsaturated fatty acids (liquid vegetable oils, fish, poultry, seafood). If there is insufficient intake of fats in the body, the probability of oncological diseases increases sharply.

Pathological changes in fat metabolism can occur at various stages in the event of a violation:

processes of digestion and absorption of fats;

transport of fat and its transition into tissues;

oxidation of fats in tissues;

intermediate fat metabolism;

fat exchange in adipose tissue (excess or insufficient formation and deposition).

The pathology of fat metabolism is manifested by various types of hyper-lipoproteidemia and alipoproteidemia .

Hyperlipoproteinemia . There are 5 types of hyperlipoproteinemia :

Type I – fat-induced lipemia ;

II type – hyper -α- lipoproteidemia (multiple nodular xanthoma). Characteristic early manifestations of atherosclerotic changes in vessels, especially coronary, xanthomatous changes in the endocardium and heart valves, tendon xanthomas (hard

deposits of fat), peri-orbital xanthelasma , rheumatoid joint pain. There are known cases of death from myocardial infarction in childhood. In these patients, a defect of LDL receptors on skin fibroblasts was detected, which leads to a decrease in the breakdown of LDL and an increase in cholesterol synthesis.

type – dys -β- lipoproteidemia (“ floating ” hyperlipemia). Patients are characterized by hypertrophy of lipocytes , atherosclerosis of coronary arteries, angina pectoris, myocardial infarction, obturation diseases of peripheral arteries, yellowish-brown deposits of lipids in the skin of the lines of the palms in places where wedding rings are stamped, and xanthomas . These manifestations are observed already in early childhood. Obesity, diabetes, and fatty liver disease develop.

type – hyperpre -γ- lipoproteidemia (familial essential hyperlipemia), in which the presence of a genetic defect is assumed. Fatty liver, diabetes mellitus, coronary sclerosis and organ angiopathy , general obesity, intermittent lameness develop. Clinical manifestations of atherosclerosis are observed more often in adults and the elderly.

Type V – hyperchylomicronemia (combined lipemia caused by disturbances in the metabolism of both fats and carbohydrates). Patients have symptoms similar to type IV. In addition, pancreatitis, neuropathy with painful paresthesias of hands and feet, and vascular complications are possible. The presumed cause is secondary inhibition of chylomicron cleavage .

Treatment of familial hyperlipoproteinemias includes limiting the intake of neutral fats and carbohydrates while introducing short-chain fatty acids into the diet.

α- lipoproteidemia . α- lipoproteidemia – Tenzhi disease . The type of inheritance is autosomal recessive. The basis of the defect is a violation of the synthesis of the protein component. The following signs are observed in homozygous representatives: there is no normal α- lipoprotein , only the altered α- lipoprotein "Tenti - LP" is present. The pathogenetic mechanism is based on insufficient evacuation of cholesterol esters.

Symptoms: enlarged tonsils, hepatosplenomegaly , enlarged lymph nodes (accumulation of cholesterol esters), diarrhea, retinitis, clouding of the cornea.

Patients feel relatively well because α- lipoprotein has a short half-life.

α-β- lipoproteidemia – Bassen-Kornzweig disease . The type of inheritance is autosomal recessive.

Etiology: inability of the liver to synthesize active aprotein or the possibility of synthesis of only inactive aprotein B.

Bassen-Kornzweig disease can also develop as part of autoimmune processes in diseases of the liver and gastrointestinal tract (the formation of LP is disturbed), in diseases of the thyroid gland (the splitting of LP increases).

Symptoms: steatorrhea , progressive dystrophy. In the walls of the intestines fat stagnation is detected. In many body systems, the structure of cell membranes is disturbed. On the surface of erythrocytes, thyroid bulges (acanthocytes) are observed, anemia develops with reticulocytosis and bone marrow hyperplasia. Damage to the myelin sheaths leads to disorders of the peripheral nerves and the central nervous system (pyramidal tract and cerebellum). The first symptom in the second year of life is the fading of tendon reflexes. Ataxic gait , characteristic nystagmus, violation of vibration sensation. Patients have mental retardation, myopathy. Pigmentary retinopathy develops, which causes scotoma and blindness.

The role of lipid metabolism disorders in the pathogenesis of

atherosclerosis. Atherosclerotic changes in blood vessels are characteristic of almost all people over 40 years old, the difference is only in the degree of changes. The development of atherosclerosis is closely related to the processes of cholesterol transport into the arterial wall, removal of cholesterol from the arterial wall. Violation of this process occurs in the absence of specific receptors on the surface of cells, increased affinity of lipoproteins with the membrane, direct damaging effect of excess cholesterol on the endothelium and vascular smooth muscle cells. An excess of lipoproteins accelerates the development of atherosclerosis.

Hereditary forms of accelerated atherosclerosis are caused by a defect in lipoprotein genes and their receptors, enzymes of lipoprotein and cholesterol metabolism, the rate of production and catabolism of lipoproteins circulating in the blood changes in the liver. Various molecular defects have been noted in different families, which lead to an imbalance of cholesterol either in the cells or in circulating blood lipids.

Cholesterol, triglycerides , and saturated fatty acids have atherogenic properties. An increase in the concentration of atherogenic lipoproteins in the blood can be caused by a decrease in the rate of their removal from the blood to the liver; increasing the speed of their synthesis; violation of metabolism in plasma, taking into account the formation of abnormal modified lipoproteins . Phospholipids and polyunsaturated fatty acids have antiatherogenic properties . They limit the absorption of dietary cholesterol in the small intestine, stimulate the synthesis of bile acids in the liver, inhibit the synthesis and secretion of various lipoproteins.

Fat infiltration and fatty dystrophy

If the fat entering the cells is not split, oxidized , or removed from it, this indicates fatty infiltration. If it is not combined with a violation of the plasma structure and its protein component, then it is called fatty dystrophy. The general cause of fatty infiltration and fatty dystrophy is considered to be suppression of the activity of oxidizing and hydrolytic enzymes of fat metabolism (in case of arsenic, chloroform poisoning, vitamin deficiency , etc.).

Fatty infiltration develops with alimentary and transport hyperlipemia and with a violation of the formation of phospholipids, which is a consequence of insufficient intake of choline, methionine and other lipotropic factors with food, insufficient secretion of lipocaine by the pancreas , which activates the formation of phospholipids in the liver and oxidation of fatty acids in it.

Disruption of fat metabolism in adipose tissue is manifested by obesity.

Obesity *is the tendency of the body to excessively increase body weight under the influence of certain conditions.*

At the same time, the body weight increases (Fig. XIV) due to the abnormal accumulation of fat in the depot.

By etiology, obesity is divided into three types: alimentary, hormonal (Fig. XV), cerebral. The essential role of heredity in the pathogenesis of obesity. Obesity develops as a result of three main pathogenic factors:

increased intake of carbohydrates and fats in food with inappropriate use of fat for energy;

insufficient use (mobilization) of fat from the depot as a source of energy;

excessive formation of fat from carbohydrates.

Consequences of obesity: impaired glucose tolerance, hyperglycemia, hyperinsulinemia ; increased excretion of glucocorticoids with urine (in contrast to

patients with Ishchenko- Cushing syndrome , the ratio of excretion of glucocorticoids and creatinine remains normal in obese patients) after exercise, during sleep; after the introduction of arginine, smaller fluctuations in the concentration of somatotropic hormone in the plasma are observed; decrease in insulin sensitivity of enlarged alipocytes and muscles; increase in the content of unsaturated fatty acids in the blood - increased consumption of them by the muscles; hypertrophied lipocytes are more responsive to norepinephrine and other lipotic substances.

Starvation is a typical pathological process that develops as a result of a complete lack of food or insufficient intake of nutrients in the body, as well as in conditions of a sharp violation of the composition of food and its assimilation.

Classification of starvation:

Physiological, pathological and therapeutic fasting are distinguished by origin. Physiological starvation is characteristic of some animal species during hibernation.

The pathological type of starvation is divided into:

1. Complete fasting: a) with drinking water; b) without drinking water (absolute).
2. Incomplete starvation (malnutrition).
3. Partial starvation (quality).

Complete fasting with water. *Pathogenesis:*

I. The period of uneconomic energy consumption . Lasts 2-4 days. A strong feeling of hunger is characteristic, due to the excitation of the food center. With complete starvation, it lasts up to 5 days, and then disappears. Rapid weight loss occurs. The main source of energy during this period is *carbohydrates* , as evidenced by the value of the respiratory coefficient, equal to 1.0. Hypoglycemia occurs, which increases the secretion of glucocorticoids by the adrenal cortex. This results in increased catabolism of proteins in peripheral tissues, in particular muscle, and activation of gluconeogenesis in the liver. The main exchange first increases slightly, and then gradually decreases and becomes 10-20% less than the original. A negative nitrogen balance develops .

II. The period of maximum adaptation . Its average duration is 40-50 days. The pace of body weight loss slows down to 0.5-1% per day. The feeling of hunger disappears. The main source of energy is *fats,* which is evidenced by the value of the respiratory coefficient, equal to 0.7. Hypoglycemia increases the flow of lipolytic hormones (adrenaline, glucocorticoids , glucagon) into the blood. As a result, fat is mobilized from the depot and hyperlipacidemia develops . It, in turn, is the cause of increased formation of ketone bodies in the liver. The resulting ketonemia can lead to metabolic acidosis. The main exchange during this period is 10-20% below the initial level. The nitrogen balance is negative.

III. Terminal period. Duration - 2-3 days. Intensive decay of tissues occurs, intoxication develops. The main source of energy is *proteins* , as evidenced by the value of the respiratory coefficient, equal to 0.8. Urinary excretion of nitrogen, potassium, and phosphates increases (signs of destruction of cells and tissue proteins). Death occurs when the body weight decreases to 50% of the original.

Absolute fasting is complete fasting without drinking water. Its duration is 2-3 times less than the duration of complete fasting with water, due to the fact that there is an increased splitting of fats to form endogenous, as a result of which ketonemia and non-gaseous acidosis develop rapidly. The severity of the course of absolute starvation is also due to the accumulation of a large number of end products of

metabolism and other toxic products, which require water to be removed from the body.

Incomplete starvation (energy deficiency) develops when the energy value of food does not satisfy the body's energy needs.

Protein-energy deficiency is a condition that occurs as a result of a combination of incomplete and high-quality protein starvation. *Species:*

a) alimentary dystrophy - in its pathogenesis, in addition to protein and energy deficiency, additional factors are also important: cold, physical fatigue, neuropsychological tension;

b) alimentary fever . It develops in children up to one year of age. Energy deficiency comes first;

c) kwashiorkor . It develops in children aged 3-6 years. the main factor in pathogenesis is protein deficiency, the energy deficit is compensated by excessive consumption of carbohydrates.

Clinical manifestations of protein-energy deficiency:

1. Insufficient intake of proteins in the body leads to a violation of the liver's biloxinthetic function. This is the cause of hypoproteinemia , which, in turn, causes the development of oncotic edema.

2. Energy deficiency is the cause of a decrease in basic metabolism. This is manifested by a decrease in body temperature (hypothermia).

3. Atrophic syndromes. Their development is associated with violations of the plastic and energy supply of cells. A manifestation of atrophic changes in the central nervous system is the slowing of mental development, in the digestive system - malabsorption and diarrhea, in the cardiovascular system - hypotension , in the immune system - a decrease in the synthesis of antibodies and increased sensitivity to infections, in the red bone marrow - the development of anemia, in the skeletal in muscles - hypodynamia and muscle weakness, in bones - retardation of skeletal growth.

Partial (qualitative) starvation is the insufficient intake of one or more nutrients with the normal energy value of food. Types: protein, fat, carbohydrate, vitamin, mineral, water fasting.

Pathophysiology of fat and carbohydrate metabolism: etiology and pathogenesis. Atherosclerosis.

The importance of fats for the body, their metabolism in the body.

Lipids and lipoproteins of blood plasma, lipid transport.

Sources of blood plasma cholesterol and its metabolism

Anatomical and physiological features of blood vessels. Prerequisites for the formation of an atherosclerotic lesion.

Atherosclerosis. Pathogenetic mechanisms of development. Stages. Signs. Complication.

Normally, the fasting blood plasma glucose level ranges from *3.3 to 5.5 mmol/l.*

Hypoglycemia is a condition characterized by a decrease in blood plasma glucose below 3.3 mmol/l.

Etiology:

• Carbohydrate starvation is observed as a result of prolonged general starvation. Deficiency in food of only carbohydrates does not lead to hypoglycemia due to the activation of gluconeogenesis .

• Liver pathology. In most hereditary and acquired diseases of the liver, the

deposition of glucose in it in the form of glycogen is disturbed and the intensity of gluconeogenesis decreases . As a result, the body is not able to maintain the level of glucose within normal limits for a long time without receiving glucose from the outside.

• Indigestion. Violation of cavity and parietal cleavage and absorption of carbohydrates lead to the development of hypoglycemia.

• Kidney pathology. Hypoglycemia develops when glucose reabsorption is impaired in the proximal tubules of the nephron of the kidneys, which leads to the development of a syndrome characterized by hypoglycemia and glucosuria (renal glucosuria).

• Endocrinopathies. The main causes of the development of hypoglycemia in endocrinopathies: insufficiency of endocrine hormones (adrenal glands, hypothyroidism, pituitary insufficiency) or excess insulin (insulinoma). Glucocorticoids , thyroid hormones, THG, catecholamines , and glucagon are included *in the contінsular hormones* . An excess of insulin activates the utilization of glucose by cells, inhibits gluconeogenesis , and inhibits glycogenolysis . These effects are observed with insulinomas or insulin overdose.

• Long-term intensive physical work leads to depletion of glycogen reserves deposited in the liver and skeletal muscles (marathon running).

• Uptake of glucose by tumor cells.

Clinical manifestations of hypoglycemia:

Hypoglycemic syndrome - a steady decrease in blood glucose below the norm, which is combined with a violation of vital activity. Manifestations of hypoglycemic syndrome can be adrenergic (due to excessive secretion of catecholamines) and neurogenic (due to disorders of the central nervous system).

• Adrenergic manifestations: hunger, anxiety, fear of death, muscle tremors, tachycardia, sweating.

• Neurogenic manifestations: headache, confusion, dizziness, visual disturbances.

Hypoglycemic coma is a condition characterized by a decrease in the level of blood glucose below normal (as a rule, less than 2.0-1.5 mmol / l), loss of consciousness, lack of reaction to external and internal stimuli, impaired cardiovascular activity and breathing.

Pathogenesis of hypoglycemic coma:

• The energy supply of cells, especially neurons, is disrupted due to a lack of glucose; deficiency of metabolites of free fatty acids - acetoacetic and β-hydroxybutyric acid , which can provide neurons with energy even in conditions of hypoglycemia. Ketonemia develops only after a few hours and in case of acute hypoglycemia cannot eliminate energy deficiency in neurons.

• Imbalance of ions and water in cells due to malfunction of energy-dependent ion carriers: loss of K^+, accumulation of H^+, Na^+, Ca^{2+}, water.

↓ influx of glucose into neurons → substrate hypoxia → violation of ATP formation → damage to neurons → coma

Principles of hypoglycemia therapy:

Etiotropic treatment is aimed at filling the deficit of glucose and eliminating the cause of its occurrence.

• Eliminating hypoglycemia is achieved by introducing glucose into the body.

• Therapy of the main disease that caused hypoglycemia (diseases of the liver,

kidneys, gastrointestinal tract, glands of internal secretion).

Pathogenetic treatment is aimed at blocking the main pathogenetic links (energy supply disorders, damage to membranes and enzymes, water-electrolyte imbalance).

Symptomatic treatment is aimed at eliminating symptoms that worsen the patient's condition (severe headache, feeling of fear of death, sharp blood pressure fluctuations, tachycardia).

Hyperglycemia is a condition characterized by an increase in blood plasma glucose level above 5.5 mmol/l.

Etiology:

• Alimentary overeating. When consuming easily digestible carbohydrates in large quantities, the glucose level rises quickly and exceeds the ability of hepatocytes to form glycogen.

• Endocrinopathies are the most common cause of hyperglycemia. In this case, they are caused by an excess of constitutive hormones or a deficiency of insulin effects. 1. *Insulin deficiency:*

a) violation of glucose utilization by cells,

b) activation of glycogen synthetase → glycogenesis ,

c) inhibition of the transition of glucose into fats,

d) activation of gluconeogenesis .

2. *Hyperproduction contrainsular hormones* (adrenaline - pheochromocytoma , glucagon , GCS - Itsenko-Cushing's disease and syndrome , thyroid hormones - thyrotoxicosis, STH - gigantism and acromegaly against the background of pituitary adenoma): activation of glycogenolysis and / or gluconeogenesis (formation of glucose from proteins and fats)

• Neurological and psychogenic disorders. States of mental excitement and stress are characterized by activation of the sympathoadrenal , hypothalamic - pituitary -adrenal and thyroid systems. Hormones of these systems (catecholamines , glucocorticoids , T4 and T3) activate glycogenolysis and gluconeogenesis , suppress glycogenesis .

• Liver pathology. With liver failure (hepatitis, cirrhosis), hyperglycemia may develop after eating due to the inability of hepatocytes to transform glucose into glycogen.

Clinical manifestations of hyperglycemia:

Hyperglycemic syndrome is a condition characterized by a long-term increase in the level of blood glucose above the norm, which is combined with a disturbance of vital activity. Hyperglycemic syndrome includes a number of interconnected symptoms.

• Glucosuria - the result of exceeding the possibility of tubular reabsorption of glucose from primary urine at a blood glucose level of more than 10 mmol / l (physiological renal threshold for glucose).

• Polyuria - the formation and excretion of urine in an amount exceeding the norm (more than 1800-2000 ml / day), which is associated with an increase in the osmolality of urine due to the presence of glucose in it (glucose increases the osmotic pressure of primary urine, which prevents water reabsorption) .

• Hypohydration (dehydration) - a decrease in fluid content in the body due to polyuria.

• Polydipsia (thirst) - increased fluid intake due to thirst caused by

hypohydration and increased blood plasma osmolality (hyperosmolar hypohydration).

• Arterial hypotension is caused by hypovolemia due to hypohydration of the body.

Diabetes mellitus (DM) Type 1 is a disease based on an absolute lack of insulin in the body, which occurs as a result of the death of b-cells of the pancreatic islets, which causes metabolic disorders.

Etiology of type 1 diabetes:

Insulin deficiency can occur under the influence of factors of a biological, chemical, physical nature, as well as inflammation of the pancreas.

• Biological factors

♦ Genetic defects of β-cells of the islets of Langerhans . Genetic defects of the MHC system cause the inclusion of immune autoaggressive damage to the pancreas or the repression of genes encoding insulin synthesis.

♦ Immune factors. Autoaggressive immunoglobulins and cytotoxic T-lymphocytes are able to damage β-cells.

♦ Viruses that are tropic to β-cells: Coxsackie , hepatitis, measles, chicken pox, epidemic parotitis, rubella. Viruses have a direct cytolytic effect and initiate autoimmune processes.

♦ Endogenous toxic substances. As a result of disruption of pyrimidine metabolism , alloxan is formed , which blocks the synthesis of insulin.

• Chemical factors: high doses of ethanol, some anticancer drugs (cytostatics).

• Physical factors: ionizing radiation, mechanical trauma, compression by a tumor.

• Inflammatory processes in the pancreas caused by factors of a chemical, physical or biological nature. Chronic pancreatitis is the cause of insulin deficiency in about 30% of cases.

Pathogenesis:

The basis of insulin deficiency is the development of an immunoaggressive process, which is accompanied by the gradual destruction of β-cells. There are two options for development:

1. A) Entry into the body of persons genetically predisposed to diabetes by carriers of foreign AGs, usually viruses. B) Formation of an immune response with the formation of AT and cytotoxic lymphocytes to foreign AGs. C) Specific AT and lymphocytes act on the antigenic structures of the β-cell, which have a similar structure to foreign AG. This phenomenon is referred to as "cross- immunoaggressive reaction". In the course of this reaction, β-cells are destroyed, and individual proteins of the plasma membrane are also denatured and become autoantigenic .

2. A) The pancreas is primarily damaged under the influence of factors of a chemical, physical or infectious nature. B) Release of "foreign" proteins for the immune system (normally they are found only intracellularly and do not enter the blood): cytoplasmic proteins of heat shock, proinsulin . Some proteins are denatured and become autoantigenic . C) Formation of an immune response with the formation of AT and cytotoxic lymphocytes to denatured and intracellular proteins that have entered the blood. D) Autoaggressive AT and lymphocytes act on the antigenic structures of their own β-cells, which is accompanied by their destruction.

Type 1 diabetes manifests itself at a young age, the blood insulin level is low. Polyuria, polydipsia , polyphagia, weight loss develop rapidly , and ketoacidosis

develops . Legitimate complications. Insulin treatment is necessary.

Diabetes mellitus (DM) Type 2 is a disease based on relative insulin deficiency or insulin resistance , which causes metabolic disorders.

Type 2 diabetes manifests itself in most cases after the age of 40, develops slowly, often in people who are obese. Polyuria, polydipsia , weakness develops. The insulin level is high or normal. Complications and ketoacidosis occur less often. Insulin is not used in its treatment.

Hereditary predisposition to type 2 diabetes, unlike type 1 diabetes, is not associated with HLA genes.

Risk factors:

• Excess body weight, which is combined with an increase in insulin resistance of target tissues and stimulation of the production of counterinsular hormones. This excessively activates the synthesis of insulin by β-cells of the pancreas, leading to their "exhaustion" and damage.

• Arterial hypertension, which leads to a violation of microcirculation in the pancreas.

• Chronic stress, which is accompanied by a steady increase in the level of counterinsular hormones in the blood.

Conditionally, two stages of pathogenesis are distinguished:

1. Hyperinsulinemic stage. Consuming a large amount of food by obese individuals causes an increase in insulin secretion (hyperinsulinemia). This reaction is aimed at activating the processes of depositing nutrients in adipose tissue in the muscles, there is no need for the action of insulin. Therefore, they protect themselves from an excess of this hormone by reducing the number of receptors on the surface of muscle cells. The phenomenon of insulin resistance of muscle tissue develops - its sensitivity to the action of insulin decreases.

2. Hypoinsulinemic stage. Increased load on the insular apparatus can lead to functional exhaustion of cells. This is facilitated by their genetically determined defects and an excess of counterinsular hormones in the body. As a result, the amount of secreted insulin decreases and its relative insufficiency develops. At the same time, the effect of insulin on adipose tissue is preserved (there are many insulin receptors on fat cells), and on muscle tissue it decreases due to the development of insulin resistance .

Metabolic disorders in diabetes.

- *Violation of fat metabolism:*

1. Hyperlipacidemia (activation of lipolysis). Increase in blood LDL and VLDL.

2. Ketonemia , ketonuria = ketoacidosis :

a) Excessive production of ketone bodies: activation of lipolysis □□ UHD in the blood □ entering the liver □ activation of beta-oxidation □□□ Acetyl CoA □ increased synthesis of ketone bodies (acetoacetic acid, beta- oxybutyric acid, acetone),

b) Violation of utilization of ketone bodies as a source of energy in the Krebs cycle.

3. Fat infiltration liver (increased intake of UHD in the liver, reduced synthesis of lipoproteins and their secretion into the blood).

- *Disorders of protein metabolism:*

1. Decreased protein synthesis (transmembrane transport of amino acids due to insulin deficiency, degradation of polysomes, disruption of translation processes) hyperaminoacidemia , aminoaciduria .

2. Activation of protein catabolism negative nitrogen balance, hyperazotemia .

3. Decrease in the synthesis of antibodies and the body's resistance to infection.

- *Violation of carbohydrate metabolism:*

1. Hyperglycemia occurs as a result of insufficient insulin effects and impaired utilization of glucose by cells.

2. Glycosuria is mainly a consequence of hyperglycemia.

3. Hyperlactatacidemia - develops due to inhibition of lactate catabolism in the Krebs cycle, violation of glycogen resynthesis from lactate.

Chronic complications of diabetes:

Microangiopathies are pathological changes in the vessels of the microcirculatory channel.

Pathogenesis:

- Glycosylation of capillary basement membrane proteins in conditions of hyperglycemia.
- Thickening and compaction of the vascular wall under the influence of excess sorbitol . Normally, no more than 1-2% of intracellular glucose is transformed into sorbitol , and with diabetic hyperglycemia, the level of conversion increases 8-10 times due to the activation of aldose reductase .
- Swelling, thickening and dystrophy of the endothelium of vessels.
- A change in the structure of the proteins of the basal membrane of vessels and their acquisition of antigenic properties, which leads to immune-mediated damage to the walls of microvessels .
- Tissue ischemia caused by a decrease in the lumen of vessels due to a decrease in the formation of NO and thickening of the vascular wall. The specified changes lead to a violation of transcapillary exchange and the formation of microthrombi .

Macroangiopathy - the development of sclerotic changes in the walls of medium- and large-caliber arteries. Atherosclerosis of blood vessels appears early and progresses rapidly in diabetes mellitus.

Pathogenesis:

- Glycosylation of basement membrane proteins and the interstitium of vessel walls. Modification of protein molecules stimulates atherogenesis .
- Accumulation of sorbitol in the wall of arterial vessels.
- An increase in the level of atherogenic LDL and a decrease in the level of anti-atherogenic HDL.
- Activation of the synthesis of thromboxane A_2 by platelets, which potentiates vasoconstriction and platelet adhesion on vessel walls.
- Stimulation of proliferation of smooth myocytes of arterial vessels.
- These changes lead to the formation and calcification of atherosclerotic plaques, thrombus formation and occlusion of arteries, impaired blood supply to tissues with the development of heart attacks and gangrene.

Neuropathies

- Glycosylation of proteins of peripheral nerves.

- The formation of AT to modified proteins with the development of reactions of immune autoaggression .
- sorbitol in neurons and Schwann cells .
- Decreased intraneural blood supply with the development of chronic ischemia and hypoxia of nervous structures. The main factor in ischemic nerve tissue is considered to be a deficiency of the vasodilator NO.
- Violation of myelin synthesis and demyelination of nerve fibers; slowing down the speed of conduction of nerve impulses.
- These changes lead to *peripheral polyneuropathy* , which is characterized by damage to several nerve trunks and is manifested by paresthesia of the feet, less often - hands; loss of pain and vibration sensitivity, more often in the distal parts of the lower extremities; decreased expression of reflexes, necrosis of foot tissues (diabetic foot syndrome). *Vegetative neuropathy* is manifested by disorders of the gastrointestinal tract (swallowing difficulties, constipation or diarrhea), dystrophy of the urinary bladder (urinary retention), impaired vascular tone (hypotension or fainting), cardiac disorders, sexual dysfunction (erectile dysfunction, decreased libido and other disorders). *Radiculopathy* due to changes in the roots of the spinal cord. They are characterized by pain and increased sensitivity along the course of one or more spinal nerves (usually in the chest and abdomen).

Retinopathy. Causes: microangiopathies in eye tissues and hypoxia of eye tissues, especially the retina. Types and manifestations:

- Nonproliferative retinopathy is manifested by the formation of microaneurysms of arterioles and venules , microhemorrhages in the retina and vitreous body (which can cause blindness), the development of microthrombi with occlusion of vessels and the formation of edema.
- Proliferative retinopathy is characterized by new formation of blood vessels of the microcirculatory bed (stimulated by hypoxia), which sprout into the vitreous body; formation of scars and detachment of the retina in the regions of large hemorrhages.

Nephropathy. Diabetic nephropathy is characterized by:

- thickening and compaction of the walls of glomerular arterioles;
- thickening of the basal membranes of the glomeruli and tubules with disturbances in the processes of filtration, reabsorption, and secretion;

an increase in blood pressure as a result of activation of the SAS and RAAS

Lecture No. 7

Topic: Pathophysiology of shock. Types, clinical manifestations, causes and mechanisms of development. Violations of general hemodynamics and microcirculation in the pathogenesis of shock states.

Purpose :

- Acquaint applicants with the definition of an extreme state and its main types (I level).

Give the etiological, pathological and stage classification of shock (I - II level). On the examples of shock and coma, demonstrate the relationship between protective - adaptive and pathological changes in the body, give the mechanisms of various types

of shock and coma (II - III level).

The material of the lecture is aimed at the formation of logical and professional thinking in the students, the doctor's responsibility for the condition of the patient's body in extreme conditions.

Show applicants the importance of M. Pirogov in the study of issues of traumatic shock.

Basic concepts: Collapse , shock, coma, extreme conditions

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

SHOCK

Shock (from the English shock, shock) is a severe pathological process, which is accompanied by exhaustion of the body's vital functions and poses a threat to its life due to a critical decrease in capillary blood circulation in the affected organs.

According to modern ideas about the main etiological factors and mechanisms of development, the following forms of shock are distinguished.

1. *Primary hypovolemic shock.* The occurrence of hypovolemic shock is associated with external or internal blood loss (trauma, including postoperative, damage to blood vessels in pathologically changed organs and tissues, blood coagulation disorders); loss of plasma (burn, fragmentation of tissues); loss of fluid and electrolytes (intestinal obstruction, pancreatitis, peritonitis, enterocolitis, overheating); redistribution of blood in the vascular bed (thrombosis and embolism of main veins).

Deficiency of blood volume at the same time causes a decrease in the amount of venous return to the heart, a decrease in the stroke and minute volume of the heart (UOS, HOS) and blood pressure.

Due to the sympathoadrenergic reaction (stimulation of p-receptors of the heart and a-receptors of peripheral blood vessels), an increase in the frequency of heart contractions and an increase in peripheral vascular resistance is ensured, which contributes to the normalization of blood pressure and blood supply, primarily to the heart and brain.

The insufficiency of these mechanisms, as well as the negative consequences of vasoconstriction, is accompanied by a sharp decrease in blood supply to organs and tissues and characteristic signs of shock.

2. *Traumatic shock.* The occurrence and course of traumatic shock have some characteristic features. Thus, traumatic shock develops against the background of acute irritation and even damage to extero- , intero- , and proprioceptors as a result of the direct action of physical factors and significant violations of the functions of the central nervous system. In its course, two stages are observed: arousal (or erectile stage—from lat. *egesis* — tense) and braking (or torpid stage — from Lat. *iogriyiz* - will be hooked nily).

The first stage is short-lived, it is characterized by a state of excitation of the central nervous

system (cortex, subcortical formations, autonomic nuclei of the sympathetic nervous system), the consequence of which is an increase in the function of the circulatory and respiratory systems, some endocrine glands (pituitary gland, medulla and cortical substance of the adrenal glands, neurosecretory nuclei of the hypothalamus) with the release of an excess amount of corticotropin, adrenaline, norepinephrine , vasopressin into the blood and the development of a stress syndrome.

The second stage is longer (from several hours to a day). It is characterized by the development in the central nervous system of the processes of inhibition, parabiosis (comparative and paradoxical phases) with the spread of these processes to the parts of the brain stem, hypothalamus and spinal cord and a decrease in the functions of vital organs and systems. These concepts are the basis of the neuro-reflex theory of the pathogenesis of traumatic shock.

In the mechanism of occurrence and development of traumatic shock, a certain role is played by toxemia caused by the entry into the blood of products of decay and histolysis of non-viable tissues. The importance of this factor was proved by V. Cannon using the example of "tourniquet" shock, which occurs 4 hours or later after the removal of the tourniquet or after the cessation of prolonged compression of body parts during collapses of mines, mines , collapses due to earthquakes, bombings, etc. A large group of tissue oligopeptides responsible for the development of toxemia-related pathophysiological changes was isolated from damaged tissues and blood plasma . The mentioned oligopeptides , however, are non-specific.

Traumatic shock is not always accompanied by absolute loss of blood or plasma. On this basis, this type of traumatic shock was mistaken for isovolemic shock for a long time. At the same time, the possibility of dysvolemic changes caused by a decrease in the efficiency of blood flow due to blood stagnation in certain vascular areas or increased transudation of the liquid part of the blood was not taken into account.

3. *Cardiogenic shock* is observed in the event of a decrease in the pumping function of the heart (myocardial infarction, myocarditis), severe heart rhythm disturbances (paroxysmal tachycardia, Morgana -Adams-Stokes syndrome), cardiac tamponade (thrombosis of the heart cavities, effusion or bleeding into the pericardial cavity), massive pulmonary embolism .

The leading mechanism of the development of cardiogenic shock is a decrease in the productivity of the heart in connection with a myogenic violation of the pumping function or with the presence of obstacles to filling the ventricles. As a result, UOS, HOS and arterial - pressure decrease, on the one hand, and heart filling pressure increases, on the other.

As in the case of hypovolemic shock, as a result of the sympathoadrenergic reaction, tachycardia and increased peripheral vascular resistance are observed, which only complicate hemodynamic disturbances due to insufficient pumping function of the heart.

4. *Vascular forms of shock.* These include septic and anaphylactic shock. Septic, or infectious -toxic, shock occurs as a result of infectious processes caused mostly by gram-negative (Escherichia coli, Proteus), rarely gram-positive (staphylococcus, streptococcus) microflora.

Anaphylactic shock develops as a result of increased sensitivity of the body to substances of an antigenic nature.

Common in the development of vascular forms of shock is a primary violation of the regulation of vascular tone, but the nature of this violation is different in one and the other form. Thus, in the case of septic shock due to the action of bacterial toxins, primary disorders of peripheral blood circulation develop in connection with the opening of arteriovenous shunts.

At the same time, the blood flows from the arterial channel to the venous channel, bypassing the capillary network. Disruption of tissue nutrition caused by limitation of capillary blood flow is complicated by the direct effect of bacterial toxins on tissue metabolism, in particular *on* oxygen consumption.

The total peripheral resistance and blood pressure during septic shock due to the opening of arteriovenous shunts is sharply reduced, the filling pressure of the heart is normal or increased. Compensatory, especially in the initial phase of shock, the stroke volume and frequency of heart contractions increase, as a result of which the cardiac output increases. However, due to the development of the myocardial form of heart failure and the increasing deficit of circulating blood volume in the late phases of septic shock, the main indicators of heart activity (UOS, HOS) also decrease sharply.

In the case of anaphylactic shock due to the accumulation of histamine and other vasoactive substances (kinins , serotonin, etc.), there is a sharp decrease in vascular tone, a decrease in blood pressure. The filling pressure of the heart decreases due to a decrease in the venous return of blood to the heart. The reason for this is the expansion of capillary and capacity vessels of the venous part of the blood stream.

Accumulation of blood in capillaries and veins causes a decrease in the volume of circulating blood and relative hypovolemia . A direct violation of the contractile function of the heart is also observed. At the same time, the sympathoadrenergic reaction is insignificant due to impaired vascular tone. All together determines the catastrophic nature of the course of anaphylactic shock. Significant features of the pathogenesis of anaphylactic shock are related to the species belonging to the organism (see section "Allergy", p. 129).

The consequence of macrohemodynamic disorders, regardless of the type of shock and the sequence in which they occur, is a microcirculation disorder, in particular, a decrease in capillary blood flow, a violation of the delivery of oxygen and energy substrates to the tissues, and a difficulty in removing the end products of metabolism.

Metabolic acidosis, which develops at the same time, causes further disorders of microcirculation, up to the complete cessation of blood flow. It is connected, in particular, with the expansion of metarterioles . increased exudation of fluid from the blood into the tissues, swelling and aggregation of blood cells, increased viscosity and blood clotting, disseminated microthrombosis in capillaries. Total disruption of cell function, primarily of the sodium-potassium pump, biosynthetic activity, integrity of the lysosomal apparatus, which puts the body on the brink of life and death, is the end result of the microcirculation disorders described above in vascular forms of shock. The lungs, kidneys, and liver are especially sensitive to microcirculation disorders. In this connection, a frequent complication ***of shock*** is acute respiratory, kidney, and liver failure.

Previous illnesses (radiation sickness, anemia, starvation, etc.) reduce the body's tolerance to shock. It is also reduced in children due to the physiological features of the child's body: a high level of fluid exchange up to 70% of the total volume per day; high frequency of heart contractions, small stroke volume of the heart; less effective regulation of vascular tone due to the predominance of sympathetic influences; lability of thermoregulation.

COLLAPSE

The concept of "collapse" is used to characterize a sharp drop in blood pressure (below some critical level, the greater the higher the initial tone), as a result of which vessels lose their stability of shape and collapse .

Clinical manifests itself as a short-term loss of consciousness, general weakness; pathophysiological - with signs of acute vascular insufficiency with hemodynamic disturbances in almost all organs and tissues and suppression of vital functions.

The development of collapse is based on the dissociation between the volume of the circling liquid and the capacity of the vascular bed. The reasons can be both a sudden decrease in blood volume (blood loss, dehydration), and a sudden expansion of the vascular bed—vasomotor collapse with an increase in the tone of the vagus nerve, orthostatic dysregulation , depletion of α- adrenoreactivity of resistive vessels.

Even from this brief description, it is clear how difficult it is to differentiate shock and collapse. The reference here should be the presence and dynamics of cellular and tissue metabolism disorders. With shock, they are present and naturally develop and progress. In the case of collapse, only hemodynamic disorders are detected, which are short-term and disappear spontaneously, but in some cases they can be complicated by shock phenomena.

Lecture No. 8

Topic: Pathophysiology of red blood. Erythrocytosis . Anemias: classification, etiology, pathogenesis. **Pathophysiology of white blood.** Leukocytosis , leukopenia: etiology, pathogenesis. Leukemias: classification, etiology, pathogenesis. Leukemoid reactions.

Purpose :

- Understanding the etiology and pathogenesis of disorders of the total volume of blood (hypo- and hypervolemia), acute blood loss, absolute and relative erythrocytosis , anemia; acquaint applicants with acute blood loss as the most frequent cause of hypovolemia and compensatory reactions - short-term and long-term mechanisms; to acquaint applicants with various types of erythrocytosis , anemia and related physiological function disorders.
- Understanding the etiology and pathogenesis of leukocyte disorders, changes in the leukocyte formula and pathological types of leukograms ; to acquaint applicants with leukocytosis and leukopenia , which occur under the influence of environmental factors (ionizing radiation, toxic food products, etc.).
- Education of the acquirers of modern clinical thinking, consideration of tumor progression in leukemias, which is a sign of the transition from benign (monoclonal leukemia) to more malignant (polyclonal); at the same time, one of the laws of dialectics about the transition of quantity into quality is manifested.

Basic concepts: erythrocytosis , anemia, blood picture, hemolysis , ESR, Leukocytosis, Leukemoid reactions. Agranulocytosis, leukemia,

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

PATHOLOGICAL PHYSIOLOGY OF THE BLOOD SYSTEM GENERAL CHARACTERISTICS OF PATHOLOGICAL CHANGES IN THE BLOOD SYSTEM

Pathological changes can occur in any of the component parts of the blood system in hematopoietic organs, in blood circulating or deposited in vessels, as well as in organs and tissues where blood is destroyed. These constituent parts are closely interconnected, as a result of which the pathological process, as a rule, is not strictly isolated, and the blood system as a whole reacts to it, although the intensity of the reaction on the part of its individual components is different.

The main signs of disorders in the blood system are changes in: 1) total blood volume; 2) the number, structure and function of blood cells — erythrocytes, leukocytes, platelets — as a result of hematopoietic or hematopoiesis pathology ; 3) hemostasis; 4) biochemical and physicochemical properties of blood. These changes occur under the influence of pathogenic factors on the blood system itself, in the event of a violation of its neurohumoral regulation, as well as in the event of damage to other systems and organs to which the blood reacts secondarily, and its reaction depends on the nature of the pathological process.

The high frequency of secondary changes in the blood system is due to its

functional features. Thus, the increase in the production of erythrocytes, which ensure the respiratory function of the blood (transport of O2 and C02), is a compensatory reaction of the blood system to hypoxia. During an infectious disease , leukopoiesis increases , the number of leukocytes in the blood increases, which participate in protective, including immune, reactions of the body. In case of damage to blood vessels, the coagulation , anti-coagulation and fibrinolytic blood systems are activated, which ensure hemostasis.

Pathology of the blood system can manifest as independent diseases (for example, pernicious anemia, lymphoblastic leukemia, hemophilia), and hematological syndromes that accompany diseases of other organs and systems (for example, erythrocytosis nry of some congenital heart defects , neutrophilic leukocytosis in pneumonia). In the pathology of the blood system, tumor (hemoblastosis) and autoimmune diseases , hereditary disorders, inhibition of hematopoiesis (hypoplastic conditions) often occur. This is due to the fact that hematopoietic tissue, which is part of the blood system, is characterized by high mitotic activity, which is associated with its increased sensitivity to the action of various factors: mutagens (viruses, ionizing radiation), drugs that affect tissue metabolism or have cytostatic effect, deficiency of plastic materials (proteins, iron), vitamins (cyanocobalamin, folic acid),

VIOLATION OF TOTAL VOLUME OF BLOOD

Normally, blood makes up 6-8% of body weight, i.e. 65-80 ml of blood per 1 kg of body weight. Cellular elements make up 86-48% of blood volume, ischazma - 52-64%,

Classification. Violation of blood volume is manifested in the form of hyiovolemia or, hynervolemia — a decrease or increase in blood volume compared to the norm (normovolemia). Hypo- and hypervolemia are divided into simple (the normal ratio of plasma and blood cells is preserved), polycythemic (blood cells predominate) and oligocythemic (plasma predominates). In addition, blood volume disorders include changes in the volume ratio between cellular elements and plasma at a normal total blood volume — oligo- and polycythemic normovolemia (hemodilution and hemoconcentration). An indicator of the volume ratio is the hematocrit number, which determines the content of cellular elements (mainly erythrocytes) in the total volume of blood (normally 0.36-0.48, or a volume fraction of 86-48%).

Etiology. Simple hypovolemia (a decrease in blood volume without a change in the hematocrit number) occurs immediately after acute blood loss and persists until the fluid passes from the tissues into the blood,

Hypovolemia oligocytemia (a decrease in the volume of blood with a predominant decrease in cells — erythrocytes) is observed in the case of acute blood loss in those cases when the influx of blood and tissue fluid into the bloodstream does not compensate for the volume and, especially, the composition of the blood,

Hypovolemia polycythemic (decrease in blood volume due to a decrease in plasma volume due to a relative increase in the content of erythrocytes) develops when the body is dehydrated (diarrhea, vomiting, increased sweating, hyperventilation). During shock, blood is deposited in the dilated vessels of the abdominal cavity, which leads to a decrease in the volume of circulating blood: the outflow of fluid into the tissues due to increased permeability of the vessel wall leads to thickening of the blood and the occurrence of nolicythemic hypovolemia .

hypervolemia (increased blood volume while maintaining the normal ratio between erythrocytes and plasma) occurs immediately after a large amount of blood transfusion. However, soon the fluid leaves the bloodstream and the tissues, and the red blood cells remain, which causes the blood to thicken. Simple gynervolemia during increased physical work is due to the entry of blood from the depot into the general bloodstream.

Hynervolemia oligocythemic (increase in blood volume due to plasma) develops in the case of water retention in the body due to kidney disease, and the introduction of blood substitutes. In the experiment, it is modeled by intravenous administration of isotonic sodium chloride solution to animals.

Hypervolemia polycythemic (increased blood volume due to an increase in the number of erythrocytes) is observed in case of a decrease in atmospheric pressure, as well as in various diseases associated with oxygen starvation (heart defects , chronic lung diseases), and is considered as a compensatory (secondary) phenomenon. In the case of true (primary) polycythemia (erythremia), hypervolemia is a consequence of tumor growth of cells of the erythrocyte row of the bone marrow,

Normovolemia oligocythemic occurs with anemia due to blood loss (the volume of blood has normalized due to tissue fluid, and the number of erythrocytes has not yet been restored), hemolysis of erythrocytes, violation of hemogenesis ,

Normovolemia polycythemia is observed with transfusion of small doses of erythrocyte mass.

Pathogenesis. Hypovolemia is accompanied by a violation of the transport function of erythrocytes and the related respiratory, trophic, excretory, protective, regulatory (humoral regulation, thermoregulation) functions of blood, which to one degree or another affects homeostasis,

Hypervolemia causes an increase in the load on the heart, in the case of a simultaneous increase in the hematocrit number (nolycythemic hypervolemia) blood viscosity (internal friction) increases, tendency to blood clot formation increases and blood circulation disorders may occur in some organs,

In the pathogenesis of disorders in oligocythemia in normovolemia, the main role is played by a decrease in the respiratory function of the blood and the development of hypoxia,

BLOOD LOSS

Blood loss is a pathological process that occurs as a result of bleeding and is characterized by a complex complex of disorders and compensatory reactions of the body to a decrease in the volume of circulating blood and hypoxia caused by a decrease in the respiratory function of the blood

Etiology. Environmental factors that cause bleeding include: violation of the integrity of blood vessels during injury or damage by a pathological process (tumor, tuberculosis); increased permeability of the vessel wall (acute radiation sickness), decreased blood clotting (hemophilia, thrombocytopenia).

Pathogenesis. With blood loss, three stages are conventionally distinguished: initial, compensatory and terminal. The initial stage is characterized by a decrease in the volume of circulating blood (simple hypovolemia), a decrease in the stroke volume of the heart, a drop in blood pressure, hypoxia mainly of the circulatory back.

The compensatory stage is caused by a complex of protective and favorable

reactions aimed at restoring blood volume, normalizing hemodynamics, and oxygen supply to the body.

Urgent compensation mechanisms are as follows: 1) reflex spasm of blood vessels, which leads to an increase in resistance to blood flow in the vessels of internal organs (with the exception of the brain and heart) and skin, the outflow of blood from the body into the bloodstream, which ultimately increases blood pressure, with a certain the volume of circulating blood and blood supply to vital organs is gradually restored;

2) reflex acceleration and strengthening of heart contractions; 3) entry of interstitial fluid into vessels; 4) reflex acceleration and deepening of breathing, which contributes to the elimination of oxygen deficiency in the body; 5) an increase in the supply of oxygen to the tissues, which is indicated by a deviation of the oxyhemoglobin dissociation curve to the right (in the lower inflection) and down; 6) increased blood clotting, which stops bleeding.

Non-urgent compensation mechanisms are revealed later in the form of increased hematopoiesis and restoration of the protein composition of the blood. During the fifth day, the number of reticulocytes in the blood increases, which is associated with an increase in hematopoietic activity of the bone marrow under the influence of increased production of erythropoietin and intrinsic factor . The protein composition of blood normalizes 8-10 days after blood loss, while in the first 2-3 days there is a mobilization of tissue resources of protein, and then - an increase in its synthesis in the liver.

The compensatory reactions of the body in case of blood loss involve the nervous system (reflexes from the receptor zones of the aorta, carotid sinus, excitation of the sympathetic part of the autonomic nervous system), the endocrine system (vasopressin, catecholamines , glyco- and mineralocorticoids), the renin-angiotensin system of the kidneys, which provide partial or complete normalization of blood volume, vascular tone and other hemodynamic indicators.

In the case of insufficient detection of compensatory reactions due to changes in the body's reactivity, large and rapid blood loss in combination with the action of unfavorable exogenous and endogenous factors (cooling, major trauma, cardiovascular diseases), as well as in the absence of medical measures, a terminal stage may occur: pathological changes in the body increases until the onset of death. A loss of 50% of the volume of circulating blood is a serious danger to human life , and a loss of more than 60% is fatal.

Pathological changes due to blood loss are manifested by a decrease in the volume of circulating blood with the development of post-hemorrhagic anemia (oligocytemic hypovolemia); hemodynamic disorder (decrease in stroke volume of the heart, blood pressure, venous blood flow to the heart, coronary blood flow volume, arrhythmias , tissue microcirculation disorders); insufficiency of external and tissue respiration; the development of circulatory , hemic and tissue hypoxia; violation of tissue metabolism and acid-base state (non-gaseous acidosis); disorder of neurohumoral regulation of the most important body functions; reduction of blood clotting.

PATHOLOGICAL CHANGES OF ERYTHROCYTES

Pathological changes in erythrocytes can be quantitative or qualitative: the appearance in the blood of immature or even pathological erythrocytes, not characteristic of normal erythropoiesis , changes in the structural (shape, size),

chemical composition, metabolism and function of erythrocytes, which is accompanied by a violation of the respiratory function of the blood, since the hemoglobin of erythrocytes carries oxygen.

Quantitative changes in erythrocytes can be caused by: 1) a violation of the ratio between their formation (erythropoiesis) and destruction (erythrodieresis); 2) loss of erythrocytes as a result of damage to blood vessels (blood loss); 3) redistribution of erythrocytes in the bloodstream. These changes are manifested in the form of an increase (erythrocytosis) or decrease (anemia) in the content of erythrocytes per unit volume of blood.

The reasons for high-quality erythrocyte snakes are as follows: 1) a violation of the maturation of erythrocytes in the bone marrow or an increase in the permeability of the bone marrow barrier, as a result of which the influx of immature cells of the erythrocyte series with a low hemoglobin content into the blood increases (cells of physiological regeneration, so-called regenerative forms of erythrocytes): 2) a change in the type of hematopoiesis in the bone marrow from erythroblastic to megaloblastic , when cells of pathological regeneration of the erythrocyte sprout appear in the blood; 8) acquired and hereditary disorders of metabolism, composition and structure of erythrocytes, including hemoglobin synthesis (decreased formation or synthesis of abnormal hemoglobins), which causes the appearance of degenerative forms of erythrocytes in the blood.

The regenerative forms of erythrocytes include reticulocytes , which are detected after supravital staining of a blood smear (normally, the blood contains 0.2-2% of reticulocytes), polychromatophilic erythrocytes (equivalent to reticulocytes , which are detected when the smear is stained according to Romanovsky), acidophilic, polychromatophilic and basophilic normoblasts , erythroblasts (normally found only in the bone marrow).

The cells of pathological regeneration include megalocytes and megaloblasts (acidophilic, polychromatophilic , basophilic).

Degenerative changes in erythrocytes can affect the size, shape, color of these cells, and other features. 1. A change in the size of erythrocytes — anisocytosis , characterized by the presence of macrocytes — erythrocytes with a diameter of more than 8 μm and microcytes — erythrocytes with a diameter of less than 6.5 μm (the average diameter of a normal erythrocyte is about 7.2 μm). 2. A change in the shape of erythrocytes — poikilocytosis, in this case, erythrocytes are erythrocyte-shaped , elongated, sickle-shaped (drepanocytes), oval (ovalocytes), as well as spherical - with increased thickness, but preserved biconcavity (spherocytes). 8. Change in the color of erythrocytes, which depends on the content of hemoglobin in them: intensely colored erythrocytes are called hyperchromic , pale colored - hypochromic ; if only the peripheral part of the erythrocyte, where hemoglobin is located, is colored in the form of a ring, and in the center there is an uncolored clarification - annulocytes ; in the case of a pronounced difference in the color of erythrocytes, they speak of anisochromia . 4. The presence of pathological inclusions in erythrocytes — a Jolly corpuscle (a formation 1-2 microns in size , which is a remnant of the nucleus, usually a megaloblast), rings Cabot (remains of the nuclear envelope, which have the shape of a ring, figures of eight), basophilic granules (remains of a basophilic substance in an erythrocyte, indicating toxic damage to the bone marrow), etc.

ERYTHROCYTOSIS

Erythrocytosis — an increase in the number of erythrocytes in the blood up to 6 • IO12 per 1 l and hemoglobin up to 10.55 mmol/l (170 g/l) and more.

Classification. Acquired and hereditary erythrocytosis are distinguished . According to the mechanism of its occurrence, it is divided into absolute, caused by increased erythrogenesis in the bone marrow, and relative, in which the increase in the number of erythrocytes per unit volume of blood is the result of a decrease in plasma volume.

Etiology. Acquired absolute erythrocytosis occurs in case of increased production of erythronoetin mainly in the kidneys, which can be caused by the following: 1) violation of neurohumoral regulation — when the sympathetic part of the nervous system is excited, hyperfunction of a number of endocrine glands; 2) hypoxic , respiratory, circulatory hypoxia - in case of altitude sickness, chronic diseases of respiratory organs and blood circulation; 8) local hypoxia of the kidneys due to their ischemia (hydronephrosis, renal artery stenosis); 4) hyperproduction of erythropoietin by some tumors (hypernephroma , liver cancer, etc.). In addition, absolute erythrocytosis develops in true polycythemia (erythremia, or Waquez's disease), which is a type of chronic leukemia.

The cause of hereditary absolute erythrocytosis can be a genetically determined increase in the formation of erythronoetin . In the case of a hereditary deficiency in erythrocytes of 2,3-diphosphoglycerate (the regulator of oxygenation and deoxygenation of hemoglobin), the affinity of hemoglobin for oxygen increases and its delivery to tissues decreases (the curve of oxyhemoglobin dissociation is deviated to the left). Tissue hypoxia develops, the production of erythronoetin is stimulated, under the influence of which erythropoiesis increases .

Relative erythrocytosis is etiologically associated with the same factors that cause dehydration of the body (increased sweating, prolonged vomiting, diarrhea, etc.) or redistribution of blood that causes polycythemia hypoaolemia (shock, burn).

Pathogenesis. Hypoxic or dysregulatory increase in the synthesis of erythronoetin leads to. increased erythrogenesis followed by an increase in the content of erythrocytes, hemoglobin, and hematocrit in the blood . At the same time, it is possible to increase the volume of circulating blood (polycythemic hypervolemia), its viscosity, slowing of the blood flow rate, heart failure. Arterial pressure increases, internal organs are full of blood ,

hyperemia of the skin and mucous membrane, thrombus formation increases, and then bleeding.

Changes in the blood in the case of acquired absolute erythrocytosis are often compensatory in nature, contributing to the improvement of tissue oxygen supply in conditions of hypoxia. With the termination of the action of the etiological factor, the number of erythrocytes and hemoglobin normalizes. Exception: there is erythrocytosis in true polycythemia , which occurs as a result of tumor proliferation of cells of the erythrocyte series and has no compensatory value,

ANEMIA

Anemia is a hematological syndrome or an independent disease characterized by a decrease in the number of erythrocytes and (or) hemoglobin per unit volume of blood, as well as qualitative changes in erythrocytes.

Table I. Classification of anemia

The indicator, which is the basis of the classification	Types of anemia
Etiology	
Pathogenesis	

Type of hematopoiesis

Ability of bone marrow to regenerate Color index (KP)

Diameter of erythrocytes Clinical course Hereditary, acquired.

Anemia due to blood loss (nosthemorrhagic); anemia due to increased blood loss (hemolytic); anemia due to impaired erythropoiesis .

Anemia with erythroblastic type of hematopoiesis; anemia with megaloblastic type of hematopoiesis.

Regenerative, hyperregenerative , hyporegenerative , areregenerative ,

Normochromic (CP 0.85—ID5), hypochromic (CP<0.85), hyperchromic (CP>1.15) Normocytic (average diameter 7.2 μm), microcytic (average diameter < 6.5 μm), macrocytic (average diameter > 8 μm).

Acute, chronic.

The classification of anemia is given in the table. 1.

The etiology of anemia is discussed in the relevant subsections. The pathogenesis of anemia, along with the actual pathological changes of the erythron , covers the body's protective and condensing reactions. To the first

primarily include changes in erythropoiesis , erythrodieresis , quantitative and qualitative composition of erythrocytes and hemoglobin" that lead to the development of gynoxic syndrome (hemic type) associated with a violation of the main function of erythrocytes — oxygen transport. Compensatory reactions in anemia are aimed at eliminating or weakening hypoxia and are manifested in increased erythropoiesis (the leukoerythroid ratio in the bone marrow changes from 3:1 to 1:1 and even 1:3, the number of cells of physiological regeneration in the blood increases), shifts in the oxyhemoglobin dissociation curve, changes in the functions of circulatory and respiratory organs, tissue metabolism.

POST-HEMORRHAGIC ANEMIA

Posthemorrhagic anemia is anemia that develops as a result of acute or chronic blood loss.

Classification • Acute and chronic posthemorrhagic anemia are distinguished.

Etiology. Acute posthemorrhagic anemia occurs after rapid massive blood loss as a result of vessel injury or destruction of the vessel wall by a pathological process.

Chronic Posthemorrhagic anemia develops as a result of repeated blood loss caused by damage to blood vessels in connection with certain diseases (gastric ulcer disease , hemorrhoids, etc.) or violation of platelet -vascular and coagulation hemostasis (hemorrhagic diathesis).

Pathogenesis. Acute posthemorrhagic anemia in the first hours after blood loss is characterized by a relatively uniform decrease in the number of erythrocytes and hemoglobin with preservation of the normal color index (normochromic anemia); there are no characteristic changes of erythrocytes in the blood smear.

2-3 days after the bleeding has stopped , the number of erythrocytes decreases slightly due to the influx of tissue fluid into the vessels (relative erythropenia) and the destruction of erythrocytes in the cells of the mononuclear phagocyte system (absolute erythropenia). On the 4th-5th day after blood loss, the proliferation of erythrocyte germ cells in the bone marrow increases under the influence of increased production of erythropoietin due to hypoxia . The number of iolichromatophilic erythrocytes and reticulocytes increases in the blood , single normoblasts appear (regenerative anemia). The color index decreases (hypochromic

anemia), because accelerated regeneration precedes the maturation of cells that do not have time to lose signs of immaturity (nucleus, iranules) and saturate with hemoglobin. In addition, massive acute blood loss can lead to iron deficiency and decreased hemoglobin synthesis.

Chronic posthemorrhagic anemia is accompanied by a decrease in iron reserves in the body and, therefore, the occurrence of iron deficiency anemia with hypochromia and microcytosis. In case of inhibition of hematopoiesis, such anemia can become hypo- and areregenerative (a sharp decrease in the regenerative forms of erythrocytes in a blood smear).

HEMOLYTIC ANEMIA

Hemolytic anemia is an anemia that occurs as a result of increased erythrodieresis , when the destruction of red blood cells prevails over their formation.

Classification. Acquired and hereditary hemolytic anemia are distinguished. Depending on the etiological factors that caused hemolysis of erythrocytes, acquired hemolytic anemia is divided into toxic, immune , and mechanical; this group also includes acquired membranopathy (Table 9).

Hereditary hemolytic anemia, depending on the nature of the genetic defect, includes anemia due to a defect in the structure of the erythrocyte membrane (hereditary membranopathy), anemia associated with impaired activity of erythrocyte enzymes (hereditary enzymopathy), and anemia caused by a violation of hemoglobin synthesis (hereditary hemoglobinopathy). which, in turn, is divided into anemia due to a violation of the synthesis of globin chains and anemia due to a defect in the primary structure of globin chains .

Pathogenesis. The mechanism of hemolysis in the case of acquired hemolytic anemia is damage to the structure of the erythrocyte membrane. Some hemolytic factors (for example, mechanical) have a direct damaging effect, others (arsine — arsenic hydride, nitrites), being strong oxidants, cause first metabolic and then structural changes in the membrane and stroma of erythrocytes, which lead to hemolysis. Many hemolytic poisons of biological origin are enzymatically active, destroy lecithin membranes (lecithinase activity of strepto- and staphylolysins , insect and snake venoms). In immune hemolytic anemias, immunoglobulins O and M attach to the membrane of erythrocytes complement, which is activated and causes enzymatic lysis of the membrane.

Under the effusion of hemolytic agents, pores are formed in the erythrocyte membrane, through which potassium ions and phosphates leave the cell, and sodium ions enter the cell. As a result of the ionic imbalance, water enters the erythrocyte, which swells, acquires a spherical shape, its cell surface decreases, and the ability to change its configuration decreases. Such spherocytes cannot pass through the interendothelial pores of the sinuses of the spleen and are phagocytosed by macrophages in it. When the erythrocyte volume reaches a critical level (146% of the initial one), and the membrane pore size exceeds 6 nm, hemolysis occurs with the release of hemoglobin into the plasma.

Hemolysis of erythrocytes in acquired hemolytic anemia occurs mainly in the bloodstream (intravascular hemolysis). However, in the case of Rhesus conflict (hemolytic disease of newborns), anti-Rhesus agglutinins formed in the body of a Rhesus-negative mother cause hemolysis of Rhesus- positive erythrocytes of the fetus or newborn not only inside the blood vessels, but also in the liver and spleen

(intracellular hemolysis).

In the case of hereditary hemolytic anemia, hemolysis is caused by a decrease in the osmotic and mechanical resistance of erythrocytes with genetically determined disorders of the membrane structure, metabolism, and hemoglobin synthesis.

Thus, in microspherocytic hemolytic anemia (Minkovsky - Shofar disease with an autosomal dominant type of inheritance), which belongs to hereditary membranoiatia , the deficiency in the membrane of erythrocytes of Ca -dependent ATPase and phospholipids causes an increase in membrane permeability. Sodium ions and water enter the cells, erythrocytes turn into spherocytes with a sharply reduced ability to deform when passing through the sinuses of the spleen. As a result of tearing off part of the shell of such erythrocytes, microspherocytes with a shortened life span (8-14 days instead of the normal 120 days) are formed due to their premature capture by macrophages of the spleen and liver.

In the case of anemia due to glucose-6-phosphate dehydrogenase deficiency (hereditary enzyme disease with dominant, X-linked inheritance), acute intravascular hemolysis, which occurs, for example, after taking antimalarial and antituberculosis drugs with high oxidizing capacity, is caused by damage to cell membranes by peroxides, since in erythrocytes with a deficiency of G 6 FDH have a reduced content of reduced glutathione (antioxidant).

Intracellular hemolysis in hereditary hemoglobinopathy is associated with the synthesis of abnormal or age-specific hemoglobin. Thus, in the case of sickle cell anemia, HBV is formed (glutamic acid is replaced by valine in |3- globin chain), which in the restored state falls into crystals and causes sickle-shaped deformation of erythrocytes; hypoxia promotes hemolysis of such erythrocytes.

The consequence of massive hemolysis of erythrocytes is anemia with a violation of the respiratory function of the blood and the development of hypoxia. Hemoglobin released as a result of the breakdown of erythrocytes circulates in the blood (hemoglobinemia) and combines with haptoglobin in a large molecular complex that does not pass through the kidney filter. If the content of free hemoglobin in the plasma exceeds 20.9 mmol/l (337 g/l) or a low initial level of haptoglobin is observed , hemoglobin not bound to the latter begins to be excreted in the urine (hemoglobinuria). Hemoglobin is partially absorbed by the cells of the macrophage system and is split into hemoeiderin . Hemosiderosis of the spleen, kidneys, liver, and bone marrow is accompanied by reactive growth of connective tissue and dysfunction of these organs. The increased formation of bile pigments from hemoglobin leads to the development of hemolytic jaundice. In addition, the intra-eudinal breakdown of erythrocytes can lead to the appearance of blood clots and impaired blood supply to tissues, resulting in trophic ulcers of the extremities, dystrophic changes in the spleen, liver, and kidneys. Due to the entry into the vascular bed of a large amount of erythrocyte thrombocyathin the development of D VZ- syndrome is also possible .

A picture of blood. Acquired hemolytic anemia is erythroblastic by type of hematopoiesis , regenerative by degree of bone marrow regeneration, normo- or hypochromic by color index , less often hyperchromic (as a result of absorption of hemoglobin on erythrocytes). The degree of reduction in the number of erythrocytes and hemoglobin depends on the intensity of hemolysis. Cells of physiological regeneration and degeneratively changed erythrocytes (poikilocytosis, ruptured,

fragmented erythrocytes, anisocytosis) are detected in the blood smear. A large number of erythroblasts and normoblasts is characteristic of hemolytic disease of newborns.

In hereditary hemolytic anemia, enhanced regeneration of the erythrocyte germline is observed, often with ineffective erythropoiesis , when the nuclear forms of erythrocytes are destroyed in the bone marrow. In a blood smear, together with regenerative forms (high reticulocytosis , nolichromatophilia , single nuclear forms of erythrocytes), degeneratively changed cells are detected (microspherocytes in Minkovsky - Shoffar disease , sickle-shaped cells in B hemoglobinopathy , target-like cells, as well as erythrocytes with basophilic granules - in thalassemia). In connection with frequent hemolytic crises, gynoregenerative anemia may occur.

ANEMIA AS A RESULT OF DISORDER OF ERYTHROPOESIS

Classification. Depending on the mechanism of erythropoiesis disruption , the following types of anemia can be distinguished: 1) dysregulatory , caused by erythropoiesis regulation disruption due to a decrease in the synthesis of erythropoietin or an increase in the synthesis of its inhibitors (in chronic kidney diseases, hypofunction of the pituitary gland, thyroid gland);

2) ..... deficient due to the lack of substances necessary for the formation of erythrocytes (iron-, B12-> folate -, protein-deficient anemia);

3) ..... enzymopathy caused by impaired activity of enzymes involved in erythropoiesis (for example, in the synthesis of porphyrin and heme);

4) ..... hypo (a) plastic when the erythrocyte sprout of the bone marrow is affected against the background of sharp suppression of bone marrow hematopoiesis;

5) ..... metaplastic when the erythrocyte sprout is replaced or displaced by another tissue.

Iron deficiency anemia

Iron-deficiency anemia is an anemia caused by a lack of iron in the body due to an imbalance between its intake, use and loss. This is the most common type of anemia (80% of the incidence of anemia).

Etiology. The most common reason for the development of iron-deficiency anemia is repeated, sometimes massive one-time bleeding, which causes the loss of iron together with erythrocytes (mainly uterine bleeding, less often - gastrointestinal, renal, pulmonary bleeding, hemorrhagic diathesis).

The development of anemia can be caused by insufficient intake of iron with food (when feeding children only cow's or goat's milk) and increased consumption of iron during the period of growth, maturation of the body, during pregnancy, lactation; decrease in iron absorption in diseases of the digestive tract (hypoacid gastritis, chronic enteritis) or after resection of its sections; violation of iron transport (hypotransferrinemia due to liver damage, hereditary atransferrinemia), its utilization from reserves (in case of infection, intoxication, helminthiasis) and deposition (in case of hepatitis, liver cirrhosis).

Pathogenesis. Exogenous or endogenous iron deficiency in the body is characterized by a decrease and gradual depletion of iron reserves, which is manifested in the disappearance of hemosiderin in macrophages of the liver and spleen, a decrease in the number of sideroblasts and siderocytes in the bone marrow. The concentration of iron in blood serum decreases, sometimes to 1.8-2.7 μmol /l (normally 12.5-30.4 μmol /l) and the degree of transferrin saturation with it , which

leads to a decrease in iron transport to the bone marrow. The supply of iron to erythrocytes is disrupted , the synthesis of heme in hemoglobin and some iron-containing and iron-dependent enzymes (catalase, glutathione peroxidase) in erythrocytes decreases, which increases their sensitivity to the hemolyzing effect of oxidants . The inefficiency of erythropoiesis increases as a result of increased hemolysis of erythrokaryocytes in the bone marrow and erythrocytes in the blood. The lifespan of erythrocytes decreases.

At the same time, compensatory reactions take place in the body - strengthening! absorption of iron in the digestive tract; increase in transferrin concentration in plasma; erythrocyte hyperplasia sprout ; an increase in the intensity of glycolysis and the activity of 2,3-diphosphoglycerate in erythrocytes, which facilitates the dissociation of oxyhemoglobin and contributes to a better supply of tissues with oxygen. However, these reactions are insufficient to eliminate iron deficiency in the body and improve the oxygen transport function of the blood. Morphological changes are observed in erythrocyte cells of the bone marrow, hypochromia associated with insufficient hemoglobinization of erythrocytes; predominance of basophilic of normoblasts over acidophilic ones in the bone marrow, microcytosis, destruction of nuclear cells (violation of mitosis, karyorrhexis , vacuolization cytoplasm of erythroblasts and normoblasts), a decrease in the number of sideroblasts to 2-5%.

Iron deficiency in the body leads not only to pathological changes in erythropoiesis , but also to a decrease in the amount of myoglobin and the activity of iron-containing enzymes of tissue respiration. The consequence of hemic and tissue hypoxia in iron-deficiency anemia is atrophic and dystrophic processes in tissues and organs, especially in the alimentary canal (glossitis, gingivitis, dental caries, damage to the esophageal mucosa, atrophic gastritis with achilles) and in the heart (myocardial dystrophy).

A picture of blood. Iron-deficiency anemia is an anemia with an erythroblastic type of hematopoiesis, hypochromic with a low color index (0.6 and less). The amount of hemoglobin is reduced to a greater extent than the number of erythrocytes. A blood smear is characterized by hypochromia , "shadows" of erythrocytes, presence of annulocytes , microcytosis, poikilocytosis. The number of reticulocytes depends on the regenerative capacity of the erythrocyte sprout (regenerative or, more often, hyporegenerative anemia).

B12- and foliodeficiency anemia

B12- and foliodeficiency anemia is an anemia associated with a violation of the synthesis of nucleic acids and the replacement of the erythroblastic type of hematopoiesis by megaloblastic as a result of a lack of cyanocobalamin - vitamin B1 and folic acid in the body (megaloblastic anemia). The disease can be acquired and hereditary.

Etiology. The reasons common to both types of deficiency anemia are as follows: 1) lack of cyanocobalamin and folic acid in food (feeding babies with goat milk, dry milk formulas); 2) impaired absorption of these vitamins in the small intestine (after resection of the jejunum, with a tumor, multiple diverticula of the intestine, tropical sprue , diphyllobotryosis , alcoholism); 3) increased consumption of vitamins during pregnancy (when the embryonic type of hematopoiesis in the fetus changes to erythroblastic , the fetus's consumption of cyanocobalamin and folic acid of the mother increases); 4) impaired deposition of vitamins in case of

diffuse liver damage (hepatitis, cirrhosis).

In addition, a deficiency of cyanocobalamin can be a consequence of a deficiency of an internal factor (Kasla) — a mucoprotector (transcorin), which is secreted by the glands of the mucous membrane of the stomach . This is observed in the case of a hereditary defect in the formation of the intrinsic factor , when the gastric mucosa is affected by a tumor, syphilitic gum, large doses of alcohol, chronic atrophic gastritis, after resection of the stomach , as well as due to the destruction of the intrinsic factor autoantibodies .

The cause of pernicious anemia (malignant anemia, Addison - Birmer disease), which is a type of B2-deficiency anemia, can be a genetically determined deficiency of an intrinsic factor (inherited according to the autosomal recessive type) or an autoimmune process, as evidenced by detection in the blood serum and in in the gastric juice of patients antibodies (^O, her A) to antigens of parietal cells, less often — to internal factor .

Pathogenesis. In case of deficiency of cyanocobalamin (its coenzyme - methylcobalamin), the conversion of folic acid into its coenzyme form - tetrahydrofolic acid, without which the synthesis of thymidinemoiophosphate , which is part of DNA, is impossible. The division of cells is disrupted, primarily cells of the hematopoietic tissue, which are actively multiplying. In the bone marrow, the reproduction and maturation of erythrokaryocytes is delayed , the erythroblastic type of hematopoiesis is replaced by the megaloblastic type , the inefficiency of erythropoiesis increases , and the lifespan of erythrocytes decreases. As a result of hematopoietic disorders and hemolysis of erythrocytes, anemia develops, in which cells of pathological regeneration and erythrocytes with signs of degeneration appear not only in the bone marrow, but also in the blood. Violation of leukocyte and thrombocytopoiesis is manifested in a decrease in the number of leukocytes and platelets, pronounced atypia of cells. Atypical mitosis and the appearance of giant cells of the epithelium of the alimentary canal lead to the development of inflammatory -atrophic processes in the mucous membrane of its various departments (glossitis, stomatitis, esophagitis , achilles gastritis, enteritis). This complicates the primary violation of secretion or absorption of the bowel factor and, therefore, increases vitamin deficiency (vicious circle).

As a result of a lack of cyanocobalamin (its coenzyme deoxyadenosylcobalamin is involved in the formation of succinic acid from methylmalonic acid), methylmalonic acid accumulates in the body , which is toxic to nerve cells, and fatty acids with a changed structure are synthesized in nerve fibers, which disrupts the formation of myelin and causes axon damage. Degenerative processes in the posterior and lateral columns of the spinal cord (funicular myelosis), cranial and peripheral nerves are affected with the development of various neurological symptoms,

Blood picture, B12- and foliodeficiency anemia is characterized by megaloblastic hematopoiesis, hyperchromic , macrocytic . The content of erythrocytes and hemoglobin in the blood can decrease sharply , but the color index is higher than 1D5 (ID — 1.8) .

In a blood smear, cells of pathological regeneration of the bone marrow appear - megalocytes (intensely stained cells with a diameter of 10-12 μm and more, which do not have a central clearing, somewhat oval in shape) and single megaloblasts (cells with a diameter of 12-15 μm with basophilic , polychromatophilic or

acidophilic cytoplasm and fine reticulated , usually eccentrically placed, nucleus), It is believed that megaloblasts and megalocytes in B] 2- and foliodeficiency anemia are not identical to embryonic cells of the erythrocyte series and only outwardly resemble them. Many signs of degenerative changes in erythrocytes are found in the blood: poikilocytosis, anisocytosis with macrocytosis, hyperchromia, megalocytes with inclusions in the form of Jolly bodies , rings Kebota , erythrocytes with basophilic granules. The number of cells of physiological regeneration (reticulocytes , polychromatophilic cells) decreases as a result of irritation of the erythrocyte sprout of the bone marrow with a predominance of megaloblastic erythronoesis over erythroblastic . Leuko- and thrombocytopenia with atypical cells is observed (for example, giant non-segmented - with 8-10 segments - neutrophilic granulocytes with a diameter of 20-30 microns).

Anemia caused by a violation of the activity of enzymes involved in erygrogenesis , many types of anemia can be attributed to this group, including those hereditary membrane-, enzyme-, and hemoglobinopathies that are included in the group of hemolytic anemia, since erythropoiesis is also disturbed due to a genetic defect in the synthesis of certain enzymes. However, the consequence of impaired erythrogenesis is increased hemolysis, which becomes the main pathogenetic mechanism in the development of these types of anemia, which makes it possible to include them in the group of both hemolytic anemia and anemia associated with impaired erythrogenesis .

A decrease in the activity of enzymes involved in the synthesis of porphyrins and heme underlies the development of hereditary and acquired sideroblastic anemia, which is also called iron-refractory (resistant to treatment with iron preparations) or sideroachrestic (ie, anemia due to iron deficiency).

Etiology. Sideroblastic anemia can occur in the event of a violation in any link of hemoglobin biosynthesis catalyzed by certain enzymes, starting from the interaction of glycine with succinic acid, through the sequential formation of 6-aminolevulinic acid (ALA), porphobilinogen , uro- , copro-, protoporphyrinogen , protoporphyrin , heme and to the formation of the hemoglobin molecule. Such anemia can be the result of a genetic defect in the synthesis of ALA or protoporphyrin (recessive inheritance, linked to the X-chromosome). However, the most common cause is a deficiency of pyridoxal phosphate , which is formed in the body from pyridoxmiu (vitamin 1%) and is a coenzyme of ALA synthetase . The decrease in the content of niridoxal phosphate is affected not so much by the lack of pyridoxine in food (in case of artificial feeding of infants), but by treatment with means that increase the consumption of pyridoxine (for example, some anti-tuberculosis drugs). Domestic and industrial lead poisoning also causes a violation of the synthesis of porphyrinia due to the fact that lead blocks sulfhydryl groups in enzymes involved in the formation of heme (ALA dehydrases , uroporphyrinogen decarboxylases , heme synthetases).

Pathogenesis. A decrease in the activity of enzymes involved in the formation of porphyrins and heme leads to a decrease in the utilization of iron and a violation of hemoglobin synthesis, which leads to the development of hypochromic anemia with a low content of hemoglobin in erythrocytes with a simultaneous increase in the content of iron in the blood serum (up to 54-80 μmol / l). In the bone marrow, there are signs of irritation of the erythrocyte germ, an increase in the number of basophils normoblasts and sideroblasts , at the same time the number of

hemoglobinized forms decreases , sometimes the ineffectiveness of erythropoiesis (hemolysis) increases, and the lifespan of erythrocytes decreases. Iron deposition in internal organs is accompanied by secondary growth of connective tissue (hemosiderosis of the liver, heart, pancreas and other organs).

Hypoplastic (aplastic) and metaplastic anemia

Hypoplastic anemia is an anemia during which the erythrocyte sprout of the bone marrow is affected against the background of deep inhibition of hematopoiesis, the production of erythrocytes, as well as granulocytes and platelets (pancytopenia).

Classification. Acquired and hereditary gynoelastic anemia are distinguished . By pathogenesis, acquired gynoelastic anemia is divided into dysregulatory , myelotoxic , and immune.

Etiology Among the exogenous factors causing the development of hyposchiastic anemia, the following are distinguished: chemical drugs (sulfanilamide, cytostatic , antituberculosis drugs, chloramphenicol), benzene and its derivatives, pesticides; ionizing radiation; infectious — viruses of hepatitis, influenza, infectious mononucleosis, pathogens of tuberculosis, scarlet fever. Endogenous factors include genetic defects of erythropoiesis ; hypofunction of endocrine glands (thymus , thyroid), ovaries; formation of autoantibodies against cells of erythropoietic tissue; violation of erythropoietin synthesis in kidney diseases and an increase in the content of erythropoietin inhibitors .

Pathogenesis. In the pathogenesis of hypoplastic anemia, three main mechanisms can be identified that lead to inhibition of hematopoiesis , including erythroiogenesis (selective depression of only erythropoietic tissue is possible in so-called partial red cell aplasia): 1) a decrease in the number of precursor cells erythrocyte series under the influence of direct damaging effect of etiological factors or mutation, as a result of which the mitotic activity of bone marrow cells is sharply reduced, their composition is disturbed (for example, the content of fetal hemoglobin increases); 2) immune damage of bone marrow erythropoietic cells and erythropoietin antibodies and T-lymphocytes; 3) stromal inferiority microenvironment erythropoietic cells, as a result of which their proliferative function and the ability to differentiate are impaired (this was proven in an experiment on mice with hereditary aplastic anemia, in which the division of transplanted bone marrow cells was restored only after the introduction of spleen tissue as hematopoietic stroma).

Thus, with hypoplastic anemia, all these mechanisms lead to a violation of the formation of cells of the erythrocyte , as well as the granulocyte and thrombocyte series (if the precursor cell common to the three series is affected at the same time). There is a sharp depletion of bone marrow for cellular elements, hematopoietic tissue is replaced by fatty tissue. The inefficiency of erythropoiesis with a reduction in the lifespan of erythrocytes is observed. Intramedullary destruction of erythrokaryocytes is combined with increased hemolysis of erythrocytes in the blood, spleen, and liver. A picture hypoplastic anemia is complicated by bleeding caused by thrombocytopenia , infectious processes that develop against the background of granulocytonene .

A picture of blood. Hypoplastic anemia is mostly normochromic , normo- or macrocytic with a sharp decrease in the number of erythrocytes, hemoglobin, leukocytes (especially granulocytes) and platelets. An increase in the number of

reticulocytes in a blood smear is an indicator of compensatory enhancement of regeneration in certain areas of the bone marrow. However, a decrease in the number of regenerative forms of erythrocytes is often observed.

Metaplastic anemia is an anemia in which the violation of erythropoiesis is caused by the displacement or replacement of erythropoietic tissue by tumor metastases, leukemic infiltrates, connective and adipose tissue

PATHOLOGY OF THE BLOOD SYSTEM. TYPICAL FORMS OF PATHOLOGY IN THE LEUKOCYTE SYSTEM. LEUKEMIA.

Pathological changes in leukocytes are manifested in the violation of their formation in hematopoietic tissue, as well as in quantitative and qualitative changes in blood leukocytes. The cause may be primary damage to cells of the leukocyte series under the influence of various adverse factors. Secondary changes in leukocytes occur as a reaction to pathological processes that take place not in the blood system, but in the organs and tissues of other body systems.

The main link in the pathogenesis of disorders in the pathology of leukocytes is a change in the body's reactivity, including immunological and allergic, which is connected with the functional features of leukocytes - their participation in the processes of phagocytosis, the formation of antibodies, the inactivation of biologically active substances (histamine , bradykinin , serotonin)). Pathological changes in leukocytes can be accompanied by a disorder of tissue trophicity and local microcirculation, since one of the functions of leukocytes is disturbed - the provision regenerating tissues with nutrients and stimulators of cell division. Granulocytes participate in the pathogenesis of vascular disorders: basophilic and eosinophilic - as carriers of vasoactive substances , neutrophilic - affecting the synthesis of these substances and their release from tissue basophils.

Violation of leukopoiesis .

The following disorders of leukopoiesis are distinguished : 1) enhancement or suppression of the formation of leukocytes in hematopoietic tissue; 2) violation of maturation of leukocytes in hematopoietic organs; 3) production of pathologically altered leukocytes.

Etiology. Violation of leukopoiesis occurs under the influence of a number of exogenous factors - biological (bacteria, viruses, protozoa), physical (ionizing, ultraviolet radiation), chemical. Endogenous factors of leukopoiesis disorders include genetic defects in the formation and differentiation of leukocytes.

Pathogenesis. An increase in leukopoiesis of a reactive nature can be due to an increase in the production of humoral stimulators of leukopoiesis (colony-stimulating factor, interleukin 1, antikeilon) or a decrease in the production of their inhibitors (keilon , prostaglandin E , lactoferrin , isoferritin). At the same time, the proliferation of leukopoietin - sensitive bone marrow cells with acceleration of their differentiation into mature leukocytes is revealed. The influx of leukocytes into the blood increases, that is, leukocytosis occurs.

Enhancement of leukopoiesis of a tumor nature occurs as a result of the action of carcinogenic factors that cause mutation of genes responsible for the reproduction and differentiation of hematopoietic cells of II-II classes, which is characteristic of leukemia.

Suppression of leukopoiesis can be caused by a violation of the regulation of the formation of leukocytes, a deficiency of plastic factors necessary for leukopoiesis (with protein starvation, lack of cyanocobalamin and folic acid).

Leukopoiesis is reduced in the case of hereditary or acquired damage to cells - the precursors of granulocytes and agranulocytes and stroma cells , which normally determine the differentiation of stem cells in the direction of myelo- and lymphocytopoiesis , or in the case of generalized damage to leukopoietic tissue. Such a decrease in leukopoiesis is observed in the case of hereditary neutropenia , exposure to ionizing radiation, tumor metastases and leukemic infiltrates that crowd out normal leukocyte producers , increased destruction of leukocyte cells in hematopoietic organs due to drug allergies.

Suppression of leukopoiesis , as well as its enhancement, covers either all types of leukocytes, or mainly one of them.

Violation of leukocyte maturation is caused by the blockade of differentiation at one or another level of cell development. This process is genetically regulated and ensured by certain metabolic reactions. Its change is caused by mutations (in leukemia, a hereditary defect in the maturation of leukocytes), the action of exogenous and endogenous factors (causing agents of purulent and viral infections, drug allergens, intoxication). Violation of the maturation of leukocytes often occurs in the case of an increase in their production in connection with tumor hyperplasia of hematopoietic tissue, but it can also occur as a result of inhibition of leukocoesis . In addition, the accelerated release of immature leukocytes from the bone marrow into the blood is associated with a change in the permeability of the bone marrow barrier, in the regulation of which glycocorticoids participate .

The production of pathologically altered leukocytes in the bone marrow can occur as a result of tumor transformation of the leukopoietic tissues in leukemia, genetically determined disorders of the structure (hereditary Pelger's anomaly of leukocytes) and metabolism in leukocytes. Hereditary deficiency of myeloperoxidase , glucose-6-phosphate dehydrogenase leads to a decrease in the phagocytic activity of leukocytes (about the syndrome Chediaka-Higashi). Inefficiency of leukopoiesis with a reduction in the life span of leukocytes can be observed. Pathological clones of lymphocytes can produce antibodies against the tissues of one's own body, which leads to the development of autoimmune diseases.

Quantitative and qualitative changes of leukocytes in the blood.

A change in the number of leukocytes in the blood compared to the norm (from 4*109 to 9*10u per 1 l) is possible in the direction of increase (leukocytosis) or decrease (leukopenia).

Leukocytosis.

Leukocytosis - an increase in the total number of leukocytes in the blood by more than 9*109 per 1 liter.

Classification. A distinction is made between absolute and relative (redistributive) leukocytosis. Absolute leukocytosis is an increase in the number of leukocytes in the blood as a result of increased leukopoiesis of a reactive or tumor nature or an increased influx of leukocytes from the bone marrow depot into the blood vessels.

Relative leukocytosis - an increase in the number of leukocytes in the blood due to the transition of leukocytes from the parietal pool to the circulating one or their accumulation in the center of inflammation.

Due to the fact that the increase in the total number of leukocytes is usually combined with a predominant increase in the number of individual types of leukocytes , leukocytosis is divided into neutrophilia, eosinophilia , basophilia,

lymphocytosis and monocytosis.

Etiology. Factors causing the development of neutrophilia are various : infectious agents (streptococci, staphylococci, fungi), tissue decay products (in myocardial infarction, acute hemolysis, malignant tumors), toxic metabolites (in uremia, hepatic coma), physical (cold, heat) and mental (fear, rage) factors, chronic myeloid leukemia.

Eosiophilia is observed in allergic diseases, helminthiasis , amebiasis, chronic myeloid leukemia.

Basophilia occurs in cases of hypothyroidism, nonspecific ulcerative colitis, chronic myelogenous leukemia, after removal of the spleen.

Lymphocytosis is caused by some viruses (infectious mononucleosis, hepatitis, measles), microorganisms (causing agents of whooping cough, tuberculosis, syphilis): high lymphocytosis is observed in chronic lympholeia - a goat.

Monocytosis develops in connection with viral diseases (infectious mononucleosis, rubella), tuberculosis, malaria, septic endocarditis, and systemic connective tissue diseases.

Pathogenesis. The following mechanisms of leukocytosis can be identified: 1) increased production of leukocytes in hematopoietic organs of a reactive nature or with tumor hyperplasia of leukopenic tissue, when the mitotic, maturing and reserve pool of leukocytes in the bone marrow increases; 2) acceleration of the release of leukocytes from the bone marrow into the blood, which may be a consequence of increased permeability of the bone marrow barrier under the influence of glycocorticoids , as well as increased proteolysis of the membrane surrounding the islet of granulocytopoiesis in septic conditions ; 3) redistribution of leukocytes due to their mobilization from the parietal pool to the circulating pool (after the introduction of adrenaline, during emotional stress , under the influence of endotoxins of microorganisms), redistribution of blood (in connection with shock, collapse) or increased migration of leukocytes into the axis rare inflammation (with appendicitis, phlegmon).

In leukemia, which arose as a result of reactive hyperplasia of leukopoietic tissue, as a rule, the functional activity of leukocytes increases , which leads to the strengthening of the body's protective reactions . Yes, with development phagocytic activity of leukocytes increases in parallel with neutrophilic leukocytosis and monocytosis . Eosinophilic leukocytosis, due to the antihistamine function of eosinophilic granulocytes, plays a compensatory role in allergic reactions. At the same time, leukocytosis in leukemia can be accompanied by a decrease in the protective properties of leukocyte cells , which causes immunological hyporeactivity , in which the body suffers from secondary and autoinfections .

A picture of blood. An increase in the total number of leukocytes is accompanied by a change in the leukocyte formula. The absolute or relative nature of these changes is determined by determining the absolute content of various forms of granulocytes and agranulocytes per 1 liter. Thus, absolute neutrophilic leukocytosis in purulent-inflammatory diseases is accompanied by a decrease in the percentage of lymphocytes in the leukocyte formula (relative lymphopenia). However, the calculation of the absolute number of lymphocytes against the background of high general leukocytosis makes it possible to establish the absence of inhibition of lymphocyte growth.

During leukocytosis, especially neutrophilic , immature cells often appear in

the blood (nuclear shift to the left).

Leukopenia.

Leukopenia - a decrease in the total number of leukocytes in the blood below 4*10u per 1 liter.

Classification. Leukopenia, like leukocytosis, can be absolute and relative, and according to the predominant decrease in the number of individual forms of leukocytes - neutro- , eosino- , lympho-, monocytopenia .

Etiology. Infection (influenza viruses, measles, causative agents of typhoid and typhoid fever), ionizing radiation, drugs (sulfanamide, cytostatic , barbiturates), benzene, cyanocobalamin and folic acid deficiency , anaphylactic shock, hypersplenism , and as well as a genetic defect in the proliferation and differentiation of neutrophil granulocytes (hereditary neutropenia).

Eosinopeia observation with increased production of corticosteroids (stress, Itsenko-Cushing's disease), administration of corticotropin and cortisone, in connection with acute infectious diseases.

Lymphocytopenia can be caused by sepsis, immunodeficiency of a hereditary or acquired (in the case of radiation sickness, miliary tuberculosis, hypothyroidism) nature.

Monocytopelia occurs in all conditions accompanied by suppression of the myeloid germ of bone marrow hematopoiesis (for example , radiation sickness, severe septic conditions, agranulocytosis).

Pathogenesis. The development of leukopenia is based on the following mechanisms: 1) suppression leukopoiesis ; 2) violation of the release of mature leukocytes from the bone marrow into the blood; 3) destruction of leukocytes in hematopoietic organs and blood; 4) redistribution of leukocytes in the vascular bed; 5) increased release of leukocytes from the body.

The main consequence of leukopenia is a weakening of the reactivity of the body, caused by a decrease in the phagocytic activity of neutrophils granulocytes and the antibody-forming function of lymphocytes due to both a decrease in their total number and a possible combination of leukopenia with the production of functionally defective leukocytes. Such patients are prone to infectious and tumor diseases, especially with hereditary neutropenia , deficiency of T- and B-lymphocytes. A vivid example of severe reactivity of the body is acquired immunodeficiency syndrome of viral (AIDS) and radiation origin, as well as agranulocytosis and alimentary toxic aleukia.

Agranulocytosis - a sharp decrease in the number of granulocytes in the blood (up to 0.75* 10u per 1 liter and below) against the background of a reduced total number of leukocytes (up to 10u per 1 liter and below) myelotoxic (damage to the bone marrow) and immune (destruction of cells of the granulocyte series of anti-leukocytes - by them antibodies) origin. In the etiology of agranulocytosis, some drugs, ionizing radiation, and certain infectious diseases play a major role.

Aleukia is a lesion of the bone marrow with a sharp suppression and even complete absence of myelopoiesis and lymphopoiesis . Alimentary-toxic aleukia develops as a result of eating grain that overwintered in the field, infected with mold fungi that produce toxic substances. At the same time, pancytopenia is observed - a sharp decrease in the number of leukocytes (anemia) and platelets (thrombocytopenia).

Violation of the ratio of mature and immature forms of leukocytes in the blood.

The appearance of immature forms of leukocytes in the blood is caused by a violation of their maturation in hematopoietic tissue and an increase in the permeability of the bone marrow barrier. Usually this happens against the background of increased production of leukocytes as a result of both reactive and tumor hyperplasia of leukopoietic tissue. If the blood is dominated by mature, segmented nuclei - no, cells of the granulocytic series (primarily neutrophilic granulocytes) and there are no rod-nuclear and metamyelocytes , then such a hematological picture is associated with inhibition of bone marrow hematopoiesis.

A picture of blood. When counting the leukogram, the presence of a nuclear shift of neutrophil granulocytes to the left or right is established.

In the event of an increase in the number of young forms of neutrophils in the blood granulocytes speak of a nuclear shift to the left, in the case of a predominance of mature cells with a large number of segments (5-6 - hypersegmentation nuclei) against the background of the disappearance of younger forms - about the nuclear shift to the right.

There are several types of nuclear shift to the left. Regenerative shift is an indicator of reactive activation of granulocytopoiesis (on the background of moderate general leukocytosis, the content of rod-nuclear granulocytes and metamyelocytes is increased , single myelocytes may occur). Hyperregenerative shift - reflects excessive hyperplasia of leukopoietic tissue with impaired cell maturation and significant rejuvenation of the blood composition. Degenerative shift - indicates suppression and deep breakdown of leukopoiesis , when the number of rod- nuclear cells increases against the background of general leukopenia in the leukogram neutrophils granulocytes with degenerative changes in their cytoplasm and nucleus with a decrease in the number of segmented nuclear forms and the absence of metamyelocytes . Regenerative-degenerative shift - is observed in case of impaired maturation of leukocytes and hyperproduction of pathologically changed leukocytes in the bone marrow.

A nuclear shift to the right is possible in 20% of healthy people, but with leukopenia it is an indicator of suppression of leukopoiesis (radiation disease, B2- and foliodeficiency anemia).

Leukosis.

Leukemia is a tumor arising from hematopoietic cells with primary damage to the bone marrow.

Classification. Leukemia belongs to the group of tumor diseases of hematopoietic tissue, which have the general name " hemoblastosis ".

Leukemia is divided into acute and chronic, depending on what is the substrate of tumor growth and how leukemic cells have retained the ability to differentiate into mature ones. In acute leukemia, the main substrate of the tumor is hematopoietic class II, III, IV cells that have lost the ability to mature, in chronic leukemia - maturing and mature cells , since the bulk of leukemic cells differentiate into mature forms.

According to morphological and cytochemical features, myelo- , lympho-, mono- , megakaryoblastic acute leukemia, erythromyelosis and undifferentiated forms (originating from cells of II and III classes of hematopoiesis , which are not morphologically identified) are distinguished. Chronic leukemia is divided into myelo- , lympho-leukosis , monocytic , megakaryocytic , chronic erythromyelosis .

Etiology. The role of oncogenic viruses, ionizing radiation, chemical

carcinogens, genetic anomaly

Oncogenic viruses cause spontaneous leukemia in birds, mice , cats and other animals. They belong to C-type RNA- containing viruses. The virus can be transmitted through feces, urine, through the nose and throat, and from mother to offspring.

Burkitt's malignant lymphoma (DNA- containing Epstein-Barr virus) and T-cell leukemia (retrovirus type C-NTU). It is considered possible to transmit the T-cell leukemia virus during blood transfusions and sexual contact.

Ionizing radiation is the cause of radiation leukemia.

Chemical carcinogens can cause acute leukemia in people with professional contact (benzene) and treatment with some drugs that have a mutagenic effect (cytostatics , immunosuppressants , butadione, chloramphenicol).

Genetic features of hematopoiesis play an etiological role in the development of leukemia.

Damage to the hematopoietic tissue by the tumor process becomes more possible under the conditions of violation of the separation of somatic and sex chromosomes , their mutation. Thus, the incidence of leukemia is higher in patients with chromosomal abnormalities (Down's disease, Klinefelter's disease), hereditary defects of the immune system.

Pathogenesis. Under the influence of etiological factors, there is a mutation of genes or an epigenomic violation of the regulation of reproduction and maturation of hematopoietic cells of classes II-III.

Leukemia viruses can cause such a chromosomal rearrangement, as a result of which oncogenes localized in chromosomes are transferred to a part of the genome , where their activation is possible. A virus embedded in a cell's genome can activate proto-oncogenes that encode various oncoproteins (some of the oncoproteins act on the cell in the same way as growth factors - platelet , epidermal, T-cell, or interleukin , or interleukin 2, insulin , others are growth factor receptors , others are protein kinases that catalyze tyrosine phosphorylation). At the same time, a clone of tumor cells is formed in the bone marrow, which are characterized by unlimited growth and a reduced ability to differentiate. The rapid growth of clone cells causes them to spread (metastasize) throughout the blood system. In the cells of the clone circulating in the blood, the same chromosomal markers are detected .

The instability of the genome of leukemic cells leads to new mutations - both spontaneous and caused by the action of carcinogenic factors, as a result of which new tumor clones are formed.

Thus, leukemia has two stages of development - monoclonal (relatively more benign) and polyclonal (malignant, terminal). The transition from one stage to another is an indicator of tumor progression, when leukemic cells become more malignant, become morphologically and cytochemically undifferentiated . In hematopoietic organs and blood, the number of blast cells with degenerative changes in the nucleus and cytoplasm increases. Leukemic cells spread outside the blood system, forming leukemic infiltrates in various organs. As a result of the selection , the cells of those clones that were affected by immune protection factors, body hormones, cytostatic agents (chemical, hormonal), and ionizing radiation during radiation therapy are destroyed. Clones of tumor cells, the most resistant to these influences, dominate.

In leukemia, hematopoiesis is disturbed , which causes pancytopenia , which is

especially significant in the case of acute leukemia. Leukemic cells not only displace the hematopoietic parenchyma of the bone marrow, but also possibly inhibit the differentiation of normal stem cells. The consequence of inhibition of hematopoiesis is the development of anemia and thrombocytopenia . The latter to a certain extent explains the occurrence of the hemorrhagic syndrome characteristic of leukemia.

Depression of granulo-, monocyte- , and lymphopoiesis leads to a violation of phagocytosis, suppression of humoral and cellular reactions of immunity (formation of antibodies). This creates conditions for the attachment of secondary infection, as well as the activation of autoinfection . The loss of the function of immunological surveillance by lymphocytes causes the formation of forbidden clones, which are able to synthesize antibodies against their own tissues - autoimmune processes develop.

A picture of blood. The content of leukocytes in the blood, depending on the form of leukemia, can be normal - leukemic form, moderately increased (20-50*10^ per 1 l) - subleukemic , very high (200-500*10" per 1 l and above) - leukemic and reduced - leukopenia form. The leukogram shows a nuclear shift to the left. Degenerative changes, atypia of cells are observed , which makes it difficult to identify them. Anemia and thrombocytopenia are also characteristic .

Acute leukemia is accompanied by the appearance of malignant cells in the blood, which are differentiated using cytochemical research methods. A leukemic failure is observed - the absence of transitional forms between blast cells and mature segmented granulocytes. This reflects deep violations of leukopoiesis - a sharp decrease in the ability of cells to differentiate.

Chronic myelogenous leukemia is characterized by an increase in the leukogram quantity neutrophilic granulocytes - metamyelocytes , rod nuclei ,

segmentonuclear cells with a shift to the left to myelocytes and single myeloblasts . There may be an increased number of eosinophilic and basophilic granulocytes (eosinophilic and basophilic leukocytosis). In the terminal stage, a blast crisis occurs , during which the content of blast cells - myeloblasts , then undifferentiated blast cells - increases sharply in the blood .

Chronic lymphocytic leukemia is characterized by lymphocytosis (the B-lymphocytic variant of leukemia occurs more often), while 80-98% of lymphocytes are mature, there are single prolymphocytes and lymphoblasts , Humprecht's shadows (lymphocytes in a state of lysis). In the bone marrow, there is an almost total replacement of other hematopoietic germ cells by lymphocytes. Blast crisis in this form of leukemia occurs rarely .

Lecture No. 9

Topic: Pathophysiology of systemic circulation. Heart failure with damage to the myocardium. Myocardial necrosis . **Arrhythmias:** etiology, pathogenesis.

Purpose :

- get acquainted with modern definitions of compensatory and pathological changes in hemodynamics .
- to be able to explain to the patient the need to give up inhibiting habits (alcohol, tobacco , drugs, etc.).
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Basic concepts: Heart failure , compensation mechanisms, non-coronary heart damage, myocardial infarction, arrhythmias.

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

PATHOLOGICAL PHYSIOLOGY OF SYSTEMIC CIRCULATION

Under normal conditions, the coordinated work of the heart and blood vessels supplies organs and tissues with blood according to their needs. In a state of complete rest, the total need for blood in an adult is about 3 l/min-m*. During intensive work, it can increase 3-4 times, and in athletes even more.

The great functionality of the circulatory system and its adequate adaptation to the needs of the body are ensured by the fact that the heart and blood vessels have a race and at the same time stable regulation. This regulation is both intracardiac and general neurohumoral. ensures not only the coordinated work of various parts of the heart, the connection with blood vessels, but also the connection with other systems - breathing and blood. Therefore, not only the heart (by increasing the minute volume of the heart) or blood vessels (by changing the tone, redistributing the intensity regional blood circulation), but also the respiratory system (increasing pulmonary ventilation, utilization of oxygen by tissues) and the hematopoietic system (actn-visaiisyu ernthropoiesis).

Pathology of blood circulation, which can occur as a result of damage to the heart or blood vessels or a violation of their regulation. will also accompany the development of the devices listed above. Thanks to this, violations in one or another chain of blood circulation can be compensated for a long time. However, if the damage is too great, and the body's compensatory capabilities are reduced or exhausted, then blood circulation insufficiency develops.

Insufficiency of blood circulation is a hemodynamic disorder , which manifests itself in the fact that organs and tissues are not supplied with the required amount of circulating blood, and this, in turn, causes insufficient supply of them with oxygen and nutrients, a violation of the removal of end products of metabolism.

Insufficiency of blood circulation can occur due to the deterioration of the heart (heart failure) or changes in the functions of blood vessels (vascular insufficiency). Combined cardiovascular insufficiency is often observed. As a rule, any isolated

form of deficiency later becomes mixed.

Overuse of each of these forms can be acute or chronic and have a different degree of manifestation, taking the form of compensated (hidden), subcompensated or decompensated (manifest) insufficiency.

DISORDERS OF BLOOD CIRCULATION ASSOCIATED WITH DISORDER OF HEART FUNCTION

The work of the heart is characterized by features related to its functioning, metabolism, blood supply and innervation , which cause qualitative differences in the pathological processes that develop in it. They include the continuity of the functioning of the heart due to the specialized automatism apparatus and high aerobic metabolism. Even under the maximum stress of glycolysis, it cannot cover more than 10-20% of the heart's energy needs, which makes the heart muscle very sensitive to a lack of oxygen.

The heart is well supplied with blood. A feature of the vessels of the heart is a high tone, which in case of increased load allows them to expand 5-6 times, the presence of anastomoses between arteries of the fourth-.fifth order, as well as between arteries and capillaries and a small number of anaetomoses between coronary arteries. Therefore, when the main artery is turned off, intracardiac anastomoses are unable to ensure normal blood circulation, since they receive no more than a quarter of the original amount of blood.

Since the myocardium, even under conditions of rest, takes a quarter of the oxygen from the incoming blood (skeletal muscle at rest, for example, takes only 20-30% of oxygen), the only way to ensure the heart's increased need for oxygen is to increase the coronary blood flow. This makes the heart, like no other organ, dependent on the state of blood vessels, the mechanisms of regulation of the coronary flow of the crown and the ability of the coronary arteries to respond adequately to changes in load.

The heart is very sensitive to disturbances in the exchange of electrolytes, which depend on automatism, conduction, the relationship between excitation and contraction, as well as the state of some enzyme systems.

The heart is innervated by the sympathetic and parasympathetic parts of the autonomic nervous system, and by saturation by adrenergic neurons lshipkipmy , p also pa imistom norldroiapipu no mas equals among other bodies. It is known that the mediator of the sympathetic nervous system increases the tension developed by the muscle fiber of the heart, increases the metabolism, consumption of oxygen and fatty acids, and the exchange of calcium and potassium ions. Such predominance of sympathetic innervation creates prerequisites for increased vulnerability of the myocardium.

It was established that muscle cells of the heart of an adult organism do not divide and are not capable of regeneration. Replacement of the function of dead cells and adaptation to long-term increased load occurs only due to the increase of intracellular structures of intact cells, their hypertrophy .

Regardless of the cause of the pathological process in the heart, its typical consequences are a violation of blood circulation and blood supply to organs and tissues.

HEART FAILURE

Heart failure develops when there is a mismatch between the load on the heart and its ability to perform work, which is determined by the amount of blood

entering the heart and the resistance to expulsion of blood in the aorta and pulmonary trunk. Therefore, heart failure occurs when the heart cannot, due to the available resistance, pump all the blood that has arrived through the veins into the arteries.

There are three pathophysiological variants of heart failure.

1. ..... Congestive heart failure develops during diseases that cause an increase in resistance to cardiac output or inflow) of blood to a certain part of the heart, for example, with heart defects , hypertension in the large or small blood circulation, rteriovenous fistulas or during excessive physical work. In these cases , the heart with a normal contractile ability is subjected to an excessive load.

Heart failure due to myocardial damage caused by infection, intoxication, hypoxia, vitamin deficiency, impaired coronary circulation, fatigue, some hereditary metabolic defects. In such cases, insufficiency develops even with a normal or reduced load on the heart.

Q. A mixed form of heart failure occurs in the case of a combination of myocardial damage and its overload, for example, in rheumatism, when there is a combination of inflammatory damage to the myocardium and a violation of the valvular apparatus of the heart. This variant of heart failure also occurs in those cases when, due to dystrophic changes or death of parts of the muscle fibers of the heart, the rest is heavily loaded.

HEART FAILURE FROM OVERLOAD, MECHANISMS COMPENSATIONS

An increased workload on the heart can be the result of an increase in the amount of blood flowing in or an increase in the resistance of the blood flowing out. The first is observed during physical work or with heart defects accompanied by insufficiency of the valvular apparatus. Due to such defects, during diastole, not only the blood that flows through normal channels, but also that which, due to incomplete closure of the valves, is forced out of the cavity during systole enters the heart cavity. The same is observed with congenital defects of the septa of the heart. In the second case, the cause of the increased load on the sickle is the narrowing of the outlet opening from the heart cavity (for example, the opening of the pulmonary artery or aorta, the atrioventricular opening). An increase in blood outflow resistance also occurs as a result of hypertension, generalized atherosclerosis, and pneumosclerosis.

In the experiment, various types of cardiac dysfunction are studied by creating an artificial valve defect or narrowing (coarctation) of the large efferent vessels — the aorta and the pulmonary trunk. The heart is able to quickly adapt to the increased load and. performing increased work, compensate for possible blood circulation disorders. With it, depending on the type of load, one or another compensation mechanism is triggered.

In case of blood volume overload, the heterometric compensation mechanism (Frank-Sterling) is activated. During diastole, the blood filling of the cavities (or one cavity) of the heart increases, which leads to increased stretching of muscle fibers. As a result of such stretching, the heart contracts more strongly during systole. This mechanism is determined by the properties of myocardial cells. Within the known limits of the load, there is a linear relationship between the amount of incoming blood and the force of heart contraction. However, if the degree of stretching of the muscle fiber exceeds the permissible limits, the force of contraction decreases.

Reduction of the activity of the tension of the back occurs when the myocardial segment is stretched by more than 25% of its initial length, which corresponds to an increase in the volume of the left ventricular cavity by approximately 100%. Under permissible overloads, the linear dimensions of the heart increase by no more than 15-20%. The expansion of the heart cavities is accompanied by an increase in stroke volume and is called tonogenic dilatation.

With increased resistance to blood outflow, the homeometric mechanism of compensation is triggered. In this case, the length of the muscle fiber of the heart does not increase so sharply, but the pressure and tension resulting from the contraction of the muscle at the end of diastole increase. The strength of heart contractions does not increase immediately, but gradually with each subsequent contraction of the heart, until it reaches the level necessary to maintain the stability of the minute volume of the heart. Within the known limits of the load, the power that develops when the heart contracts is linearly related to the value of the outflow resistance of the heart. If these limits are exceeded, the force of heart contraction decreases.

In terms of energy, both mechanisms for compensation of increased load are unequal. Thus, with the same increase in the external work of the heart, calculated by the product of the minute volume of the heart by the average systolic pressure in the aorta, the oxygen consumption by the heart will not change in the same way, depending on whether the increase in work is caused by an increase in blood flow to the heart or an increase in aortic resistance. If the work is doubled due to the doubling of the minute volume of the heart, then the oxygen consumption increases by only one quarter, if the work is doubled due to the doubling of the blood flow resistance, then the oxygen consumption by the myocardium increases by 200%. This is explained by the fact that with the homeometric compensation mechanism, a significant increase in systolic pressure is required to overcome the increased resistance to blood flow, which can be achieved by increasing the amount and speed of muscle fiber tension. It is the phase of isometric tension that is the most energy-intensive and determines ATP consumption and oxygen consumption by the myocardium. So, the heteromechanic mechanism of compensation is more economical than the homeometric one , which, perhaps, explains the more favorable course of those pathological processes accompanied by the development of the Frank-Sterling mechanism, for example, valve insufficiency compared to orifice stenosis.

The compensatory mechanism that ensures the constancy of the minute volume of the heart can also be the acceleration of heart contractions — tachycardia. It can occur both due to the direct effect of increased blood pressure in the right atrial cavity on the pacemaker axillary-atrial node, and due to nervous and humoral extracardiac influences. From the energy point of view, this is the least beneficial compensation mechanism, since it is accompanied, firstly, by the consumption of a large amount of oxygen, secondly, by a significant reduction of diastole — the period of recovery and rest of the myocardium, and, thirdly, by the deterioration of the hemodynamic characteristics of the heart: during diastole the ventricles do not have time to fill with blood, the systole becomes less complete, since it is impossible to mobilize the heterometric compensation mechanism.

The described mechanisms of compensation for heart overload can be demonstrated on an isolated sulfur, devoid of regulatory connections with the body.

They are due to the properties of the heart muscle, its conduction system and to some extent the function of the internal organs heart nervous system. The latter is represented by neurons located in the sulcus to the level of the atrioventricular septum, which form reflex arcs within the heart. It is believed that the function of the intracardiac nervous system consists in adapting the activity of the heart to the load and coordinating the work of the atria and ventricles of the heart, its left and right halves.

Intracardiac regulatory mechanisms are affected by extracardiac ones - nervous and humoral. Among them, a special role belongs to the sympathetic part of the autonomic nervous system, the mediators of noradrepaline and adrenaline. The first is released by nerve endings, the second by cells of the medulla of the adrenal glands.

These mediators (catecholamines) interact with receptors on the cardiomyocyte surface . Receptors of the sympathetic nervous system are divided into two classes: a- and p-receptors. Each of which is divided into subclasses: ai , a"; you _ in>. In the heart of mammals, there are mainly ri -receptors, and in the undisturbed muscle tissue of vessels -on and ri- receptors . The intracellular effects of receptor stimulation are due to an increase in cAMP , an increase in the activity of nAMP - dependent protein kinase. by changing the flow of Ca ions and the binding of Ca2+ by cellular structures. When the sympathetic nervous system is stimulated, the strength and speed of heart contractions increase significantly, the volume of residual blood in the heart cavities decreases due to more complete expulsion of blood during systole (with a normal load, about half of the blood in the ventricle remains at the end of systole), the frequency of heart contractions increases. In the case of an increase in the tone of sympathetic nerves and the release of a large amount of catecholamines , the overload is more effectively compensated due to intracardiac regulatory mechanisms.

Violation of the sympathetic innervation of the heart, in particular after the introduction of some pharmacological agents or during experimental smpathectomy , complicates the mobilization of compensatory mechanisms, which reduces the functional capabilities of the heart.

If the load on the heart is excessive, compensatory mechanisms cannot cope with it and acute heart failure develops. At the same time, changes occur in the heart muscle in the form of intracellular accumulation of sodium and calcium ions, disruption of the synthesis of macroergic compounds , acidification of the intracellular environment from the onset due to a violation of the processes of contraction and relaxation of the cardiac muscle fiber. This leads to a decrease in the strength and speed of contraction of the heart muscle, an increase in residual systolic volume and diastolic pressure, and expansion of the heart cavities. Acute heart failure is accompanied by serious disorders — an increase in venous pressure, a decrease in cardiac output, tissue hypoxia. Structural changes may occur in the cardiac muscle, along with metabolic ones, due to which, even with a reduction in further load, the function of the heart may not normalize.

Acute heart failure also develops with ventricular fibrillation, paroxysmal tachycardia, myocardial infarction, myocarditis, thrombosis of the valve orifice, pulmonary embolism, and heart disease. At the same time, insufficient blood filling of the arterial system is observed, which causes ischemia of the brain with severe changes in its function, which resemble a picture of shock and are often

accompanied by loss of consciousness and convulsions.

In case of long-term overload of the heart, for example, with valve defects , hypertensive disease, long-term compensation mechanisms develop in the form of specific exchange and structural changes in the myocardium, which leads to an increase in the mass of the heart and strengthens its function.

In case of long-term overload of the heart, for example, with valve defects , hypertensive disease, long-term compensation mechanisms develop in the form of specific exchange and structural changes in the myocardium, which leads to an increase in the mass of the heart and strengthens its function.

Myocardial hypertrophy. A long-term increase in the load on the heart muscle is accompanied by an increase in the load per unit of muscle mass and requires a greater intensity of functioning of its structures. In response to increased load, the genetic apparatus of muscle and connective tissue cells is activated. Thus, in the experimental animal, a few hours after the narrowing of the aorta, signs of increased nuclear function, increased RNA synthesis and the number of ribosomes are found in the heart cells. At the end of the first forehead, protein synthesis increases, which causes a rapid increase in the volume of the muscle fiber, its hypertrophy and. as a rule, it is accompanied by hypertrophy of the part of the heart that bears the increased load. At the same time, the volume of each cardiac muscle fiber increases, while the total number of fibers remains unchanged. Due to hypertrophy of the myocardium, the load per unit of muscle mass decreases to a normal level.

When the load is reduced, for example, after elimination of stenosis, restoration of valves, the mass of the myocardium decreases to normal. Tss indicates that the intensity of protein synthesis in myocardial cells is largely regulated by the level of load. In addition, this process is controlled by the mechanisms of neuro-humoral regulation.

Myocardial hypertrophy is an adaptive phenomenon aimed at performing increased work without significantly increasing the load per unit of myocardial muscle mass. This is quite a perfect device. So. hypertrophy of the myocardium in athletes allows the heart to perform a very large amount of work. At the same time, the nervous regulation of the heart also changes, which significantly expands the range of its adaptation and the ability to bear significant loads. But during pathological processes, hypertrophy of the heart compensates for the resulting disturbances for a long time. So, for example, during autopsies, it was found that about 4% of people have valvular defects , which are accompanied by hypertrophy of the heart, and only 0.5-1% of people have the disease manifested clinically.

hypertrophy development . the characteristics of metabolism and functions of the hypertrophied myocardium, the causes of decompensation of the heart contributed to the study of the process in the experiment. A great merit in the creation of various experimental models of heart diseases, in particular experimental heart defects , belongs to O. B. Focht.

When experimentally reproducing a valve rupture or narrowing of the aorta, the load increases sharply and the hemodynamics changes . This can be observed in a number of cases and in humans, for example, during traumatic damage to the valvular apparatus, acute overload of the heart, hypertensive crisis. The experimental model of acute overload of the heart will make it possible to find out the sequence of changes that occur, to determine their cause and effect relationship.

A hypertrophied heart differs from a normal one in a number of metabolic

processes. Functional and structural signs, which reflect, on the one hand, the ability to overcome the increased load during the maned time, and on the other hand, the presence of prerequisites for the occurrence of pathological changes.

The increase in the mass of the heart occurs due to the thickening of each muscle fiber, which is accompanied by a change in the ratio of intracellular structures. At the same time, the volume of the cell increases in proportion to the cube of the linear dimensions, and the surface increases in proportion to the square of them. which leads to a decrease in the cell surface per unit of cell mass. It is known that through the surface of the cell, its exchange with the extracellular fluid takes place - absorption of oxygen, nutrients, removal of metabolic products, exchange of water and electrolytes. As a result of the listed changes, conditions arise for the deterioration of the supply of muscle fiber, especially its central parts.

The cell membrane plays a major role in conducting excitation and in combining the procession of excitation and contraction, carried out through the tubular system and the sarcoplasmic reticulum. Since the growth of these formations with muscle fiber hypertrophy also lags behind, the prerequisites are created for the disruption, contraction and relaxation of cardiomyocytes : as a result of the slowing down of the release of calcium ions into the sarcoplasm, contraction worsens, and as a result of the difficulty of the reverse transport of calcium ions, relaxation. Sometimes local contractures of individual cardiomyoitis may occur .

In the case of hypertrophy, the increase in the volume of the cell exceeds the increase in the volume of the nucleus. The ability of the nucleus of a highly differentiated T cell to divide is sharply limited. At the same time, only the linear dimensions of the nucleus increase due to the increase in the number of chromosomes, which is accompanied by some increase in the content of DNA. Since the role of the nucleus is to ensure protein synthesis, and therefore the processes of restoration of intracellular structures, the relative decrease of the nucleus can cause disruption of protein synthesis and deterioration of the plasticity of the cell.

During the development of hypertrophy, the mass of mitochondria initially increases faster than the mass of contractile proteins, creating conditions for sufficient energy supply and full compensation of heart function. However, in the future, as the process becomes more complicated, the increase in the mass of mitochondria begins to lag behind the growth of the cytoplasm. Mitochondria begin to experience extreme stress, destructive changes develop in them, the efficiency of their work decreases, and oxidative phosphorylation is disrupted . Cs causes deterioration of the energy supply of the hypertrophied cell.

An increase in the mass of muscle fibers is often not accompanied by an adequate increase in the capillary network, especially in cases of rapid development of cardiac hypertrophy. Large coronary arteries are also not capable of the necessary adaptive growth. Therefore, during exercise, the vascular supply of the hypertrophied myocardium deteriorates.

In a hypertrophied heart, the structure of intercalated disks and 1-lines is disturbed, as a result of which the electrical activity of the myocardium changes, the coordination of heart contraction as a whole deteriorates .

The nervous system of the heart is involved in the process of myocardial hypertrophy. Enhanced functioning of intra- and extracardiac nerve elements is observed. However, the growth of nerve elements lags behind the growth of the

mass of the contractile apparatus of the myocardium. Depletion of nerve cells occurs; trophic effects are disturbed, the content of norepinephrine in the myocardium decreases, which causes deterioration of contractile properties, difficulty in mobilizing its reserves. Therefore, the regulatory support of the heart is also disturbed.

Hypertrophy of the heart due to an increase in the mass of contractile and energy providing the apparatus is able to perform much more work for a long time than a healthy heart, while maintaining a normal metabolism. However, the ability to adapt to a change in load, the range of adaptation capabilities of a hypertrophied heart is limited. Reduced functional reserve. Imbalance of intracellular and tissue structures leads to greater vulnerability of the hypertrophied heart in case of exposure to adverse factors.

Long-term intense load on the cardiac muscle fiber leads to exhaustion of its function. The cause may be a disorder of the contractile function of the muscle fiber as a result of the reduced generation of energy by the mitochondria and a violation of the use of energy by the contractile apparatus. With various forms of heart failure, one of them pathological options may prevail, in particular, in the case of long-term hyperfunction of the heart leading to a violation of energy use. At the same time as the contractile function decreases, it becomes difficult to relax the muscle fiber, local muscle contractures occur , and later - dystrophy and death of cardiomyocytes .

The increased load is unevenly distributed among different groups of muscle fibers: those that function more intensively are exhausted faster, and die and are mixed with connective tissue, while the rest take on the load, which is increasing. Replacement of cardiomyocytes with connective tissue elements causes compression of neighboring cells, changes in the mechanical properties of the heart, further worsening of diffusion, deepening of metabolic disorders. It is believed that if 20-30% of the mass of the heart is replaced by connective tissue, its normal operation is impossible.

Dystrophic changes in the heart muscle are accompanied by an expansion of the heart cavities, a decrease in the strength of heart contractions— myogenic dilation of the heart occurs, in which the volume of blood that remains in the heart cavities during systole increases, and the veins overflow. Increased blood pressure in the cavity of the right atrium and in the mouths of the vena cava directly (due to the effect on the sinus-atrial node) and reflexively (Bainbridge's reflex) causes tachycardia, which complicates the disturbance of exchange in the myocardium. Therefore, the expansion of the heart cavities and tachycardia are formidable symptoms of the development of decompensation.

Evaluating the biological significance of myocardial hypertrophy, attention should be paid to the internal contradiction of this phenomenon. On the one hand, it is not a sufficiently perfect adaptive mechanism, which ensures that the heart performs increased work in normal and pathological conditions for a long time, and on the other hand, the features of the structure and function of the hypertrophied heart are a prerequisite for the development of pathology. 1 The evaluation of the first or second in each specific case determines the peculiarities of the course of the pathological process.

According to the dynamics of changes in metabolism, structure and function of the myocardium in the phase of compensatory hyperfunction of the heart, three main

stages are distinguished (F. 3. Meerson).

1. The emergency stage develops immediately after an increase in load, characterized by a combination of pathological changes in the myocardium (disappearance of glycogen, decrease in creatine phosphate, decrease in intracellular potassium content and increase in sodium content, mobilization of glycolysis, accumulation of lactate) with mobilization of reserves of the myocardium and the body as a whole. In this stage, the load per unit of mass of the myocardium, the intensity of the functioning of the structure (IFS), is increased, there is a rapid, within weeks, increase in the mass of the heart due to increased synthesis of proteins and thickening of muscle fibers.

2. ..... The stage of complete hypertrophy and relatively stable hyperfunction. In this stage, the mass of the myocardium is increased by 100-120% and does not increase anymore, IFS has normalized. Pathological changes in the metabolism and structure of the myocardium are not detected, oxygen consumption, energy production, the content of macroergic compounds do not differ from the norm. Hemodynamics normalized. The hypertrophied heart has adapted to the new load conditions and compensates for it over a long period of time.

3. ..... The stage of gradual exhaustion and progressive cardiosclerosis is characterized by profound metabolic and structural changes in the snsargotivnogo and contractile elements of the myocardium. Part of the muscle fibers dies and is replaced by connective tissue, IFS increases. The regulatory apparatus of the heart is disturbed. The progressive depletion of compensatory mechanisms leads to the development of chronic heart failure, and subsequently to circulatory failure.

Chronic, or congestive, heart failure develops gradually, mainly as a result of metabolic disorders in the myocardium with long-term hyperfunction of the heart or various types of myocardial damage. Due to the insufficiency of blood ejection from the heart, the blood filling of the organs on the outflow tracts decreases. At the same time, as a result of the inability of the heart to pump all the blood coming to it, stagnation develops in the blood flow paths, that is, in the veins. Since the volume of the venous bed is approximately 10 times greater than the volume of the arterial bed, a significant amount of blood accumulates in the veins.

In the case of a malfunction of mainly one ventricle of the heart, circulatory insufficiency acquires some specific features and is called insufficiency according to the left ventricular or right ventricular type, respectively. In the first case, blood stagnation is observed in the veins of the small circulatory circle, which can lead to pulmonary edema, in the second - in the veins of the large circle, while the liver enlarges, swelling of the legs, ascites appear.

Violation of the contractile function of the myocardium does not immediately cause the development of circulatory failure. As an adaptive mechanism, the peripheral resistance in the arterioles of the large circulatory circle first reflexively decreases , which facilitates blood flow to most organs. The arterioles in the small circulatory circle reflexly narrow , as a result of which the blood flow to the left atrium decreases and, at the same time, the pressure in the pulmonary capillary system decreases. The latter is mechanism of protection of pulmonary capillaries from overflowing with blood and prevents the development of pulmonary edema.

A certain sequence of dysfunction of different parts of the heart is characteristic. Hook. decompensation of the function of a strong left ventricle quickly leads to a violation of the function of the left atrium, stagnation of blood in

the small circle of blood circulation, narrowing of the pulmonary arterioles. Then, the less strong right ventricle is forced to overcome the increased resistance in the small circle, which leads to its decompensation and the development of insufficiency according to the right ventricular type.

Hemodynamic indicators in chronic heart failure change as follows: cardiac output decreases (from 5-5.5 to 3-4 l/min); the speed of blood flow slows down by 2-4 times; arterial pressure changes little, venous pressure increases; capillaries and post-capillary veins expand, blood flow in them slows down, pressure rises.

There are pathological changes in other organs and systems. Slowing of the blood flow in the large circle of blood circulation and violation of blood circulation in the lungs lead to an increase in the amount of restored hemoglobin in the blood. As a result, the skin and mucous membrane acquire a characteristic bluish color (cyanosis). Tissues lack oxygen.

Hypoxia is accompanied by the accumulation of underoxidized metabolic products and CO2 — acidosis develops. Acidosis and hypoxia lead to respiratory dysregulation, shortness of breath occurs. To compensate for hypoxia, erntrocntopoiesis is stimulated , the total volume of circulating blood and the relative content of blood cells increases. however, causes an increase in blood viscosity and rustling hemodynamic properties of it.

As a result of increased pressure in the venous areas of the capillaries and acidosis in the tissues, edema develops, which, in turn, increases hypoxia, as the diffusion path from the capillary to the cell increases. The development of congestive edema is facilitated by general disturbances in the exchange of water and electrolytes (retention of sodium and electrolytes in the body). This is yet another proof of the internal contradiction of compensation mechanisms in a pathological process. Mechanisms that have evolved to ensure sufficient salt and fluid content in the body in the event of a threat of dehydration or loss of body shape . in case of insufficiency, the series act to the detriment. In patients with heart failure, the excess salt used is not excreted by the kidneys, as it happens in a healthy person, but is retained in the body along with an equivalent amount of water.

Disruption of tissue nutrition due to prolonged insufficiency of blood circulation causes a deep and irreversible disorder of intracellular metabolism, which is accompanied by a violation of protein synthesis, including respiratory enzymes, and the development of hypoxia of the histotoxic type. These phenomena are characteristic of the terminal phase of circulatory failure. In combination with significant dysfunction of the digestive tract, progressive insufficiency of blood circulation leads to severe exhaustion of the body - cardiac cachexia.

HEART FAILURE DUE TO MYOCARDIAL DAMAGE

As already mentioned, another pathophysiological mechanism of heart failure is heart muscle damage. It can be inflammatory or dystrophic in nature, the result of genetic defects, infection, intoxication, immunopathological processes, diseases that cause myocardial hypoxia or lead to a violation of protein, lipid, mineral and vitamin metabolism.

At the same time, the formation of macroergic phosphates in cardiomyocytes or the use of their energy may be disturbed. Prolapses of the first kind occur in the case of insufficient oxygen supply to the cardiomyocytes , a decrease in the content of oxygen in the blood or ischemia, as well as a violation of the supply of oxidation substrates and the functioning of mitochondria . creatine kinase system — creatine

phosphate ; the second - as a result of damage to proteins of myofibrils , sarcoplasmic reticulum and disorder of exchange of basic calcium, potassium, and sodium ions. One of the mechanisms of damage to the cardiomyocyte can be a violation of its membrane structures as a result of peroxidation of lipids, which are part of them, by free radicals and hydroperoxides . An increase in the level of free-radical oxidation, in turn, can occur in the case of disturbances in the oxidative metabolism in the cardiomyocyte or as a result of insufficient antioxidant systems. First of all, the functions of specific membrane pumps (ICha +. K- ATPase , Ca-ATPase) are disturbed, membrane permeability gradually increases, then phospholipids are damaged and defects appear. Violation of the membrane leads to a change in the flow of sodium, potassium, chlorine and water ions, which, in turn, leads to swelling of the cell, as well as to a significant influx of calcium ions with the toxic effects of this cation. The number of detected α- and β- receptors and the release of catecholamines from nerve endings can increase , which deepens the primary damage.

In cases of metabolic disorders that have gone too far, the death of cardiomyocytes is possible .

Non-coronary damage of the heart. There are a number of experimental models of necrosis of the heart muscle, the occurrence of which is not related to the pathology of the heart vessels. These models to some extent reflect the situation observed under natural conditions.

Hypoxic necrosis of the myocardium can be reproduced with the help of various types of hypoxia: hypoxic , hemic . Against the background of a general lack of oxygen in the body, which leads to an increase in the load on the circulatory system, necrotic damage to the muscle fibers of the heart develops. The development of necrosis is facilitated by fixing the animal in an uncomfortable position, for example, stretching in a machine, or additional load running in a treadmill .

Electrolyte -steroid cardiopathy with necrosis. According to the observations of Sels , in the case of the introduction of a large amount of heating salts in combination with some anions (sulfates, phosphates), the foci of damage of the degenerative -necrotic type appear in the heart, which are often accompanied by hyalinosis of the vessels of other organs. These lesions spread or occur after administration of smaller amounts of salts, such as when some steroid hormones of the adrenal glands are administered at the same time. Against this background, heart damage caused by other causes develops more easily and is more severe. For example, even small doses of norepinephrine , Kalmspherol derivatives , hypoxia, muscle tension or. on the contrary, a significant restriction of mobility causes the spread of myocardial necrosis. Potassium and magnesium salts with it have a protective effect.

Immune damage to the heart is possible after the introduction into the body of an experimental animal of heterogeneous serum containing antibodies against the proteins of the heart of the animal of this species (cardiocenthoxins). It has also been proven that antibodies and sensitized lymphocytes directed against the tissues of one's own heart can be formed in the body. And (it helps the penetration of denat into the blood of necrotized components cardiomyoints . In an experiment, a similar process can be induced by injecting a myocardial suspension with an immune response stimulator (Freid's adjutant) into the animal. Damage to the heart can be

caused by circulating antigen-antibody-complement immune complexes, as well as fixation on its structures of food-type cytophilic antibodies: and their subsequent reaction with the antigen.

Coronary damage of the heart. Ischemic heart disease, myocardial infarction. As mentioned earlier, the features of the functioning, metabolism and blood supply of the heart make it extremely vulnerable in the event of a mismatch between the myocardial oxygen demand and the level of blood flow through the coronary arteries.

accompanying pathological conditions characterized by a violation of blood circulation in the myocardium, which is caused by damage to the coronary arteries, mainly of an atherosclerotic nature, combined into a special nosological unit, which received the name of coronary heart disease (CHD). CHD can be manifested primarily by functional disorders and pain syndrome (angina) or cause necrotic changes in the myocardium. The latter can have a large- and small-focal nature, an acute or chronic course. Among the forms of coronary artery disease, myocardial infarction should be singled out according to the features of pathogenesis and clinical significance.

Myocardial infarction is central ischemia and necrosis of the heart muscle, which occur as a result of the cessation of blood flow through one of the branches of the coronary arteries or when the amount of blood is insufficient to cover the energy needs of the myocardium. In most cases, damage to the wall of the coronary arteries causes atherosclerosis.

Recently, the violation of the blood supply to the heart has become so widespread and the mass has such a high specific weight among other types of pathology in a person that they speak of a peculiar epidemic of coronary heart disease, which has covered industrialized countries, where mortality from diseases of the circulatory organs ranks first. There is a clear trend towards an increase in the frequency of myocardial infarction and the incidence of it in younger and younger people.

Factors creating prerequisites for myocardial infarction carla _ got our risk factors. They are: hereditary conditioning; hypertension, diabetes, gout:

environmental factors — a sedentary, emotionally stressful lifestyle, overeating with a large amount of fat, smoking. In most cases, a myocardial infarction develops as a result of calcification and ulcerative changes of an atherosclerotic plaque with subsequent occlusion of a vessel by a thrombus. Clogging of one of the branches of the coronary artery is usually not accompanied by the mobilization of collateral vessels, since atherosclerosis also damages other vessels of the heart to some extent.

Stenosing sclerosis of blood vessels is a strict limit on the supply of nutrients to the heart muscle, when even a slightly greater degree of narrowing of the blood vessel or an increase in the oxygen content of the muscle can cause necrosis. Following it, in the center of ischemia, microcirculation disorders appear in the form of paralytic expansion of capillary vessels, stasis, edema. They complicate central nervous system disorders.

The following pathogenetic options for the development of myocardial infarction are possible: 1) blockage of a vessel, which causes an absolute decrease in the amount of coronary blood flow below a critical level (usually more than 3/4 of the original); 2) stenosis , which is not detected at rest, but with a small load, physical or mental, causes ischemia of the heart muscle: 3) significant physical load

or emotional stress, which, even without atherosclerotic damage, can cause a discrepancy between the myocardial oxygen demand and the possibility blood supply In the latter case, an increased secretion of catecholamines and hormones of the adrenal cortex plays a major role. In addition, r data about that. that vessels, even slightly sclerosed , can respond with spasm when normal vessels expand, for example, under the influence of catecholamines . This may be a consequence of impaired secretion (or action) of the so-called endothelial relaxation factor , which turned out to be nitric oxide (MO), which is synthesized in the cells of the vascular endothelium. (Nitric oxide analogs, for example , nitrites are used in therapeutic practice as vasodilators.)

There are several experimental models of myocardial infarction:

ligation of one of the branches of the coronary arteries in an acute or chronic experiment; clogging of the artery with the help of a catheter or the introduction of embolizing particles (mercury and agar); perfusion of the coronary artery through the catheter with oxygen-deprived blood or blood containing antimyocardial antibodies.

After a blood circulation disturbance, already within the first minutes, there are changes on the electrocardiogram in the form of a shift of the O-H segment. changes in the complex (Lv and tooth 7

Morphologically, the earliest possible violation of the structure of mitochondria can be noted, then swelling or pyknosis occurs nuclei , transverse striation of muscle fibers disappears. Cardiomyoblasts lose glycogen and potassium, and the number of lysosomes increases .

A heart attack develops in the area supplied with blood by the damaged vessel. The main consequence of a heart attack is local coagulation necrosis, lysis of cardiomyonitis , myocardial edema. There are several zones in the heart of the heart attack. In the central, mostly subendocardial zone, irreversible damage prevails (overstretched myofibrils , lump-like nuclear chromatin, mitochondria with amorphous matrix condensations . plasma membrane defects). Necrotized muscle cells with signs of calcium overload are found in the intermediate zone (shortening myofibrils , contractures, deposits of calcium phosphate in mitochondria), amorphous matrix condensations , lump-like chromatin, drops of fat. In the outer zone of the infarct, the accumulation of fat droplets prevails in the muscle cells, there are no necrotic changes. The ratio of the sizes of these zones is of great importance for the prognosis of the disease and the choice of treatment tactics. Dead cells are quickly surrounded by neutrophilic granulocytes, which are later replaced by macrophages, lymphocytes, and plasma cells . In the future, the cardiomyocytes are resorbed and mixed with fibroblasts, forming a connective tissue scar.

A center of necrosis in the myocardium disrupts the work of the heart as a whole, which is manifested in a rhythm disorder and a decrease in the pumping function of the heart. The degree and nature of the violations depend on the location and spread of the heart attack.

Under the influence of ischemia, cardiomyocytes can acquire the ability to automatism, and then an ectopic focus of excitation appears, causing extrasystole. Decreased conduction in the affected areas of the heart, and sometimes blockade together with the multiplicity of ectopic cells create conditions for recirculation of excitation and the occurrence of paroxysmal tachycardia, as well as such a formidable complication as ventricular fibrillation, which is the main cause of early

death in myocardial infarction.

Myocardial infarction can be accompanied by acute or chronic heart failure, and the deterioration of hemodynamics is more significant, the larger the area of the infarction. At the same time, the blood pressure on the ways of its inflow to the heart increases and the cardiac output decreases. One of the most serious complications of a myocardial infarction is cardiogenic shock, in which cardiac output decreases against the background of a significant increase in total peripheral vascular resistance due to an increase in the activity of the empathoadrenal and angiotensinal systems. The addition of microcirculation disorders in tissues leads to hypoxia, acidosis, impaired functions of the brain and other organs, and death.

The effects of myocardial infarction are characterized by painful and resorptive -necrotic syndromes. Pain during a heart attack is characterized by chain localization (soreness in the upper part of the body and behind the sternum), as well as severe emotional coloring. Ts is explained by the irradiation of excitation in the spinal cord from visceral neurons to the corresponding projection zones of somatic sensory neurons. However, a painless course of myocardial infarction also occurs .

An acute myocardial infarction in a person is often accompanied by an increase in the function of the sympathoadrenal system and the release of large doses of catecholamines into the blood . This, in turn, leads to an increase in the function of the heart, the level of free fatty acids in the blood, which leads to a decrease in glucose transport in cardiomyocytes and the intensity of glycolysis in them, an increase in oxygen consumption, complications of metabolic disorders and. as a result, complications of the course of a heart attack. In such cases, protecting the heart from the effects of catecholamines (for example, using (p- adrenoblockers) gives a positive result.

The resorption of necrotized areas of the myocardium into the blood of the content of damaged cells causes: the appearance of intracellular enzymes in the blood (creatine kinase , asparagaminotransferase , cardiac isoenzymes of lactate dehydrogenase), as well as myoglobin, which can be used for diagnostic purposes. Resorption of cellular proteins is accompanied by leukocytosis, fever, increased erythrocyte sedimentation rate (IIIOE).

myocardial proteins into the blood can be accompanied by autoimmunization with the formation of anti-cardiac antibodies and lymphocytes sensitized to cardiac antigens, eosinophilia and hypergammaglobulinemia . Naturally, such an immune reaction complicates myocardial damage, causes the appearance of secondary necrosis centers. In addition, the development of post-infarction syndrome (Dressler's syndrome), which is characterized by inflammation of the serous membrane of the heart, lungs, and joints, is associated with the formation of autoantibodies . At the same time, treatment with antibiotics is ineffective, a positive result is observed when corticosteroids are administered.

Neurogenic damage to the heart. Dystrophic changes and necrosis of the myocardium can be caused by acute or chronic irritation of the cervical -thoracic node of the sympathetic trunk, vagus nerve , hypothalamus, brain stem or other parts of the brain, by injecting large doses of adrenaline or noradrenaline into the blood . At the heart of neurogenic damage is a discrepancy between the functional capabilities, metabolism and blood supply of the heart. During irritation of the sympathetic nerves of the heart, the consumption of oxygen by the myocardium increases to a greater extent than the coronary blood flow, as a result of which

myocardial hypoxia develops. When the coronary arteries are calcified , the difference between the levels of blood flow and exchange is more significant, which can have serious consequences.

Irritation of the vagus nerve leads to opposite changes in the ratio between the level of metabolism and the amount of coronary blood flow, improving the conditions of blood supply to the heart. In an athlete, the tone of the cardiac branches of the vagus nerve is increased, and in a person who leads a sedentary lifestyle (" detrained heart", according to V. Raab), sympathetic influences prevail. This, perhaps, causes the increased vulnerability of the heart of a modern person, who leads a sedentary, emotionally saturated life, in contrast to the life of his distant ancestors, which was associated with significant physical exertion.

HEART RHYTHM DISORDER

The work of the heart, as a single pumping device, depends on the coherence of the work of the muscle fibers of each of its departments, the sequence, rhythm and frequency of contractions of these departments. As you know, these requirements are provided by the main properties of the heart: automatism, excitability, conduction and contractility. Under normal conditions, automatism is provided by the pacemaker — the axillary - atrial node, conduction — by the conduction system of the heart, which consists of the conducting bundles of the atria, the atrioventricular bundle , the atrioventricular node, and the conducting muscle fibers (Purkinje), from which excitation will be transmitted to the cells of the contracting myocardium. Despite the fact that the ability to automaticity is characteristic of other parts of the conduction system of the heart, the frequency of generated impulses decreases in the direction from the atria to the ventricles (the law of the cardiac gradient) and under normal conditions, the ability of the lower parts of the heart to detect automaticity is suppressed by formations located above.

Rhythm disturbances occur in inflammatory, ischemic or toxic damage to the myocardium, in the event of a change in the ratio between the intracellular and extracellular content of potassium, sodium, calcium and magnesium ions, in connection with hormonal dysfunctions. and may also be the result of impaired interaction of sympathetic and parasympathetic innervation of the heart. Under the influence of the mentioned etiological factors, the activity of the normal pacemaker, the refractory period of various excitable structures, or the conduction of excitation between various links of the conduction system and between the conduction system and the contracting myocardium may be disturbed, and ectopic foci of excitation may occur. All these changes, individually or in combination, cause arrhythmia. In addition, the presence of structures with different speeds of excitation (in the form of a certain structural anomaly or as a result of focal pathological drift) can play a significant role in its occurrence, which creates conditions for the continuous circulation of the excitation wave.

Violation of automatism. The ability to automatically generate pulses, as is known. depends on cells of the conducting system of the heart (p-cells), in which spontaneous slow depolarization of the cell membrane occurs during diastole. As a result, upon reaching a certain critical level, action potential arises. The frequency of pulse generation depends on the maximum diastolic potential of these cells, the level of that critical potential on the membrane, after which the action potential arises. and slow diastolic depolarization rates.

A change in the level of the maximum diastolic potential, critical potential or

speed of diastolic depolarization in one direction or another causes changes in the frequency and operation of impulses or the appearance of other sources of impulses , if these changes occur in other areas of the heart that are capable of being excited and lead to the appearance of action potentials there. In the event of a decrease in the level of the maximum diastolic potential of cells of the axillary - atrial node, when the threshold critical potential approaches it, or when the speed of slow diastolic depolarization increases, impulses are generated more often, tachycardia develops. This is observed due to the influence of increased body temperature, sympathetic mediator, stretching of the axillary - atrial node. On the contrary, a decrease in the speed of slow diastolic depolarization, hyperpolarization in diastole, and the removal of the critical threshold potential, as observed in the case of irritation of the vagus nerve , are accompanied by a slowdown in the generation of impulses, and therefore, in heart contractions — bradycardia. Fluctuations in the tone of the vagus nerve during breathing can cause respiratory arrhythmia (rapid heartbeat during inhalation, slowed heartbeat during exhalation). Respiratory arrhythmia normally occurs in children, but occasionally it can be observed in adults.

Under pathological conditions, the automaticity of the lower parts of the conduction system of the heart (potential pacemakers) may appear. Such conditions can occur when the automatism of the sinus-atrial node decreases or when the ability to generate impulses in other areas of the myocardium increases. In these cases, the frequency of impulses generated by a normal pacemaker is insufficient to suppress the automatism of other departments, which causes the appearance of additional impulses from ectopic foci of excitation.

Another mechanism for the appearance of ectopic foci of excitation can be the occurrence of a potential difference between adjacent myocytes as a result of, for example, non-simultaneous termination of repolarization in them. it can cause excitation in fibers that have already left the refractoriness phase . This phenomenon is observed with local ischemia of the myocardium and in case of poisoning with cardiac glycosides.

In all the mentioned cases, there is an extraordinary contraction of the heart or only the ventricles - extrasystole.

Depending on the localization of the cell from which the out-of-order impulse originates, several types of extrasystole are distinguished : sinus (or nomotopic), atrial . atrioventricular and ventricular . Since the wave of excitation, which originated in an unusual place, spreads in a different direction, the structure of the heart's electric field, which is reflected on the electrocardiogram, changes. Each type of extrasystole has its own electrocardiographic picture, which makes it possible to determine the location of the ectopic center of excitation.

Sinus extrasynstole occurs as a result of premature excitation of part of the cells of the sinus-atrial node. Electrocardiographically, it does not differ from normal contraction, except for a decrease in the diastolic T-P interval. As a result of the shortening of diastole and reduced filling of the ventricles, the pulse wave during extrasystoles is reduced.

Atrial extrasystole is observed in the presence of a focus of ectopic excitation in different areas of the atria. It is characterized by distortion of the shape of the P wave (decreased, biphasic, negative) with a preserved OKBT complex and a slightly prolonged diastolic interval after extrasystole. This is due to the fact that the

excitation, which follows a retrograde path, prematurely discharges the normal sinus impulse, which coincides with the excitation of the ventricles. The next atrial impulse, which occurs after a normal interval, lags behind the moment of the end of ventricular excitation - an incomplete compensatory pause.

Atrioventricular extrasystole is observed when an additional impulse occurs in the atrioventricular nodes _ The excitation wave emanating from the upper and middle part of the node spreads in two directions: in the ventricles—in the normal, in the atria—in the retrograde. At the same time, the negative wave P can coincide with the complex C'B. The diastolic interval after extrasystole is somewhat prolonged. Extrasnstola can be accompanied by simultaneous contraction of the atria and ventricles. In the case of atrioventricular extrasystole, coming from the lower part of the node, there is a compensatory pause, the same as in the case of ventricular extrasystole.

Ventricular extrasystole is characterized by the presence of a complete compensatory pause after an extraordinary contraction. It arises as a result of the fact that the excitation that covers the ventricles will not be transmitted through the atrioventricular node to the atria and the next normal impulse of excitation coming from the axoatrial node does not spread to the ventricles, which are in the refractory phase . The next contraction of the ventricles occurs only after another normal pulse. Therefore, the duration of the compensatory pause together with the interval preceding it is equal to the duration of two normal diastolic pauses. However, if the series of contractions is so rare that at the time of arrival of the next normal impulse the ventricles manage to leave the state of fragility , then there is no compensatory pause . An extraordinary contraction falls into the interval between two normal ones and in this case has the name of inserted extrasystole. Since the wave of excitation during ventricular extrasystole spreads in the ventricles both in the normal and in the retrograde direction, it is accompanied by a significant distortion of the shape of the OILV complex .

Abnormal contractions can occur singly or in groups. In the case of a group of extrasystoles, which are quickly repeated and completely suppress the physiological rhythm, paroxysmal tachycardia develops. The normal rhythm of the heart is suddenly interrupted by a bout of contractions with a frequency of 140 to 250 per 1 minute. The duration of an attack can vary from a few seconds to several minutes, after which it stops just as suddenly and a normal rhythm is established.

The atrial form of paroxysmal tachycardia is mostly observed . And since the duration of action potentials and refractory periods increases along the course of the conducting system, its distally located sections are not always able to reproduce the frequency of impulses coming from the proximal parts. Therefore, most of the impulses in atrial tachycardia cannot be conducted by the atrioventricular node. Since the duration of refractory periods and action potentials in the fibers of the right leg of the atrial - ventricular bundle are greater than in the left, the conduction of excitation to the right ventricle is often disrupted at a high frequency of impulses.

Conduction disorders. An arrhythmia caused by a violation of impulse conduction is called a block.

The cause of the blockade may be damage to the conductive paths, which leads to a lengthening of the refractory period, deterioration of other functional characteristics and is accompanied by a slowing down or complete cessation of impulse conduction. Conduction disorders can occur between the axillary node and

the atrium, within the atria, between the atria and ventricles, and in one of the legs of the atrioventricular bundle. In the case of intraatrial and intraventricular blockade, the frequency of heart contractions does not change, and the disturbance is manifested in a change in the shape of the electrocardiogram.

Atrioventricular blockade can be accompanied by a change in the rhythm and frequency of heart contractions. Atrioventricular or transverse heart block can be complete or incomplete. There are three degrees of incomplete heart block.

Atrioventricular block and degree is characterized by an increase in the time of the impulse from the atria to the ventricles, which is accompanied by a lengthening of the P —O interval (0.2—0.5 s). Blockade of the 2nd degree (Samoylov-Wenkebach periods) is characterized by a progressive increase in the P-O interval until then. until one of the excitations, usually the eighth or tenth, is not carried out. After the contraction of the ventricles stops, the P-O interval is restored, gradually lengthening with each contraction of the heart. It is believed that this phenomenon is associated with the increasing difficulty of conducting impulses through the node. With blockade of the III degree, the loss of every second — third contraction is observed or, on the contrary, only every second, third or fourth excitation of the atria is carried out. In the case of complete atrioventricular blockade, the atria and ventricles contract independently of each other, each in its own rhythm: the atria with a frequency of about 70. the ventricles — about 35 contractions per 1 minute (idioventricular rhythm).

Of particular importance is the moment of transition from incomplete blockade to complete, when impulses from the atria do not reach the ventricles. Slow diastolic depolarization in potential pacemakers occurs only after some time after the cessation of impulses from the atrial node. This period can be called the pre-automatic pause, during which ventricular asystole is observed. At the same time, as a result of the cessation of blood flow to the brain, fainting occurs, convulsions (Morgana -Adams-Stokes syndrome), death is possible. However, usually when the contractions of the ventricles resume, these phenomena disappear. Attacks can be repeated many times.

In case of a conduction disturbance in one of the legs of the atrial - ventricular bundle, the frequency of contractions does not change, but the contraction of the corresponding ventricle is delayed due to the fact that the excitation wave reaches it in a circular way.

Violation of learning rhythm. Arrhythmia can consist of fatigue, which disrupts the reproduction of the excitation frequency (rhythm transformation, frequency division) or the action and contraction potentials, which follow one another, are not the same (alternation).

The transformation of the rhythm can be observed when the conduction of excitation is disturbed through various areas of the conduction system of the heart or during the transition of excitation from the conducting fibers of Purkinje to muscle fibers. It is clearly manifested when the functional state of the heart is disturbed due to intoxication, hypoxia or ischemia in combination with tachycardia. At the same time, the frequency of myocardial excitation may not correspond to the frequency of contractions: for example, at every second action potential, contraction does not occur. This is explained by the fact that the contractile apparatus of the cell, the system of combining excitation and contraction has a longer recovery period than the excitable membrane of a cardiomyocyte . Therefore, such a phenomenon occurs

in the case of such lesions of the myocardium, when the functional properties of the membrane are still preserved, and the contractile apparatus is already disturbed, and is considered as an unfavorable prognostic sign.

Alternation is a difference in the amplitude and duration of excitations and contractions that follow one another. Alternation of only excitations, or only contractions, or both at the same time is possible. This is mostly due to the fact that when the myocardium is damaged, psi fibers are excited and shortened in response to one impulse, and only part of them are in response to the next one. Therefore, action potentials and amplitude of contractions are not the same. However, alternating contractions of each muscle fiber are possible.

Violations of rhythm acquisition indicate a deep metabolic disorder and are often observed in terminal states.

Arrhythmia due to simultaneous violation of automatism and conduction. In the presence of numerous ectopic foci of excitation and such a change in the conduction of the impulse, when the speed of its conduction through different areas of the myocardium or masses is disturbed, the place of propagation of the impulse is only in one direction, conditions are created for the long-term circulation of the excitation wave in a certain part of the heart, rhythm disorders occur - tremors and flickering .

Under normal conditions, a wave of excitation, originating in one place, spreads to both sides of the cardiac chamber. Having reached the opposite wall, it fades, meeting with another wave, which left behind a refractoriness zone . If, due to the occurrence of a temporary blockade or delay in the arrival of impulses by some fibers of the myocardium, the excitation reaches a place that has already left the state of refractoriness , then the conditions for long-term circulation of the impulse are created.

In some cases, the frequency of atrial contractions reaches 250-400 per minute. This condition is defined as atrial fibrillation, it can last for several months or years. At the same time, as a result of the inability of the ventricles to reproduce the high rhythm of the atria, relative heart block develops; the ventricles respond to contractions every second, third, or fourth atrial contraction, as the rest of the excitation waves enter the refractory phase . Reduction of their previously sufficient filling with blood, which causes severe circulatory disorders.

If the number of atrial contractions reaches 400-600 in 1 minute. they talk about fibrillation, or fibrillation, of the atria. At the same time, only individual muscle fibers contract, and the entire atrium is in a state of incomplete contraction, its participation in blood pumping ceases. Most of the impulses that randomly reach the atrioventricular node through individual muscle fibers of the atrium are unable to cause excitation, because they find the node in a refractory state or do not reach the threshold level. Therefore, the atrioventricular node is excited irregularly and the contractions of the ventricles are random. As a rule, the number of reductions goes nights per 1 minute exceeds normal. Shortening of the path is common nocturnes occur before they are filled with blood and are not accompanied by a pulse wave. Therefore, the pulse frequency will be lower than the frequency of heart contractions — a pulse deficit . This pathological condition of the heart is called atrial fibrillation. It occurs mostly in the case of stenosis of the left atrioventricular opening, thyrotoxicosis, cardiosclerosis.

With certain pathogenic effects (passage of electric current through the heart,

anesthesia with chloroform or cyclopropane, occlusion of coronary arteries or other causes of acute myocardial hypoxia, heart injury, effect of toxic doses of digitalis and calcium preparations) ventricular fibrillation occurs. At the same time, due to the chaotic contraction of individual muscle fibers, there are practically no contractions of the ieropulsive force, blood circulation stops, loss of consciousness and death quickly occur. Fibrillation leads to a decrease in the concentration of intracellular potassium, which leads to a decrease in the membrane potential of cardiomyocytes and facilitates the occurrence of depolarization and excitation in them, as well as a change in the content of nerve mediators, especially catecholamines .

The most effective means of eliminating ventricular fibrillation is electrical defibrillation (effect on the heart with a short-term electric discharge). At the same time, simultaneous depolarization of all myocardial fibers occurs and asynchronous excitation of muscle fibers ceases. To prevent the development of fibrillation, correction of the salt composition of the blood is used.

INSUFFICIENCY OF BLOOD CIRCULATION IN DISORDER OF BLOOD FLOW TO THE HEART

This type of failure develops in those cases when the blood supply to the heart comes through the veins or when the heart cannot accept all the blood that comes. The first is observed in the case of hypo-volemia (blood loss) or sudden dilation of blood vessels (collapse), the second is when fluid accumulates in the pericardial cavity, which causes difficulty in the expansion of the heart cavities during diastole.

Accumulation of fluid in the pericardial cavity can be fast or slow. Rapid accumulation occurs as a result of hemorrhage after injury or rupture of the heart, or in the mouth of rapidly developing pericarditis. As a result of the insufficient distensibility of the pericardium , the pressure in the cavity increases, which prevents diastolic expansion of the heart, and acute cardiac tamponade occurs. In the experiment, this diarrhea is simulated by the introduction of liquid into the pericardial cavity (O. 5. Focht), which makes it possible to study in detail the pathological and compensatory mechanisms that arise in this case. First of all, blood filling of heart cavities decreases , stroke volume and blood pressure decrease. There is a clear inverse relationship between these indicators and intrapericardial pressure: the higher it is intracardiac pressure, the lower arterial pressure. At the same time, venous pressure increases.

Activation of compensatory mechanisms in pericarditis occurs reflexively with the participation of signals coming from three receptor zones: 1) from the zone of the openings of the vena cava and pulmonary veins — as a result of increased pressure on the blood flow paths;

2) from the aorta and carotid sinuses (ennocarotid zones) — as a result of a decrease in pressure on the blood outflow pathways and a significant reduction in the depressant effect; 3) from the pericardium — under the influence of an increase in pericardial pressure. After cutting the vagus and depressor nerves, as well as in the case of suppressing the receptor zones with the help of novocaine, the adaptive mechanisms do not function and blood circulation is impaired, accompanied by significant complications. In case of cardiac tamponade, the mobilization of powerful compensation mechanisms to increase heart contractions (homeo- and heterometric mechanisms, inotropic effect of catecholamines) is ineffective or

impossible. Therefore, only a relatively low-power and energetically inefficient mechanism of compensation and maintenance of blood pressure works - acceleration of heart contractions, which is then joined by narrowing of peripheral vessels. This explains the severe clinical course of acute tamponade of the heart.

In the case of a slower accumulation of fluid in the pericardial cavity, the work of the adaptive mechanisms is more effective, the increase in intrapericardial pressure over a certain period of time can be compensated.

The slow accumulation of fluid, which is observed in chronic exudative pericarditis and gyropsricardia , is accompanied by continuous stretching of the pericardium and an increase in the volume of its cavity. As a result, the intrapericardial pressure changes relatively little, and circulatory disorders do not occur for a long time.

Lecture No. 10

Violation of blood circulation is caused by a violation of the function of blood vessels. Etiology and pathogenesis of hypo and hypertension. Atherosclerosis .

Purpose :

- get acquainted with the pathogenesis of atherosclerosis.
- get acquainted with the pathogenesis of disorders of the sedin functions .

Basic concepts: atherosclerosis, arteriosclerosis, hypotension , hypertension.

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

Violation of blood circulation is caused by a violation of the functions of blood vessels. General characteristics of the occurrence of hypertension. Pathogenesis of atherosclerosis.

Mechanisms and causes of hypertension .

In what cases can develop acute and chronic arterial

Hypotension ? Hypertensive disease: etiology and pathogenesis. Name the mechanisms that stabilize blood pressure at an elevated level during the development of hypertensive disease. Etiology and pathogenesis of atherosclerosis.

Today, cardiovascular pathology occupies a leading place in the structure of the disease of the population. Heart failure occurs in case of damage to the myocardium itself (coronary circulation disorders, hypoxia, intoxication, etc.) and damage to blood vessels (cardiosclerosis, hypertension, etc.). The resulting heart pathology can remain hidden for a long time, but sooner or later it will lead to cardiosclerosis and heart failure. Knowledge of the nature of compensatory and specifically pathological processes is necessary for the fight against cardiovascular diseases.

The importance of fats for the body, their metabolism in the body.

Lipids and lipoproteins of blood plasma, lipid transport.

Sources of blood plasma cholesterol and its metabolism

Anatomical and physiological features of blood vessels. Prerequisites for the formation of an atherosclerotic lesion.

Atherosclerosis. The first concept of "atherosclerosis", proposed by Marchand in 1904, is reduced to only two types of changes: the accumulation of lipids in the form of mushy masses on the inner lining of the vessel (from the Greek athere - porridge) and sclerosis itself - the connective tissue compaction of the arterial wall (from the Greek scleros - hard).

The modern interpretation of atherosclerosis is much broader. According to the definition of the WHO, atherosclerosis is a different ratio of changes in the intima of arteries, manifested in the form of focal deposition of lipids, complex carbohydrate compounds , blood elements and products circulating in it, the formation of connective tissue and calcium deposition.

Atherosclerosis *risk factors are a set of* internal and external conditions that increase the probability of developing this disease in people many times over.

1. ***Age*** , especially after 30 years. This has led some scientists to believe that atherosclerosis is a function of age and is an exclusively biological problem. But the majority of scientists still adhere to the opinion that age-related and atherosclerotic changes in blood vessels are different forms of atherosclerosis, especially in the later stages of their development. At the same time, age-related changes in arteries contribute to the development of atherosclerosis.

2. ***Sex*** . At the age of 40-70, men suffer from atherosclerosis and myocardial infarction of an atherosclerotic nature more often than women (3-4 times on average). After the age of 70, the incidence in women and men is approximately the same. This is due, on the one hand, to a low initial level of cholesterol and its retention in the fraction of non-atherogenic high-density lipoproteins in blood serum in women. On the other hand, this indicates the antisclerotic effect of female sex hormones.

3. ***Heredity*** . The role of heredity is confirmed by statistics on the high frequency of coronary heart disease in individual families, as well as in identical twins. We are talking about hereditary forms of hyperlipoproteinemia

and hereditary metabolic defects of the arterial wall.

4. ***Excessive consumption of food*** . It has been proven that the cholesterol content in the blood and the incidence of atherosclerosis are directly dependent on the amount of consumed animal fats and cholesterol-containing products. There is a relationship between the incidence of atherosclerosis and the amount of sugar consumed. 75-85% of patients with diabetes suffer from atherosclerosis and die from it. 4/5 patients with atherosclerosis have reduced glucose tolerance, and 1/3 of them are in a prediabetic state.

5. ***Stress*** . There are observations that indicate that the incidence of atherosclerosis is higher in people in "stressful" professions, that is, professions that require long-term and strong nervous tension (doctors, teachers, lecturers, pilots, people in managerial positions). In general, the incidence of atherosclerosis is higher among the urban population than among the rural population.

6. ***Hypodynamia*** . After physical activity, the level of cholesterol in the blood normalizes faster. Atherosclerosis is more common among people who do mental work due to hypodynamia, and less often among people who do physical work.

7. ***Intoxication*** . Influence of alcohol, nicotine, intoxication of bacterial origin and chemical origin (fluorides, CO, H_2S, lead, benzene, mercury compounds). With these intoxications, there is a violation of fat metabolism in general, as well as typical dystrophic and infiltrative-proliferative changes in the arterial wall.

8. ***Arterial hypertension*** . An increase in blood pressure, especially above 160/90 mmHg . contributes to the development of atherosclerosis. So, with the same level of cholesterol in the blood, with hypertension, myocardial infarction occurs 5 times more often.

9. ***Hormonal disorders*** , metabolic diseases. Atherosclerosis often occurs against the background of hormonal changes (diabetes, insufficiency of the function of the gonads, myxedema, etc.) or against the background of metabolic disorders (gout, obesity, hereditary form of hyperlipoproteinemia , etc.)

hypercholesterolemia that is important for the development of atherosclerosis , but

quantitative and qualitative changes in blood plasma lipoproteins. The basis of this stage of the plasma theory was the proposition: "without atherogenic lipoproteins, there is no atherosclerosis. "

of hypercholesterolemia are fundamentally important :

1. Excess intake of cholesterol in the body with food.
2. Excess synthesis of cholesterol in the body itself.
3. Violation of the removal of cholesterol from the body in the form of bile.
4. Violation of the use of cholesterol by peripheral cells.

The possibilities of etiopathogenetic treatment of atherosclerosis today are limited to the correction of lipid metabolism disorders: diet and a narrow range of hypolipidemic drugs. In the presence of hemodynamic disorders and secondary complications, appropriate symptomatic therapy is carried out . The primary importance is given to the primary prevention of atherosclerosis.

Arterial hypertension. A distinction is made between primary and secondary arterial hypertension. In the case of a primary increase in blood pressure, it cannot be associated with a specific disease or pathological process in certain organs and systems. The reason for the increase in blood pressure in this case remains unclear. Different countries use two different terms to denote this form of hypertension : "essential hypertension" and "hypertensive disease". Secondary arterial hypertension occurs as a result of pathological processes in various organs and systems:

1. Kidney diseases (glomerulonephritis , pyelonephritis, polycystic kidney disease , etc.). The main pathogenetic mechanisms of blood pressure increase are activation of the renin-angiotensin- aldosterone system, and in the case of renal failure, sodium and water retention.

2. Tumors of the adrenal glands (pheochromocytoma , aldosteroma). With aldosteroma (tumor of the cortical layer of the adrenal glands), excessive production of aldosterone leads to retention of sodium and water and an increase in intravascular fluid volume. The formation of renin decreases, hypokalemia develops , and arterial hypertension develops. Pheochromocytoma is a tumor of chromaffin cells of the medulla of the adrenal cortex that produce catecholamines , mainly norepinephrine and adrenaline.

3. Damage to the heart and blood vessels (some heart defects, coarctation of the aorta).

4. Diseases of the nervous system (poliomyelitis, encephalitis, injuries , concussions and brain tumors.)

In all these cases, the etiology of increased blood pressure is clear. Eliminating the cause leads to normalization of blood pressure.

Hemodynamic variants of arterial hypertension

1. The hyperkinetic type is caused by a significant increase in the work of the heart, as a result of which the minute volume increases.
2. The eukinetic type occurs with a moderate increase in the minute volume of the heart and the total peripheral vascular resistance.
3. Hypokinetic type - its development is associated with a significant increase in peripheral vascular resistance.

Arterial hypertension is treated both non-medicated and medicated.

Non-pharmacological treatment includes smoking cessation, weight loss, limiting alcohol consumption, increasing physical activity, limiting salt consumption, relaxation, etc.

Medical treatment includes the use of calcium antagonists, angiotensin-converting enzyme inhibitors, diuretics , and beta-blockers.

Lecture No. 11

Topic: Pathological physiology of the respiratory system. Respiratory failure.

Purpose :

- get acquainted with the pathogenesis of respiratory failure.
- to be able to distinguish pathological types of breathing

.

Basic concepts: Respiratory failure, ventilation and parenchymal failure, tachypnea , hyperpnea , bradypnea , apnea, terminal breathing.

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

Breathing is a set of processes that ensure the entry of oxygen into the organism , its use in the biological oxidation of organic substances and the removal of carbon dioxide.

External respiration: a) gas exchange in the alveoli between the lungs and the external environment; b) exchange between alveolar gases and blood gases; c) transport of gases by blood to tissues and cells - specifically to functional elements of organs.

Respiratory insufficiency is a state of the body in which either maintenance of the normal gas composition of the blood is not ensured , or the latter is achieved due to the intense work of compensatory mechanisms: an increase in the minute volume of breathing due to its depth and frequency - that is, shortness of breath; increase in the number of red blood cells and hemoglobin, which leads to a decrease in the functional capabilities of the organism .

Types of respiratory failure:

I. According to the clinical course: acute (asphyxia) and chronic respiratory failure (bronchial asthma, COPD).

II. According to the severity of clinical signs: compensated (blood gas composition has not yet changed) and decompensated (gas homeostasis is disturbed).

III. According to pathogenesis: ventilation and parenchymal insufficiency of external breathing.

Pathogenetic variants of ventilatory failure of breathing:

1. Dysregulatory insufficiency (violation of the central regulation of breathing).
2. Restrictive insufficiency.
3. Obstructive insufficiency.

Dysregulatory insufficiency can manifest itself in the following types:

1) tachypnea - frequent but shallow breathing in case of fever, functional disorders of the central nervous system (hysteria), damage to the lungs (atelectasis, pneumonia, congestion), pain localized in the areas of the body involved in the act of breathing (chest, abdominal wall, pleura).

2. hyperpnea - deep frequent breathing - when the partial pressure of oxygen in the inhaled air decreases or when the CO2 concentration in it increases, during anemia, acidosis, etc. The extreme degree of excitation of the respiratory center manifests itself in the form of Kussmaul breathing , which is most often observed in patients in a state of diabetic coma. It is loud, frequent breathing, in which a deep breath is followed by an intensified exhalation with the active participation of the expiratory muscles.
3) bradypnea - shallow shallow breathing with increased blood pressure (reflex from baroreceptors of the aortic arch and carotid sinus), with hyperoxia (due to periodic excitation of chemoreceptors sensitive to a decrease in oxygen tension in arterial blood).
Deep liquid breathing can appear with increased resistance to air movement in the upper respiratory tract - stenotic breathing. The alveoli are filled slowly, their irritation is weak and the change of inhalation to exhalation slowly occurs (slowing down of the Hering-Breuer reflex).
4) apnea - temporary cessation of breathing, which may be associated with a decrease in reflex or direct chemical stimulation of the respiratory center (hypoxia, intoxication, organic brain lesions).
Periodic breathing is such a violation of the breathing rhythm, in which periods of breathing alternate with periods of apnea:
Cheyne -Stokes breathing is characterized by a gradual increase in the frequency and depth of breathing, which, reaching a maximum, gradually decreases and disappears completely. There is a complete, sometimes lasting up to (0.5 min) pause - apnea, and then a new wave of respiratory movements. Etiology: 1) chronic nephritis, 2) nephrosclerosis, 3) uremia, 4) heart decompensation, 5) severe pulmonary failure, 6) liver failure, 7) diabetic coma, 8) brain damage - tumors, hemorrhages, injuries, brain edema .
Pathogenesis: as a result of a decrease in the excitability and lability of the respiratory center, the usual concentration of CO2 in the blood becomes insufficient to excite it. The respiratory center is not disturbed, breathing stops and CO2 accumulates. Its concentration reaches such a significant level that it begins to act on the respiratory center, despite the decrease in its excitability, and leads to the appearance of breathing. But since lability is reduced, breathing increases slowly. As breathing increases, CO2 is removed from the blood and its effect on the respiratory center weakens. Breathing becomes less and less and finally stops completely - again a pause.
Biot's breathing - occurs with deeper damage to the respiratory center - morphological, especially inflammatory and degenerative lesions in nerve cells. It is characterized by the fact that the pause occurs after 2-5 respiratory movements. The pause is long, that is, the smallest decrease in pCO2 leads to a pause. Etiology: 1) meningitis , 2) encephalitis, 3) severe poisoning, 4) heat stroke, etc.
Restrictive insufficiency - when lung distensibility is reduced in pneumonia, atelectasis, fibrosis, edema and congestion in the lungs, complete blockage of the large bronchi, after removal of part of the lung.
Obstructive insufficiency is observed as a result of a decrease in the patency of small-caliber bronchi due to a decrease in their lumen: spasm of the bronchial muscles, edema of the mucous membrane and accumulation of sputum in the lumen

of the bronchi. First of all, exhalation is disturbed due to the narrowing of the bronchi.
Terminal breathing.
Gasping breaths are single, rare, decreasing in strength "sighs", which are observed in agony, for example, in the final stage of asphyxiation.
Apneic breathing is characterized by a convulsive effort to inhale, which is occasionally interrupted by exhalation.
Breathing insufficiency is called parenchymatous, which occurs as a result of disturbances in the gas exchange between the alveoli of the lungs and the blood. Its causes are focal lesions of the lung parenchyma (exudative and proliferative inflammatory diseases), which lead to disturbances in pulmonary blood circulation.
There are three main mechanisms of gas exchange violations between alveoli and blood:
1) violation of gas diffusion;
2) violation of pulmonary perfusion (blood circulation);
regional violations ventilation-perfusion relations.
Violation of gas diffusion in the lungs. Etiology:
1) reduction of the diffusion coefficient;
2) reduction of the diffusion area (respiratory surface of the lungs);
3) an increase in the thickness of the alveolar-capillary membrane;
4) reduction of the difference between the partial pressure of gases in the alveolar air and their tension in the blood of the pulmonary capillaries;
5) reduction of blood contact time with alveolar air.
Violation of pulmonary perfusion. Etiology:
a) decrease in pressure in the right ventricle (right heart failure, decrease in venous return in case of blood loss, shock, collapse);
b) increased pressure in the left atrium (stenosis of the mitral valve opening, left ventricular heart failure);
c) an increase in the resistance of the blood vessels of the small circle of blood circulation (increased blood viscosity, the presence of obstacles to the movement of blood - thrombosis, embolism).
Asphyxia is a pathological process, a syndrome with an acute course, which occurs due to a lack of oxygen in the blood and tissues, with the subsequent accumulation of carbon dioxide in the body.
And the period of asphyxia is characterized by a rapid increase in the depth and frequency of breathing with a predominance of the inhalation phase over the exhalation phase. General excitement develops, the tone of the sympathetic part of the autonomic nervous system increases - pupils dilate, tachycardia appears, blood pressure increases, convulsions are possible.
In the II period, the frequency of breathing gradually decreases while maintaining the maximum amplitude of respiratory movements, the exhalation phase increases. The tone of the parasympathetic part of the autonomic nervous system prevails - the pupils narrow, blood pressure decreases, and bradycardia is noted.
In the III period of asphyxia, there is a decrease in the amplitude of breathing, its frequency and, finally, cessation of breathing. Blood pressure is significantly reduced. After a short-term cessation of breathing, several rare convulsive breathing movements (gasping breathing) usually appear , after which respiratory paralysis occurs.

Lecture No. 12

Topic: Gastrointestinal pathophysiology tract Ulcer disease of the stomach and duodenum. Pancreatitis. **Liver failure.** Commies. Jaundice Etiology and pathogenesis.

Purpose :

- Modern ideas about the pathogenesis of peptic ulcer disease of the stomach and duodenum, pancreatitis, intestinal obstruction.
- Peculiarities of the digestive system in newborns and young children, which are characterized by insufficient development of neurohumoral regulation and secretory-fermentative function, which contributes to the development of dyspepsia.
- The material of the lecture is aimed at the formation of logical and professional thinking in the students, the doctor's responsibility for the condition of the patient's body and diseases such as stomach and duodenal ulcers.
- To know the etiology and pathogenesis of jaundice, which develops in diseases of the liver and other organs and systems.

2. To know that the functional immaturity of the liver in young children determines increased sensitivity to various harmful factors, including medicines, to diet disorders.

Basic concepts: peptic ulcer disease, intestinal digestion, cavity and membrane digestion, acholia, hypocholia , pancreatitis, jaundice, cholestasis .

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

Pathology of digestion in the intestines. Ulcer disease.

Ulcer disease is characterized by the appearance of defects on the mucous membrane of the stomach or duodenum and a chronic course.

In the etiology of peptic ulcer, extraordinary effects on the body are of great importance: mental trauma, emotional and physical overstrain, various stressful situations. This conclusion was made on the basis of data on the high incidence of peptic ulcer during the Second World War.

A certain etiological role is played by local adverse effects on the stomach, irregular diet, consumption of excessively hot food, alcohol, abuse of spicy, salty dishes, smoking, as well as hereditary predisposition, in particular, the predominance of the tone of the parasympathetic part of the autonomic nervous system. The role of coarse, inadequate food in the occurrence of ulcerative lesions was proved experimentally by L. Aschoff . Previous starvation of animals contributes to the reproduction of ulcers in them through sensory and other effusions.

Recently, the etiological role of infectious agents - the herpes virus, as well as the gram-negative spiral bacterium Helicobacter (Campilobacter) pylori , which, according to the data obtained, causes a violation of the protective mucous barrier, has been assumed to play an etiological role in the development of peptic ulcer disease.

In the pathogenesis of peptic ulcer disease and duodenum, the main importance of masses

is the imbalance between damaged (aggressive) and protective factors. Factors of aggression include the effect of acidic gastric juice (peptic factor), mechanical, thermal, and chemical damage to the gastric mucosa by food and medicinal substances, etc. A protective role is played by the mucous barrier, which prevents the back diffusion of H+ ions and their damaging effect, adequate blood supply and high regenerative potential of the mucous membrane. The hook itself plays the role of neutralization of the acidic secretion by saliva and pancreatic juice.

The role of the peptic factor is confirmed by the fact. that in many patients, in the case of localization of an ulcer in the duodenum and prepyloric part of the stomach, the acidity and digestive capacity of the gastric juice is increased. In experiments on animals, the formation of gastric and duodenal ulcers can be caused by the introduction of substances that increase gastric secretion and increase the acidity of gastric juice (pentagastrin , histamine , reserpine, atophane , etc.), as well as by chronic irritation of the vagus nerve, which stimulates gastric secretion and production of gastrin .

The ulcer is more often localized in those departments (small curvature, portal part) that contain relatively few parietal cells that produce hydrochloric acid and, therefore, are less adapted to the action of acidic gastric juice.

An important protective role is played by the mucus covering the mucous membrane of the stomach. In phylogeny, a weak mucous barrier of the stomach, characteristic of herbivorous mammals, was formed in humans, but in terms of high acid secretion (induced by meat food), humans are close to carnivores. In an experiment on animals, the formation of an ulcer can be caused by injecting salicylates, bile acids, and other substances that break the mucous barrier into the stomach.

Adequate neurotrophic support plays a decisive role in maintaining the high resistance of the gastric mucosa, which, according to modern radioautographic studies, causes rapid (in 4-6 days) renewal of the surface cells of the stomach. The important role of the neurotrophic factor is confirmed by clinical and experimental observations of the development of ulcers in the stomach and intestines in case of damage to the hypothalamus, which contains the higher centers of the autonomic nervous system.

According to the cortico -visceral theory of the pathogenesis of peptic ulcer, formulated by K.M. According to Vykov and L.T. Kurtsyn (1949), the triggering factor in the development of the disease is the disruption of the activity of higher nerve centers as a result of long-term adverse exteroceptive and interoceptive influences, which, in turn, causes disruption of the relationships between the cerebral cortex and subcortical nodes. As a result, the autonomic nervous system disintegrates, the secretion of gastric juice increases, a long-term spasm of blood vessels and the muscular membrane of the stomach occurs, and dystrophic processes develop in the mucous membrane. Research in recent years has supplemented the position of the cortico -visceral theory with the idea that signaling from internal organs first excites the corresponding subcortical structures of the brain and only then, due to the activation of emotional stimuli, spreads to the cortex of the cerebrum.

Important importance in the pathogenesis of peptic ulcer disease is given to humoral disorders - an increase in the concentration of histamine in the blood and in the mucous membrane of the stomach, as well as a decrease in the activity of histamine . It is believed that acting on H2-receptors, histamine increases the production of hydrochloric acid by parietal cells and disrupts microcirculation.

Exacerbation or the appearance of new ulcers in the stomach or duodenum as a result of long-term therapeutic administration of glucocorticoids or corticotropin has been established. In experiments on dogs, it is shown that these hormones increase the secretion

and acidity of gastric juice and reduce the content of mucus, which plays a protective role. They also inhibit protein synthesis and cell regeneration. It is well known about the increase in the production of these hormones during stress, which play the role of an etiological factor in the development of peptic ulcer disease. It is also believed that with peptic ulcer, the production of mineralocorticoids decreases , the consequence of which is an increase in the concentration of potassium ions inside cells and in the blood plasma.

The development of ulcers in the stomach and duodenum in case of a gastrin-producing tumor of the pancreas or stomach (Zollinger - Ellison syndrome), as well as in insuloma and tumors of the parathyroid glands, is described. It was found that prostaglandins EI and E2 inhibit gastric secretion, preventing the development of experimental gastric ulcers in rats. The action of prostaglandins is based on inhibition of adenylate cyclase and the formation of cAMP in the gastric mucosa. Estrogens , secretin and epidermal growth factor (EGF) also inhibit ulcerogenesis . The protective effect of FRE is associated with a trophic (proliferation-stimulating) effect, inhibition of hydrochloric acid secretion, and stimulation of mucus glycosaminoglycan synthesis . In patients with an active ulcer process, the concentration of FRE in saliva is reduced.

Thus, neurogenic (too trophic) and humoral disorders play an important role in the pathogenesis of peptic ulcer disease. The manifestation of such disorders in the form of a stomach or duodenal ulcer is caused by local adverse effects and hereditary constitutional features.

DISORDER OF INTESTINAL DIGESTION

The intestines perform secretory, motor, absorptive, incretory and secretory functions.

Cavity (distant) and membrane (parietal) digestion is carried out in the intestines. Recently, there is also a stage intermediate between cavity and membrane digestion: hydrolysis of food substances in the layer of mucous overlays. Cavity digestion takes place in the lumen of the intestines and consists in the destruction of supramolecular systems and large molecules, membrane digestion - on the membrane of columnar cells of intestinal villi. The final stages of hydrolysis of food substances and the transition to absorption take place here. Disturbance of cavity digestion depends primarily on the disorder of secretion of pancreatic juice and bile. Disruption of enzyme production by columnar cells plays a decisive role in the pathology of membrane digestion.

According to modern concepts, the intestinal crypts (Lieberkün's glands) are involved in the secretion of the liquid component of the intestinal juice and do not secrete enzymes. Enzymes are produced by columnar cells of intestinal villi. Being released on the surface of cells, enzymes take part in membrane digestion (O.M. Ugolev). The penetration of enzymes into the intestinal juice occurs mainly due to the rejection and disintegration of columnar cells (under normal conditions, their renewal cycle is 3 days). Therefore, the mucous membrane of the intestines as a whole can be considered as a single glandular apparatus. The most important part of the small intestine is the duodenum, into which the secretion of the duodenal glands, bile, and pancreatic juice merge.

Experiments by Yu.S. London with complete or partial removal of the duodenum in animals for the first time showed its vital importance for the body. It was found that the extirpation of the duodenum in cats and dogs causes profound disturbances of metabolism, functions of the nervous and endocrine systems, caused mainly by the loss of secretory function of the intestine (O.M. Ugolev). The duodenum produces secretin, cholecystokinin , gastroinhibitory and vasoactive intestinal peptides and other hormones that regulate the activity of the digestive system, as well as described by O.M. Coal arentherin and dinenterin , which affect appetite, general metabolic processes and have a neurotropic, in particular,

potalamotropic effect.

DISORDER OF DIGESTION. ASSOCIATED WITH BILE AND PANCREATIC JUICE DISORDERS

Absence of bile (**acholia**) or its decrease (**hypocholia**) with insufficient entry into the duodenum is the result of a violation of the functions of formation and secretion of bile and is accompanied by a disorder of digestion and absorption of fats, slowing down of intestinal peristalsis and strengthening of the processes of putrefaction and fermentation in them.

Serious indigestion is caused by a change in pancreatic secretion, since the pancreas produces all the main digestive enzymes. The main mass of proteins of pancreatic juice (more than 70%) are proteolytic enzymes: trypsin, chymotrypsin , elastase , carboxypeptidase (A and B) and kallikrein . All these enzymes, as well as phospholipase A, are produced in an inactive state (in the form of zymogens). The remaining enzymes - lipase, α-amylase, RNAase and DNAase - are secreted in an active form.

Violation of the secretion of pancreatic juice is observed in the case of obstruction or compression of the pancreatic duct, with cystic fibrosis (cystic fibrosis of the pancreas), acute and chronic pancreatitis or duodenitis, violation of the neurohumoral mechanisms of pancreatic secretion regulation. The secretory nerve of the pancreas with the vagus nerve, humoral regulation is carried out with the help of secretin, which activates the release of water and hydrocarbons, cholecystokin (pancreozymin), which stimulates the production of enzymes, and pancreatic polypeptide, which inhibits it.

In the absence of pancreatic juice, a large part of fats is not digested and is excreted with feces (steatorrhea). Violation of protein digestion occurs as a result of insufficient production of peptidases by the pancreas, as well as in the event of a violation of their activation. Thus, trypsinogen is activated by enterokinase of intestinal juice and autocatalytically , the rest of proteolytic enzymes and phospholipase A are activated by trypsin. In the case of a decrease in pancreatic secretion, the hydrolysis of nucleic acids of food and, to a lesser extent, the breakdown of starch are disturbed.

PANCREATITIS

Inflammation of the pancreas often has an acute course and can be accompanied by the development of life-threatening pancreatic shock.

In the etiology of pancreatitis, alcohol abuse and overeating, which accompanies excessive consumption of fatty foods, gallstones and polyps of the pancreatic duct, mechanical damage to the pancreas and the sphincter of the hepatopancreatic ampulla during injuries and surgical interventions are of great importance in the etiology of pancreatitis ; infectious factor (viruses of parotitis, hepatitis, Coxsackie , bacterial infection); intoxication, including some drugs (immunosuppressants , thiazides , corticosteroids, etc.).

In the pathogenesis of pancreatitis, an increase in the secretion of pancreatic juice under the influence of etiological factors plays an important role; violation of secretion outflow; increased sand in the duct of the pancreas; getting into the bile duct and duodenal chyme (containing enterokinase); violation of microcirculation, trophic and barrier properties of exocrine pancreatocytes . The main link in the pathogenesis of pancreatitis is the premature activation of enzymes (trypsin, kallikrein , elastase , phospholipase A) directly in the ducts and cells of the gland, which occurs under the action of enterokinase , bile, or autocatalytically , when pancreatic cells are damaged . The consequence of this is the autolysis of the gland tissue, the necrosis of its individual areas and the formation of toxic (lysolecithin) and biologically active substances, including kinins , which have a strong

hypotensive effect. The release of peptidases and other pancreatic enzymes into the blood leads to severe disorders of hemodynamics, breathing, and other vital functions (pancreatic shock). Of great importance in the pathogenesis of these mass disorders is a change in the balance between proteolytic enzymes and their inhibitors. The latter are produced by the pancreas itself and other organs (salivary glands, lungs) and are successfully used to treat patients with pancreatitis.

A certain role in the pathogenesis of pancreatitis, especially chronic, is played by impaired blood circulation in the pancreas (at atherosclerosis, hypertension), as well as immune (autoallergic) factors, as evidenced by the detection of anti-pancreatic antibodies in the blood of some people with pancreatitis.

DISORDER OF MEMBRANE DIGESTION

Membrane (wall) digestion is carried out by enzymes fixed on the surface of a striated border formed by microvilli of columnar cells of intestinal villi. It is characterized by a combination of processes of fermentation and absorption of food substances, a high rate of hydrolysis and sterility due to the small size of the pores between the microvilli (10-20 nm), into which microorganisms cannot penetrate. Enzymes of membrane digestion are synthesized inside columnar cells and translocated to the surface of the cell membrane (oligosaccharidases , oligopeptidases , phosphatases, etc.), as well as partially adsorbed from chyme (pancreatic amylase, lipase, etc.).

Disorders of membrane digestion are caused by the following factors: violation of the structure of villi and the ultrastructure of the surface of columnar cells; change in the enzymatic layer of the intestinal surface and the sorption properties of the cell membrane; disorders of peristalsis, in which the transfer of substrates from the intestinal cavity to its surface is disturbed. Thus, a decrease in the digestive surface due to atrophy and a reduction in the number of villi or microvilli was found in cholera, sprue , ileojejunitis , after intensive antibiotic therapy (neomycin), gastrojejunostomy and gastric resection. An example of a violation of the enzymatic layer of the intestinal surface can be milk intolerance in the case of lactase (P- galactosidase) deficiency or sucrose intolerance in the case of sucrase (α-glucosidase) deficiency. A decrease in the sorption properties of the intestine in relation to pancreatic amylase is observed in children after gastric resection.

In order to detect violations of membrane digestion enzymes in the cell, the technique of aspiration biopsy of the mucous membrane of the small intestine is used followed by histochemical (histoenzymological) research.

Violation of enzyme synthesis by columnar cells can also affect cavity digestion. This especially applies to enterokinase . that activates pancreatic trnpsinogen .

DISORDER OF THE ABSORPTIVE SECRETORY FUNCTIONS OF THE INTESTINES

hydrolyzed food substances . as a rule, before the stage of monomers, it is carried out mainly in the small intestine. In the process of membrane digestion, the hydrolysis of food substances and their transfer through the cell membrane are closely connected. Therefore, all factors that lead to disorders of membrane digestion lead to malabsorption.

The syndrome of malabsorption (impaired intestinal absorption) can be primary (hereditary) or secondary (acquired). **Hereditary** malabsorption syndrome mostly has the character of a selective deficiency of enzymes or a violation of their transport. As a result, the absorption of one or more structurally similar food substances is disrupted. This group of disorders includes intolerance to monosaccharides - glucose, fructose, galactose, disaccharides - lactose, sucrose, isomaltose (deficiency of disaccharidases), celiac disease, or gluten disease (deficiency of peptidases); malabsorption of amino acids (cystonuria ,

triiggofan malabsorption , methionine malabsorption) and vitamins (cyanocobalamin , folic acid).

Acquired malabsorption syndrome is observed after gastrectomy , with diseases of the intestines (enterocolitis, Crohn's disease, etc.), pancreas (pancreatitis, cystic fibrosis), liver, as well as after long-term radiation and drug therapy.

Absorption disorders in the small intestine can be observed in case of weakening of cavity digestion, which prepares food substances for final hydrolysis on the cell membrane, in case of impaired motor function of the intestines and motility of villi, as well as in disorders of blood circulation and lymph circulation. Blood circulation disorders disrupt the removal of absorbed substances, their concentration gradients and energy supply of active transport. Weakening of the active transport of nutrients also occurs under the influence of toxins that block the activity of enzymes, and in the event of a violation of the water-electrolyte balance. A special role belongs to sodium ions and ATP energy in the active transport of glucose, amino acids and other compounds .

Many of the above-mentioned mechanisms are involved in malabsorption during inflammation of the small intestine (enteritis), intestinal obstruction, hypovitaminosis , etc.

And an increase in the permeability of the vessels of the intestinal wall as a result of its inflammation and hyperemia can be accompanied by absorption of substances of an antigenic nature and sensitization of the body.

The absorptive function of the intestines is closely related to their excretory (excretory) function. End products of hemoglobin and cholesterol metabolism, metal salts, lactic acid, purines , some hormones, phenols, salicylates, sulfonamides, dyes, etc. are released through the intestines. In case of kidney failure, the compensatory release of products of nitrogen metabolism (urea, uric acid, etc.) increases.

DISORDER OF THE MOTOR FUNCTION OF THE INTESTINES

Disorder of the motor function of the intestines can be manifested by strengthening or weakening of peristaltic and local (segmenting and pendulum-like) movements. An increase in the motor function of the intestines occurs during inflammatory processes (enteritis, colitis), under the influence of mechanical or chemical irritation from insufficiently digested food, due to the action of bacterial toxins, and during disorders of nervous and humoral regulation. The contraction of the muscular lining of the intestines is enhanced and inhibited by stimulation of the vagus nerve. Serotonin, substance P, gastrin , motilin activate intestinal peristalsis, and vasoactive inertial peptide - inhibit it. An example of a violation of the nervous and humoral regulation of the motor function of the intestines is irritable bowel syndrome, in which negative emotions change the peristalsis and absorption function of the intestines, cause pain and diarrhea, which often turns into constipation. In the mucous membrane of the jejunum, obtained with the help of an aspiration biopsy, an increased content of motilin is found .

Increased peristalsis usually causes accelerated movement of food masses in the intestines, worsens digestion and absorption, leads to the development of diarrhea (diarrhoea). Diarrhea can play a protective role by helping the body rid itself of toxic substances (in case of food poisoning) or excess undigested food. However, prolonged diarrhea, especially in childhood, causes dehydration of the body and loss of electrolytes (Na +, K+), the development of hypovolemia , and in severe cases - cardiovascular collapse.

BOWEL OBSTRUCTION

Acute intestinal obstruction (ileus , from the Greek eiieo - to turn, to close) can be mechanical (when squeezed , twisted, blocked by fecal masses) and dynamic (as a result of

spasm or paralysis of the muscular membrane of the intestines). Intestinal obstruction can be caused by congenital anomalies, helminthiasis, it can develop as a postoperative complication, as well as with malnutrition and consumption of poor-quality food. The initial stages of the pathogenesis of obstruction are largely determined by the causes that caused it. Thus, paralytic obstruction (post-operative or with peritonitis) is often caused by the activation of α- and β-adrenergic receptors, which inhibit the contraction of the muscular lining of the intestines. Spastic obstruction in carcinoid can be associated with increased activity of the intestinal muscle under the influence of an excess of serotonin.

Further development of disorders in the body has a lot in common with obstruction of various etiology. A decisive role in this is played by a disorder of water and electrolyte exchange caused by a violation of secretion (of course, an increase) and reverse absorption of digestive juices. There is vomiting, dehydration (up to 5-7 liters of digestive secretions can be lost per day), loss of sodium , potassium, hydrogen, bicarbonate and chloride ions. Hypovolemia , hypotension , and hemoconcentration develop , as a result of which blood circulation is disturbed and a picture similar to shock appears. Loss of potassium ions causes intestinal atony.

Intestinal obstruction also leads to a violation of the acid-base balance. Often the excretion of hydrocarbons (pancreatic and intestinal juices) exceeds the loss of hydrogen ions (gastric juice), as a result of which non-gaseous acidosis develops. The development of acidosis also contributes to the deterioration of blood supply and impaired kidney function. If the elimination of acidic gastric contents prevails, non-gaseous alkalosis occurs.

A significant role in the pathogenesis of intestinal obstruction is played by disturbances in the digestion of food, the processes of fermentation and decay, the formation of toxic substances and their absorption into the blood. Of great importance is the formation of an increased amount of biologically active substances, especially kinins , which is caused by premature activation of pancreatic enzymes (intestinal contents entering the pancreatic duct from an overfilled intestine).

In the development of the changes described above, an important place is occupied by disorders of neurohumoral regulation" that occur reflexively under the influence of impulses from the receptors of the affected intestine (intestinal distension, pain, etc.). They are especially significant in strangulation obstruction (vertigo, hernia), which is accompanied by compression of the mesentery and impaired blood supply to the affected part of the intestine.

INTESTINAL AUTOINTOXICATION

In human intestines, especially in the large and lower part of the ileum, a diverse microflora is represented mainly by obligately anaerobic sporeless Escherichia coli ; facultative anaerobic Escherichia coli, lactic acid bacteria, streptococci, etc. make up about 10%. The normal microflora of the intestines plays a certain protective role, inhibiting the development of pathogenic microorganisms and contributing to the development of natural immunity, which was also proven by experiments on gnotobionts (germ-free animals). Gut microflora synthesizes vitamins.

At the same time, the contents of the intestines can have a toxic effect due to the presence of decay products (indole, skatole, proteogenic amines, etc.). Normally, these products are formed in small quantities and do not have a noticeable toxic effect on the body, due to the barrier function of the intestinal wall and liver. Intensification of decay processes due to inflammation of the large intestine (colitis), constipation, intestinal obstruction and dysbacteriosis (pathological change in the composition and distribution of microflora in the intestines) is accompanied by a violation of barrier functions and intoxication of the body.

I. I. Mechnikov first suggested using microbial antagonism to combat intestinal autointoxication . Mechnikov's ideas developed in the plan of eliminating intestinal dysbacteriosis, which develops under extreme conditions, when the body is weakened, and sometimes under the influence of antibacterial drugs.

DISORDER OF THE SYNTHESIS OF DIGESTIVE SYSTEM HORMONES

Today, more than 20 substances are known, which are proven or suspected hormones of the digestive system.

Together with the regulation of digestion and absorption processes, the hormones of the digestive system affect blood circulation, metabolism, and the activity of the nervous and endocrine systems. It is believed that their function is to support the trophic processes of the body by influencing digestion and assimilation processes, trophics, appetite, etc.

Hormones of the digestive system are characterized by certain features that determine their role in the pathology of the digestive organs. Such features include the similarity of the chemical structure and biological action of some hormones. Currently, the family of gastrin (various forms of it and cholecystokinin) and secretin (which also includes glucagon , gastroinhibitory and vasoactive intestinal peptides). Thus, similar disorders of digestion and other body functions can occur as a result of excessive or reduced production of various hormones of the digestive system. Hormones are produced by cells of the diffuse neuroendocrine system originating from the neural crest and localized in the mucous membrane of the alimentary canal and digestive glands. This is due to their close connection with the nervous system Gak, peptides of nervous genesis (somatostatin , substance P, endorphins, enkephalins) are found in cells that produce hormones of the digestive system, and vasoactive intestinal peptide, cholecystokinin , gastrin and bombesin were found in the central nervous system and in nerve fibers. It is believed that some hormones are simultaneously neurotransmitters and can reach the target organs both with blood and through nerves. Data were also obtained on the possible role of disruption of the synthesis of digestive hormones in the pathology of the nervous system, in connection with which they speak of the " neurointestinal axis".

There is a close connection between the hormones of the digestive and endocrine systems and the function of the hypothalamic-pituitary system. Somatostatin , which inhibits the production of somatotropin , also suppresses the production of some digestive hormones. The connection with the pancreas is manifested in the clear influence of secretin on the production of insulin and glucagon , which determines the important role of digestive hormones in the pathogenesis of obesity and weight loss. Stimulation of calcitonin production by gastrin, cholecystokinin , and glucagon determines their participation in the pathogenesis of calcium metabolism disorders.

An important feature of the hormones of the digestive system is their entry into the blood and external secretions, which leads to the possibility of spilling onto the cells of the mucous membrane from the lumen of the digestive organs and the close connection of disorders of the internal and external secretion of these organs.

In many respects, the hormones of the salivary glands are similar to the listed hormones, which should also be classified as hormones of the digestive system.

It has been found that the violation of the production of hormones of the digestive system leads to serious disorders of digestion, metabolism and the activity of various organs and systems of the body. The most studied pathological processes associated with the emergence of tumors, the source of which is a hormone product and cells of the digestive organs.

Jaundice

Violation of the bile-forming function of the liver is manifested in an increase or decrease in the secretion of bile, as a rule, with a simultaneous change in its composition.

Etiology. Disorders of bile formation can cause:

1. A change in neurohumoral regulation (for example, an increase in bile secretion due to an increase in the tone of the vagus nerve or an increase in secretion of secretin and gastritis)
2. Alimentary factors (fats, egg yolk, protein starvation), some medicinal plants and drugs (infusion of corn syrup, sorbitol, etc.);

Exogenous and endogenous factors that disrupt energy metabolism in the body (hypoxia, overheating, hypothermia, cyanide poisoning)

4. Damage to the liver and bile ducts (hepatitis, hepatosis , cholecystitis), which causes a disorder of the secretory function of hepatocytes due to their dystrophy and destruction and impaired reabsorption of bile components
5. Pathological processes in the small intestine, the effect of antibiotics, which lead to a decrease in the activity of intestinal microflora, a decrease in the hepatic - intestinal circulation of bile components and, therefore, their concentration in bile
6. Violation of the formation and exchange of bilirubin and bile acids and a change in their content in bile.

Pathogenesis. The mechanisms that cause qualitative and quantitative violations of bile secretion include:

1. Change in the secretory activity of hepatocytes;
2. Violation of reabsorption of bile components in the bile ducts and intestines (hepato -intestinal circulation)
3. Changes in the trans- and intercellular filtration of some substances from the blood into the liver capillaries.

Due to the fact that the secretion of bile and the reabsorption of its components are energy- dependent processes , their disorders are based on energy shifts in tissues (disruption of the activity of enzymes of biological oxidation, the relationship between tissue respiration and oxidative phosphorylation, etc.). The change in filtration is caused by fluctuations in the osmotic gradient and the permeability of the membranes.

Hepato -intestinal circulation of some components of bile is disturbed when the enzymatic activity of intestinal microflora changes, which ensures the biochemical transformation of bile acids and bound bilirubin (formation of their derivatives, deconjugation , destruction) and subsequent reabsorption in the small intestine, return with blood to liver and repeated excretion with bile . The amount of bile acids reabsorbed in the intestine determines the intensity of their biosynthesis in the liver and affects the cholatocholesterol index of bile, is an important indicator of its lithogenic properties, that is, the ability of bile to form stones.

Violation of bile secretion. Etiology. The reasons for impaired flow of bile into the duodenum can be:

1. Mechanical obstruction of the outflow of bile - compression of the bile ducts from the outside (by a tumor of the head of the pancreas, inflamed tissue, a scar) or their blockage (by a stone , helminths, thick bile)

2. Violation of the innervation of the biliary tract - hyper - or hypokinetic dyskinesia (for example, a decrease in bile secretion during a spasm of the sphincter of the gallbladder neck)
3. Change in the humoral regulation of bile secretion (bile secretion increases with hyperproduction of secretin, cholecystokinin , and motili).
Pathophysiological syndromes caused by impaired bile formation and bile secretion.
Disorders of bile formation and bile secretion are manifested in the form of the following syndromes: jaundice, cholemia , acholia, dyscholia .
Jaundice (icterus) is a syndrome that occurs when the content of bilirubin in the blood increases and is characterized by a yellow color of the skin, mucous membrane, and sclera due to the deposition of bile pigments in them.
Classification. Depending on the primary localization of the pathological process and the mechanism of occurrence, the following types of jaundice are distinguished:
Hyperhepatic , caused by increased production of bilirubin, mainly due to increased breakdown of erythrocytes (hemolytic jaundice), and less often - a violation of plasma transport of bilirubin
Hepatic (parenchymal), caused by a violation of capture, conjugation and excretion of bilirubin by hepatocytes as a result of their damage during various pathological processes, as well as hereditary defects in the structure of hepatocytes and enzymes involved in the metabolism and transport of bilirubin in liver cells
Subhepatic (mechanical), which occurs when the outflow of bile through the extrahepatic bile ducts is obstructed.
Etiology. The causes of hemolytic jaundice are the same as those that cause hemolysis of erythrocytes and the development of hemolytic anemia.
Pathogenesis. As a result of increased hemolysis of erythrocytes, such a large amount of indirect bilirubin is formed in stellate reticuloendotheliocytes , macrophages of the spleen, and bone marrow that the hepatocytes of the liver are unable to completely remove it from the blood and bind it to uridine - diphosphoglucuronic acid (relative liver failure). In addition, hemolytic poisons are often hepatotoxic substances, and the metabolism and transport of bilirubin are impaired in affected hepatocytes. The content of indirect bilirubin (indirect hyperbilirubinemia), which is not excreted in the urine because it is associated with plasma albumin, increases in the blood. The level of direct (conjugated) bilirubin may rise , which is caused by its back diffusion into the blood after hepatocytes are no longer capable of excreting direct bilirubin into bile.
With very high indirect hyperbilirubinemia (260-550 μmol / l), when all free bilirubin is included in the bilirubin-protein complex, the so-called nuclear jaundice develops (staining of the nuclei of the brain with bile pigments) with damage to the central nervous system and neurological symptoms (encephalopathy). which is especially typical for hemolytic disease (anemia) of newborns with Shi -antigenic incompatibility of erythrocytes of the mother and the fetus. The toxic effect of free bilirubin on the nervous system can be manifested even with a slight increase in the level of bilirubin in the blood against the background of hypoalbuminemia , an increase in the permeability of nerve cell membranes (with a violation of lipid metabolism, hypoxia).
With hemolytic jaundice, an excess amount of glucuronides of bilirubin, urobili - nogen , stercobilinogen is synthesized in the liver, bile ducts, and intestines, hypercholia is observed (increased formation of bile and its excretion into the

intestines), which causes increased secretion of stercobilin and urobilin with feces and urine. However, there is no cholemic syndrome (bile acids do not enter the blood) and intestinal digestion disorders (as in other types of jaundice). Hemolytic jaundice can be joined by hepatic jaundice, if damage to hepatocytes is observed along with hemolysis, and mechanical jaundice due to obstruction of the bile ducts by bile thrombi and stones made of bilirubin, cholesterol and calcium.

Hepatic jaundice. Etiology. The cause of hepatic jaundice is first of all the influence of factors causing damage to hepatocytes (infection, toxic substances, including medicinal substances, intrahepatic cholestasis), as well as a hereditary defect of the mechanisms of capture, conjugation and removal of bilirubin from hepatocytes.

Pathogenesis. There are several pathogenetic varieties of hepatic jaundice.

1. Jaundice due to violation of bilirubin capture by hepatocytes. The following mechanisms are important in its occurrence: a) a decrease in the content of B proteins in hepatocytes and ensure the transfer of bilirubin through the cytoplasmic membrane from the blood into the cells (during protein starvation) b) competitive inhibition of the uptake of bilirubin (a radiopaque substance, some drugs, for example , anthelmintics) c) a genetically determined violation of the structure of the membrane of the vascular pole of hepatocytes (this leads to a change in the permeability of the membrane), the splitting of the bilirubin-protein complex in it and the transfer of bilirubin into the hepatocyte (in hereditary Gilbert- Meilengracht syndrome), when the conjugation of bilirubin does not occur a second time and there is indirect hyperbilirubinemia , the content of stercobilin in urine and feces decreases due to the violation of the formation of bilirubin glucuronides in hepatocytes and, therefore, their derivatives in the bile ducts and intestines.

2. Jaundice due to violation of the conjugation of bilirubin with uridine - diphosphoglucuronic acid in the membrane of the endoplasmic reticulum. It occurs when the activity of UDP- glucuronyltrans - ferrase , which catalyzes this process, decreases. This mechanism is observed in physiological jaundice of newborns; development of hepatic jaundice in premature babies; as a result of breastfeeding with a high content of pregnanediol (estrogen suppresses the activity of UDP-glucuronyltransferase , competing with bilirubin for the connection with the enzyme), the use of certain drugs (Vikasol) in hypothyroidism , as well as hereditary deficiency of the enzyme (Criglerar Nayar syndrome). Absence or decrease in UDP- glucuronyltransferase activity leads to a violation of the formation of direct bilirubin, the amount of which decreases in bile, which causes a decrease in the excretion of stercobilin with feces and urine. At the same time, the concentration of indirect bilirubin in the blood increases - indirect hyperbilirubinemia . A high level of indirect bilirubin in Crigler-Nayar syndrome causes severe encephalopathy due to the development of nuclear jaundice.

3. Jaundice due to disorders of bilirubin excretion from hepatocytes into the bile ducts. It develops in violation of the permeability of the cytoplasmic membrane in the zone of the biliary pole of hepatocytes, cytolysis of hepatocytes, rupture of bile ducts, thickened bile and blockage of intrahepatic channels (intrahepatic cholestasis).

An isolated violation of the excretion of direct bilirubin is observed in the hereditary syndromes of Dubin-Johnson (with pigmentation of the liver due to the accumulation in it of substrates similar to melanin, as a result of a decrease in the excretory function of hepatocytes) and Rotor (an increase in the content of direct

bilirubin in the blood, bilirubinuria and a simultaneous decrease in the excretion of stercobilin with feces) and urine).
Much more often, the reduced release of bilirubin is combined with a violation of its capture, intracellular transport and conjugation. This is the mechanism of jaundice when liver cells are damaged (hepatocellular jaundice) and intrahepatic cholestasis (cholestatic jaundice), which is observed in hepatitis of viral, parasitic (toxoplasmosis), toxic (including medicinal) origin, hepatosis , cirrhosis of the liver (for example, primary biliary cirrhosis), diffuse infiltration of the liver in leukemia, hemochromatosis .
Damage to liver cells is associated with communication between bile ducts, blood and lymphatic vessels, causing bile to enter the blood and partially into the bile ducts. Edema in the region of the periportal space can also cause reverse absorption of bile from the bile ducts into the blood. Swollen cells squeeze the bile ducts, creating a mechanical obstacle to the outflow of bile. Metabolism and liver functions are disturbed.
With hepatocellular and cholestatic hepatic jaundice, the excretion of direct bilirubin into bile sharply decreases, and it enters the blood from pathologically changed hepatocytes, direct hyperbilirubinemia occurs . At the same time, the level of indirect bilirubin in the blood increases - indirect hyperbilirubinemia , which is associated with a decrease in its capture, intracellular transport and formation of bilirubin glucuronides . The entry of bile acids into the blood determines the development of cholemic syndrome. Reduction or cessation of the flow of bile into the intestines (hypocholia , acholia) leads to a decrease in the formation of bilirubin metabolites and their excretion with feces and urine (traces of sterkobilin), as well as the appearance of symptoms of acholic syndrome. The rich yellow color of urine is explained by the increased content of direct bilirubin (bilirubinuria) and urobilin, which, due to insufficient "destruction in the liver, enters the general bloodstream and is excreted by the kidneys. Damage to liver cells of an inflammatory -dystrophic nature in hepatocellular and cholestatic liver jaundice is accompanied by the development of liver failure with a violation of all its functions.At the same time, blood clotting is often reduced.
Subhepatic jaundice (mechanical, obturation). The etiology is associated with a violation of bile secretion. Pathogenesis. Mechanical obstruction of the outflow of bile is caused by stagnation (beyond its cholestasis) and an increase in bile pressure of more than 2.7 kPa (270 mm H2O), the expansion and rupture of bile capillaries and the entry of bile directly into the blood or through the lymphatic channels. The appearance of bile in the blood leads to direct hyperbilirubinemia , hypercholesterolemia , the development of cholemic syndrome, bilirubinuria (hence the dark yellow color of urine - "the color of beer") and the presence of bile acids in the urine. Failure of bile to enter the intestines due to mechanical blockage in the bile ducts leads to the fact that stercobilin is not formed and, therefore, not excreted with feces (discolored, acholic feces) and urine. Aholic syndrome develops , most pronounced in the case of complete obstruction of the biliary tract. Cholemic syndrome, which is observed in mechanical and hepatic (hepatocellular and cholestatic) jaundice, occurs as a result of the penetration of bile acids into the blood. It is characterized by bradycardia, a decrease in blood pressure, which is explained by the action of bile acids on receptors and the center of the vagus nerve , axillary nodes of the heart and blood vessels. The toxic effect of bile acids on the

central nervous system is manifested by general asthenia, irritability, which is replaced by depression, drowsiness during the day and insomnia at night, headache, increased fatigue. Irritation of the sensitive nerve endings of the skin by bile acids causes itching of the skin. An increase in the content of bile acids in the blood can lead to hemolysis, leukocytolysis , a decrease in blood clotting , an increase in the permeability of membranes and the development of an inflammatory process in the place of their contact with tissues (necrosis of the liver, peritonitis, acute pancreatitis). Aholic syndrome is caused by the absence of bile entering the intestines in case of obstruction of the bile ducts or violation of the excretory function of hepatocytes (mechanical and hepatic jaundice). It is characterized by a disorder of intestinal digestion. Due to the absence of bile acids in the intestines, lipase is not activated, and fats are not emulsified, soluble complexes of bile acids with fatty acids are not formed, therefore 60-70% of fats are not digested, absorbed and excreted from the body together with feces (steatorrhea). Violation of absorption of fat-soluble vitamins (retinol, tocopherol, phylloquinone) leads to vitamin deficiency . Without phylloquinone (vitamin Ki), prothrombin and other blood coagulation factors (V, VII, IX, X) are not formed in the liver, which leads to increased bleeding. The absence of bile acids leads to a violation of the motor function of the intestines - their tone and peristalsis are weakened, constipation appears, which, however, is often replaced by diarrhea due to the increase in putrefactive and fermentation processes in the intestines and a decrease in the bactericidal properties of bile. Feces are discolored because stercobilin is not formed , which also disappears from urine. Dyscholia , in which bile acquires lithogenic properties, causes the formation of gallstones in the gallbladder and bile ducts and the development of gallstone disease.

Etiology. The causes of dyscholia are different: inflammatory processes, dyskinesia of the gallbladder and bile ducts, diseases of the stomach and intestines, consumption of food rich in cholesterol, metabolic disorders (especially cholesterol and bilirubin metabolism). Pathogenesis. One of the main mechanisms of bile acquisition of lithogenic properties is a change in the concentration of bile components. A decrease in cholatocholesterol and lecithinocholesterol indices (the ratio of bile acids and lecithin to bile cholesterol) is observed. This may be due to a decrease in the hepatic -intestinal circulation of bile acids in intestinal pathology and a change in their microflora by suppressing the synthesis of bile acids in the liver (with a decrease in the activity of 7a-hydroxylase) by accelerating absorption by the mucous membrane of the inflamed gallbladder; a decrease in lecithin content and an increase in cholesterol synthesis. In the case of a decrease in the concentration of bile acids and lecithin, which ensure the suspended state of cholesterol, the latter precipitates and gives rise to the formation of cholesterol stones. Infection, stagnation of bile also contribute to the process of stone formation, as they are accompanied by a change in the physicochemical properties of bile - a shift in pH to the acidic side, a decrease in the solubility of salts, their precipitation, coagulation of proteins from cells, disintegration. In addition to cholesterol stones, pigment stones (with hemolysis of erythrocytes), calcareous and mixed stones are formed (for example, cholesterol stones - in a pigment-calcareous manner). The presence of stones leads to impaired bile secretion and the development of mechanical jaundice.

Lecture No. 1 3

Topic: Kidney pathophysiology. Violations of the main functions of the kidneys. Kidney failure. Kidney syndromes and diseases.

Purpose :

- To acquaint applicants with the modern definition of kidney damage and integral mechanisms in case of damage, the applicant must know the general mechanisms of renal dysfunction in case of damage and the mechanisms of the development of pathological conditions, which are the main links of the pathogenesis of this process; must be able to determine the role of many organs in the pathogenesis of renal dysfunction; to distinguish actual pathological manifestations and protective and compensatory reactions in case of kidney damage.
- The material of the lecture is aimed at the formation of logical and professional thinking in the applicants; the role of environmental factors in the development of renal dysfunction is emphasized; assimilation of the leading importance of domestic clinical and research schools in the development of problems of kidney pathophysiology is ensured.

Basic concepts: filtration, reabsorption, excretion, urinary syndrome , OPN, CKD.

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

PATHOLOGICAL PHYSIOLOGY OF THE KIDNEYS

Kidneys play an important role in maintaining homeostasis, which is normally characterized by the constancy of the volume of liquids (isovolemia), their Demotic concentration (isotonicity), ionic composition (isoionicity), and the concentration of hydrogen ions (isohydria). In this regard, certain disorders of the kidneys can cause secondary changes in these indicators. The extreme degree of change of these indicators indicates a violation of the main homeostatic constants, which cannot be compensated, and kidney failure. At the same time, the first changes in the internal environment of the body, for example, the loss of accumulation of electrolytes, water, hydrogen ions, can significantly complicate or disrupt the functions of the kidneys (dyelectrolytic cropathy — hypokalemic , hyponatremic , in a pronounced form with signs of kidney failure).

No less important is the role of the kidneys in removing nitrogenous metabolism products and foreign substances from the body. Accordingly, impaired excretion of substances is one of the main manifestations of kidney failure in case of direct damage to them, as well as due to the action of extrarenal factors. The kidneys are characterized by an intensive blood supply, a high level of energy metabolism, which determines increased sensitivity to blood circulation disorders, the action of various toxic agents and medicinal substances with the development of pathological syndromes, in particular, acute kidney failure.

Kidneys are the most important not only excretory, but also incretory organ, participating in the regulation of vascular tone (renin- angiotensin system, prostaglandins) and erythropoiesis (erythropoietin , erythropoiesis inhibitor). This

is related to the high frequency of development and severity of hypertensive and anemic syndromes in conditions of kidney pathology.
The protein composition of kidney tissue, especially the glomeruli, is characterized by antigenic similarity with the proteins of connective tissue and some microorganisms, in particular streptococci. This determines the relationship of some kidney diseases (acute and chronic diffuse glomerulonephritis) with diffuse connective tissue lesions and streptococcal diseases, and also determines the important role of immune and autoimmune mechanisms in the pathogenesis of acute and chronic glomerulonephritis .
Finally, since urine can be a nutrient medium for microorganisms, and the resistance of the kidneys to pathogenic microorganisms is small, the occurrence of some kidney diseases is often associated with hematogenous or ascending infection (acute and chronic pyelonephritis).

VIOLATION OF BASIC KIDNEY FUNCTIONS

The amount of urine produced by the kidneys per unit time equals the difference between the amount of fluid filtered in the glomerulus and reabsorbed in the tubules. An increase in the daily amount of urine (diuresis, normally 1.5 L) is called polyuria, a decrease (less than 500 ml) is called oliguria , the absence of urine output or a decrease in daily diuresis below 100 ml is called anuria. Changes in diuresis can be based on both isolated and combined disorders of the functions of glomeruli (filtration) and tubules (reabsorption and secretion).

DISORDERS OF THE FUNCTIONS OF NEPRON GLOSSES

Violation of filtering. Changes in the rate of glomerular filtration (normally from 100 to 140, on average 120 ml/min) can be of renal or extrarenal origin. The following filtering reduction mechanisms are possible.
1. Reduction of hydrostatic pressure on the capillary wall. This, in turn, can be caused by a drop in blood pressure below 10.4 kPa (80 mm Hg) as a result of shock and collapse, insufficient blood circulation, and a decrease in the volume of circulating blood; decrease in intensity of cortical renal blood in case of spasm of supplying arterioles or organic changes of renal arteries, intrarenal vessels.
2. An increase in oncotic blood pressure (over 3.25-3.9 k 25-30 mm Hg) as a result of hemoconcentration during dehydration of the body, transfusion of large volumes of protein blood substitutes, as well as in some diseases that occur with hyperproteinemia .
3. Increased pressure in the glomerular capsule (over 2.6 kPa at 20 mm Hg), which is observed with slowed reabsorption of fluid in the proximal part of the tubules of the nephrons, blockage of the lumen of the tubules with cylinders, necrotic masses, in the presence of obstructions to the excretion of urine in the urinary tract (necrosis, clots, stones , tumor)
4. Change in the state of the glomerular filter — a decrease in the number of functioning glomeruli (normally about 2 million), the total filtration surface (normally about 1.5 m2), the number, area and diameter of pores (normally up to 5 nm); an increase in the thickness of the glomerular membrane (normally 80-120 nm), a change in its physical and chemical properties. Such violations are observed primarily in the inflammatory process that directly affects the glomerular membrane (glomerulonephritis , pyelonephritis).

Damage to the renal filter and, as a result, a decrease in glomerular filtration and diuresis can be observed in trophic disorders in the glomerular membrane caused by impaired blood supply to the kidneys, hypoxia, intoxication.
The following factors play a role in increasing filtration.

- An increase in the hydrostatic pressure on the wall of the glomerular capillaries, which is observed in the case of an increase in the volume of intravascular fluid; an increase in the speed of cortical blood flow in connection with a decrease in the tone of the supplying arterioles (in the stage of temperature increase during fever, under conditions of excess sodium in the diet); increasing the tone of peripheral arterioles in connection with neuro-reflex and humoral effects observed in the early stage of hypertensive disease.
- Reduction of blood oncotic pressure due to the redistribution of protein fractions of blood towards the predominance of coarsely dispersed globulins (in case of hepatitis, liver cirrhosis).

Increased permeability of the glomerular membrane. Under normal conditions, proteins filtered in the glomeruli of nephrons are almost completely reabsorbed in the tubules and are not definitively detected in the urine by conventional clinical and laboratory methods.
A cardinal sign of increased permeability of the glomerular membrane is proteinuria - excretion of plasma proteins in the urine in excess of the physiologically acceptable (30-80 mg/ day) amount, as well as the appearance of proteins with a large molecular weight (over 70,000) in the urine.
The mechanism of proteinuria caused by an increase in the permeability of the glomerular filter is associated, on the one hand, with an increase in filtration due to the expansion of pores, and on the other hand, with physicochemical changes in the basal membrane that facilitate diffusion or eliminate the electrical barrier for filtration.
Such changes on the part of the glomerular membrane can be observed with functional disorders of renal hemodynamics caused by increased production of adrenaline and noradrenaline ; in a standing position in children (orthostatic proteinuria); during heavy work (march proteinuria); in case of fluid loss in infants (dehydration proteinuria); upon cooling. Proteinuria can be observed after eating food with a high protein content, especially in children (alimentary proteinuria). In most such cases, functional proteinuria is insignificant (usually 1 g/l) and disappears after the cause is eliminated.
In contrast to functional organic proteinuria (in acute and chronic glomerulonephritis , nephrotic syndrome, and other organic kidney lesions), it is characterized by persistence, often significant excretion of proteins (in the case of nephrotic syndrome, from 10-15 to 120 g/l), the presence of plasma protein fractions in the urine with a large molecular weight (from 70,000 to 820,000).
An intermediate position is occupied by proteinuria in connection with insufficient blood circulation, infectious diseases, some toxic conditions, with thyrotoxicosis, mechanical and parenchymal jaundice, enterocolitis, intestinal obstruction, burns .
In those cases when proteins are not excreted by the kidneys, but are mixed with urine during the inflammatory process in the urinary tract, extrarenal , or false, proteinuria occurs (protein usually does not exceed 1 g/l).
Damage to the glomerular membrane, in particular the capillary wall, can be accompanied by hematuria — the release of erythrocytes into the tubular world and

their appearance in the urine (renal glomerular hematuria), often in the form of shadows due to hemolysis. Such hematuria is one of the leading symptoms of focal nephritis, acute and chronic glomerulonephritis .
Renal hematuria should be distinguished from extrarenal hematuria caused by trauma or inflammation of the urinary tract. A distinctive feature of extrarenal hematuria is the presence of a large number of fresh, unbleached erythrocytes and protein- erythrocyte dissociation (absence of a significant amount of protein in the urine) in the urinary sediment.
Violation of excretion of substances. The most important pathophysiological manifestation of impaired filtration in the glomeruli is a delay in the elimination of products of nitrogen metabolism from the body and an increase in their (residual nitrogen) concentration in the blood - azotemia. The latter is caused mainly by the accumulation in the blood of urea, uric acid, creatinine, to a lesser extent amino acids, as well as toxic products formed during putrefaction in the intestines - indican, phenols, indole, skatole.
The level of azotemia can be different — from 35.7 mmol/l (slightly higher than the upper limit of normal values of residual nitrogen) to 142.8-357 mmol/l. The determining factor is the degree of reduction of glomerular filtration.
As a result of a violation of the excretory function of the glomeruli, the removal of phosphates, sulfates and organic acids is delayed and their concentration in the blood increases - hyperphosphatemia , hypersulfatemia , hyperacidemia . The indicated anions in the extracellular fluid squeeze out hydrocarbons, reduce the alkaline reserve of the blood (to 18-13.5 mmol/l, normally - 25-31 mmol/l), which causes the development of acidosis (renal azotemic acidosis).
Delay in the removal of electrolytes from the body (potassium, sodium, magnesium, and chlorine ions) and their redistribution between the extracellular and intracellular spaces—accumulation of magnesium and potassium ions in the extracellular space, including in the blood (hyperkalemia , hypermagnesemia), and sodium and chlorine in the intracellular space with a decrease in their concentration in the blood plasma (hyponatremia and hypochloremia) is a consequence of a malfunction of the sodium- potassium pump, which occurs as a result of azotemic acidosis. This is accompanied by a violation of volume homeostasis — an increase in the content of water in the intracellular and extracellular space with the subsequent development of edema.

VIOLATION OF CHANNEL FUNCTIONS
Violation of the functions of the tubules, which is accompanied by a violation of the constancy of the internal environment of the body or a selective disorder of the partial functions of the tubules, is called tubular insufficiency (tubular syndrome).
By origin, tubular insufficiency can be hereditary (defect of enzyme systems responsible for the reabsorption or secretion of certain substances) and acquired.
The main causes of acquired tubular insufficiency are overstrain of reabsorption processes due to an excess of reabsorbable substances in primary urine; suppression of enzyme systems by toxic substances, drugs; disorder of hormonal regulation of enzymatic processes and mechanisms of transport of substances in tubules; structural changes in the tubules of nephrons of an inflammatory and dystrophic nature, arising as a result of impaired blood circulation, direct toxic effects, dysmetabolic disorders, and the action of infectious agents.

Violation of reabsorption of sodium ions and water. Increased reabsorption of sodium ions and water can be observed in such cases.

1. In the case of excess production of aldosterone, a hormone of the adrenal cortex, which stimulates the reabsorption of sodium ions in the tubules of the nephrons and the release of potassium ions (in exchange for sodium ions). Increased reabsorption of sodium ions due to the osmotic gradient leads to increased reabsorption of water. As a result, sodium ions and water accumulate in the extracellular and intracellular space, hypokalemia develops . A significant loss of potassium ions causes dystrophic changes in the tubule epithelium and a decrease in its sensitivity to vasopressin, as a result of which water retention may not be the cause of polyuria.
2. With acute kidney failure in the stage of oligoanuria . It is assumed that the passive diffusion of contents into the renal stroma increases sharply in the proximal part of the tubules of the nephrons.
3. In case of increased secretion of H+ ions (increased ammonogenesis , diabetic ketosis).

The main reasons for the decrease in the reabsorption of sodium ions and water are as follows:

1. Disruption of hormonal regulation due to insufficient formation of aldosterone or blocking of its action with the help of diuretics such as spironolactone (artificial analogue of progesterone). At the same time as the reabsorption of sodium ions and water decreases, there is potassium retention in the body, increased excretion of sodium in the urine, and low relative density of urine. As a result of increased diuresis, the development of hypohydration is possible . A decrease in the reabsorption of sodium ions and water can also occur in connection with the congenital insensitivity of nephron tubules to aldosterone. A decrease in water reabsorption occurs with insufficient production of vasopressin, which affects the water permeability of the wall of the distal part of the tubules of the nephrons and collecting renal tubules. This condition is characterized by the release of a large amount of urine of low relative density (diabetes insipidus — diabetes insipidus, or sugar enuresis). There is also a nephrogenic form of diabetes insipidus, which is characterized by reduced sensitivity of the tubular epithelium to vasopressin.
2. Violation of tubular processes acidosis and ammonogenesis , in which the exchange of hydrogen and ammonium ions secreted in the urine for sodium ions is disrupted.
3. The suppressive effect of some metabolic inhibitors, which include: strophanthin O, or ouabain (inhibits the sodium-dependent ATP phase and the active transport of sodium ions from cells into the peritubular intercellular fluid); mercury diuretics (block sulfhydryl groups of enzymes involved in active transport of ions); diamox (by suppressing carbonic anhydrase , disrupts the tubular secretion of hydrogen ions and their replacement by sodium ions).
4. An increase in the content of osmotically active substances (glucose, urea) in the primary urine , which, keeping water in the lumen of the tubules, limit its reabsorption (osmotic diuresis).
5. Renal denervation or administration of adrenoblockers .
6. Inflammatory, dystrophic, atrophic and necrotic changes in the epithelium of tubules and surrounding interstitial tissue. Disturbances in the reabsorption of sodium ions that occur in this case are among the most severe and are manifested in

a decrease or complete loss of the ability of the tubular apparatus to concentrate and dilute urine.

In the first case, hyposthenuria develops (the relative density of urine, depending on the nature of the diet and water regime, approaches 1.010, that is, the relative density of primary urine), in the second case, isosthenuria (the relative density of urine is 1.010 and does not change under the influence of the water-food regime). In the case of normal function of nephron tubules, the relative density of urine varies in a wide range — from 1.002 to 1.035 and more due to the kidney's ability to limit water reabsorption in conditions of water load or, on the contrary, to increase water absorption in conditions of dehydration. Hypo- and isosthenuria are often combined with increased diuresis. Such polyuria contributes to the removal of toxic metabolic products from the body . Its main clinical and pathophysiological manifestations are caused by hypovolemia and hypokalemia . If oliguria develops against the background of hypo- or isosthenuria , then disorders of homeostasis and kidney functions become more severe.

Violation of protein reabsorption. Tubular proteinuria resulting from a violation of protein reabsorption can be of two types: 1) proteinuria associated with a violation of protein reabsorption from the glomerular filtrate; 2) proteinuria caused by protein molecules of destroyed tubule cells.

Tubular proteinuria of the first type is observed in case of poisoning with cadmium, phenacetin, with hypoxia, burns , hypervitaminosis E, kidney transplantation, septicemia, acute kidney failure, Fanconi syndrome , dysmetabolic kidney damage. It is characterized by a low content of albumins and proteins in the urine, mainly of low molecular weight (up to 40,000). Since under normal conditions the tubule epithelium carries out almost complete reabsorption of such proteins, their appearance in urine is considered a sign of a selective (selective) violation of the reabsorption mechanism.

In severe forms of damage to the tubular apparatus, characterized by the presence of gross dystrophic changes in tubular cells, proteins with a large molecular weight (more than 40,000) appear in the urine. Such proteinuria is considered non-selective. In the mechanism of its occurrence, the violation of the ability of the epithelium of the tubules to subject large molecular proteins to enzymatic cleavage is important .

Tubular proteinuria of the second type is characterized by the appearance in the urine of hyaline , epithelial and granular cylinders — peculiar casts of the lumen of nephron tubules, consisting of salted protein or of epithelial cells that have disintegrated.

Violation of glucose reabsorption manifests itself in the form of glycosuria — excretion of glucose in the urine. Glycosuria of extrarenal origin occurs in all cases of hyperglycemia exceeding the renal threshold — 9.4—10 mmol/l (170—180 mg%). Renal glycosuria manifests against the background of normal or even reduced blood glucose levels. It is observed in chronic kidney diseases, lead, mercury, and uranium intoxication, as well as as a hereditary anomaly that is inherited according to the dominant type.

The basis of renal glycosuria is a decrease in activity (acquired glycosuria) or a genetically determined deficiency of enzymes (hexokinase , glucose-6-phosphatase), which ensure tubular reabsorption of glucose.

In the experiment, renal glycosuria is reproduced with the help of phloridzin , an inhibitor phosphorylation in cells of tubules of nephrons. With significant renal

glycosuria, polyuria also occurs, which develops by the mechanism of osmotic diuresis.

Violation of reabsorption of inorganic phosphate and calcium. Hereditary phosphate renal diabetes. It is manifested by a significant increase in the daily excretion of phosphates and, as a result, a decrease in their level in the blood plasma; normal or slightly reduced level of calcium in the blood, increased calciuria ; demineralization of bones; various forms of rickets (in children) and osteomalacia (in adults), resistant to treatment with large doses of ergocalcium Ferol .

Phosphate renal diabetes is characterized by the primary movement under normal conditions of tubule epithelia, which carries out almost complete reabsorption of such proteins, so their appearance in urine is considered a sign of a selective (selective) violation of the reabsorption mechanism.

Hereditary osteodystrophy (pseudohypoparathyroidism) characterizes is characterized by the same changes in the blood as true hypoparathyroidism , hypocalcemia , hyperphosphatemia . However, the use of parathyrin does not eliminate these changes and does not increase the excretion of phosphates with urine due to the resistance of nephron tubules to the action of hormones. It is believed that such resistance is caused by the absence or defect of the corresponding parathyrin receptors in the tubules of the nephrons.

Violation of the reabsorption of amino acids is manifested in aminoaciduria — increased excretion of free amino acids with urine (normally about 1.1 g/ day). A violation of the transport mechanism of one or more amino acids is possible. Aminoaciduria is characterized by renal or extrarenal tubular dysfunction, can be genetically determined (primary) or acquired (secondary).

Renal aminoaciduria develops against the background of normal or reduced content of amino acids in the blood plasma.

The main mechanism of renal aminoaciduria is a hereditary deficiency of enzymes or coenzymes involved in the transport of amino acids. Hereditary tubular syndromes are described, which are characterized by cystinuria , glycinuria , etc. Most of them are accompanied by symptoms of urolithiasis and its complications.

Extrarenal aminoaciduria in some cases is a consequence of hereditary diseases of metabolism and secondary tubule damage in connection with an increase in the content of amino acids in the blood (phenylketonuria , leucinosis , hyperprolineemia , hyperglycinemia , cystinosis , oxalosis , etc.). Violation of reabsorption of amino acids is caused by insufficient enzymes due to overloading of the transport mechanism or the toxic effect on the kidneys of the products of intermediate metabolism.

On the part of the kidneys, at the same time, violations of acidosis , ammonogenesis , exchange of water and electrolytes, as well as other partial functions in the form of proteinuria, glycosuria , and calciuria are observed . Calcification of various kidney structures (nephrocalcinosis), the development of kidney stone disease are not uncommon .

Aminoaciduria can also develop as a result of increased catabolism of proteins, violation of the intermediate exchange of amino acids, its conditions of hypoxia, starvation, deficiency of nicotinic acid, vitamins of group B, with burn disease, myocardial infarction, severe liver damage . Its occurrence is associated with hyperaminoacidemia and the predominance of the transport mechanism of nephron tubules.

Combined tubulopathy . Anatomical proximity of the structures and a certain biochemical commonality (energy dependence) of the mechanisms that ensure the reabsorption of glucose, phosphates, and amino acids cause combined violations of tubular functions and the appearance of the corresponding tubular syndromes. The most famous of them are glycophosphate diabetes, glycosuria with aminoaciduria , combined impairment of reabsorption of amino acids and hydrocarbons, phosphates and some amino acids. Fanconi's syndrome is the most complex in appearance and severe in clinical course . This genetically determined condition is characterized by a simultaneous violation of the reabsorption of glucose, phosphates, hydrocarbons, and amino acids, as well as the development of tubular acidosis (due to the loss of hydrocarbons) and hypokalemia . In some cases, violations of the concentration ability of the kidneys and dehydration of the body due to osmotic diuresis are observed. As a rule, this condition is accompanied by hypophosphatemic rickets with normocalcemia , resistant to treatment with ergocalciferol .
A clinical picture similar to that of Fanconi syndrome was observed in intoxication with salts of heavy metals (mercury, lead, uranium).
Violation of tubular secretion. Violation of the secretion of hydrogen ions. Tubular acidosis. Tubular acidosis is the leading tubular syndrome, the basis of which is a violation of tubular secretion .
The main mechanism of the development of tubular acidosis is the inhibition of ammonio- and acidogenesis and the secretion of H+ ions in the tubules of nephrons, which complicates the interdependent reabsorption of ions and hydrocarbons and the removal of acidic products from the body in the form of titrated acids.
The specific causes and mechanisms of inhibiting the secretion of hydrogen ions in tubular acidosis have not been elucidated. It is believed that it occurs when enzymatic processes of the Krebs cycle are disrupted and tubular insufficiency occurs glutaminase , which is involved in the formation of ammonia from glutamine.
Mostly tubular acidosis as a result
tubulointerstitial syndrome — a separate form of kidney damage, which is characterized by atrophy of the epithelium of the tubules of the nephrons, mainly in their distal part, in combination with pronounced sclerosis of the stroma and a violation of the main tubular functions in response to various toxic, metabolic, physical (ionizing radiation), infectious influences.
Violation of uric acid secretion is accompanied by an increase in the concentration of uric acid and its salts in the blood (hyperuricemia) and the development of the renal form of gout. This condition is hereditary and is transmitted according to the dominant type.
Violation of the secretion of foreign substances: drugs (antibiotics), dyes (phenol rot), iodine-containing contrast agents, etc., is observed in kidney lesions with pronounced tubulointerstitial syndrome. Retention of these substances in the blood, in particular penicillin and its transformation products, can be accompanied by toxic manifestations.

KIDNEY FAILURE

Kidney failure is understood as such a change in kidney functions that leads to a disturbance in the state of the body's internal environment. Acute and chronic kidney failure are distinguished. Each of these forms is divided into tubular and

total, caused by a combination of violations of the functions of glomeruli and tubules.

The main indicator that determines the combined or isolated nature of kidney function disorders is the degree of reduction in the mass of functioning nephrons (MDN). Regardless of the etiology of the disease, in the case of a decrease in MDN more than 2 times, there is a violation of all renal processes (glomerular filtration, proximal reabsorption of glucose, tubular transport of sodium, osmotic concentration and dilution of urine, etc.). With a moderate degree of reduction of MDN, isolated disorders of renal functions are observed.

Acute kidney failure is characterized by an acute disturbance of the stability of the body's internal environment as a result of a significant and sharp decrease in the rate of glomerular filtration (normally 120 ml/min, with oligo- , anuria - 1--10 ml/min).

Etiology. Factors causing the development of acute renal failure (ARF) can be divided into three groups: prerenal , renal , postrenal . Prerenal factors: 1) blood loss, burns, incessant vomiting, profuse diarrhea, a sharp decrease in the volume of intravascular and extracellular fluid when using diuretics ; 2) vascular forms of shock (septic, anaphylactic), collapse, accompanied by an increase in the capacity of the vascular bed and a drop in arterial pressure; 3) acute (myocardial infarction, pulmonary embolism) and chronic heart failure. Renal factors: 1) local blood circulation disorders in the kidneys (thrombosis, renal artery embolism, renal vein thrombosis, ischemia due to prerenal factors, disseminated intravascular blood clotting); 2) acute inflammatory kidney diseases (acute interstitial nephritis, acute glomerulonephritis , vasculitis); 3) nephrotoxic effects (antibiotics, heavy metal salts, organic solvents, radiopaque substances, fungal and snake venoms, anaerobic infection; endogenous intoxication in toxicosis of pregnant women, diabetic coma, sepsis, peritonitis, liver failure); 4) the damaging effect of hemoglobin pigments — in massive intravascular hemolysis, myoglobin — in massive traumatic and non-traumatic rhabdomyolysis). Postrenal factors: 1) obstruction of the ureters (stones , tumor, clots, necrotic masses - from the inside; tumor, enlarged lymph nodes, adhesions - from the outside); 2) delay in the release of urine at the level of exit from the bladder (adenoma, tumor of the prostate gland). Pathogenesis. The main mechanism of the development of ARF is temporary ischemia of the kidneys, mainly of the cortical substance, caused by hypovolemia , spasm of afferent arterioles, disseminated intravascular blood clotting with microthrombosis or direct damage to the renal vessels. The consequence of this is a significant decrease in filtration pressure and glomerular filtration, loss of function of a certain number of nephrons. If the disturbance of renal blood flow is short-lived, then ARF is the reverse state (functional phase of ARF). Prolonged ischemia causes irreversible structural changes in the glomeruli and tubules, which corresponds to the structural phase of ARF. In the case of nephrotoxic factors, together with a violation of the cortical blood flow, direct damage to the structures of the glomeruli and tubules is important. At the same time, the rate of glomerular filtration can also decrease secondarily - in connection with the obstruction of the lumen of the tubules by necrotic masses or in connection with the exit of the filtrate through the wall of the damaged tubules into the interstitial tissue. An increase in pressure in the glomerular capsule or in the interstitial tissue causes a drop in the effective filtration pressure. The possibility of a secondary decrease in the rate of glomerular filtration by the mechanism of glomerular-tubular feedback is assumed. In conditions of damage to

the cells of the proximal part of the tubules, the reabsorption of Na + ions is disturbed. The increased concentration of Na + ions in the distal sections of the tubules is perceived by a dense spot (macula densa), which causes activation of the renin- angiotensin system, spasm of afferent arterioles, reduction of blood flow and glomerular filtration rate. In the case of obstruction of the urinary tract, the reason for the decrease in the rate of glomerular filtration is the early (up to 12 hours) increase in pressure in the capsule of the glomerulus. Subsequently, the intensity of renal blood flow also decreases (under the influence of angiotensin and thromboxane Ah). In the clinical course of ARF, four stages are distinguished: 1) initial, 2) oligo -, anuria, 3) polyuria, 4) recovery. The most significant disorders are observed in the stage of oligo -, anuria, which are caused by a violation of homeostasis. Along with a sharp decrease (or absence) of diuresis, hyperazotemia , violation of water and electrolyte exchange and acid-base balance is observed. The main clinical manifestations of this stage: cerebral edema, interstitial pulmonary edema, severe circulatory disorders (decreased myocardial contractility, heart rhythm disturbances in the form of extrasystole, bradycardia, blockade, arterial hypotension with subsequent transition to hypertension), Kussmaul breathing , severe disorders of the functions of the nervous system (headache, vomiting, areflexia, impaired consciousness, convulsions, coma), progressive anemia, etc. With acute kidney failure, most patients die at the height of this stage. In the case of a more favorable course, and most importantly, with the implementation of effective therapeutic measures, after 5-10 days the disease passes into the stage of restoration of diuresis and polyuria. The increase in glomerular filtration is caused both by the restoration of this process in functioning nephrons (at the beginning of polyuria) and by the subsequent (after several months) increase in MDN.
At the same time, although not always in parallel, other functions of the kidneys (concentration, ammonio- and acidogenesis , etc.) are restored.
Chronic kidney failure. Uremia. Chronic progressive kidney diseases of an inflammatory (chronic glomerulonephritis , chronic pyelonephritis, etc.), vascular (hypertensive disease, renal artery stenosis) and metabolic (diabetic glomerulosclerosis , amyloidosis, gout) nature play a role in the etiology of chronic renal failure (CKD).
Pathogenesis. CKD develops as a result of a simultaneous or sequential decrease in the mass of functioning nephrons and, accordingly, changes in renal functions.
The initial signs of CKD appear when the MDN decreases to 50-30% of the initial number of nephrons, a clinically pronounced picture develops when the MDN decreases to 30-10% and the value of glomerular filtration is below 20%. A further decrease in MDN and glomerular filtration (below 10%) leads to uremia (end-stage renal failure). The main manifestations of CKD are caused primarily by azotemia due to a decrease in the excretion of end products of nitrogenous metabolism. The degree of azotemia reflects the degree of reduction of MDN. More than 200 toxic substances have been identified, the accumulation of which in the blood in CRF determines the intoxication of the body and related anorexia (lack of appetite), dyspeptic phenomena (vomiting, diarrhea), weight loss, general weakness, headache, apathy, taste disturbances, hearing loss, unbearable itching of the skin, polyneuritis, respiratory disorder, progressive anemia, uremic pericarditis , myocarditis, pleurisy, arthritis, convulsions, coma.

In the initial stage of CKD, diuresis is slightly increased (polyuria), which is caused by a sharp limitation of water reabsorption in the distal part of the nephron tubules and collecting tubules, a decrease in the concentrating ability of the kidneys (hypo- , isosthenuria). Oliguria is characteristic only for the terminal stage of CRF. (Disruptions of osmotic and volume homeostasis in CRF are not as constant and do not play a decisive role, as in CRF.) These phenomena, as well as azotemia, are largely determined by a decrease in MDN. In the case of polyuria, hypovolemia , intracellular and extracellular dehydration, hyponatremia , more permanent hypokalemia , hypocalcemia , and hypermagnesemia are also possible . In the oligoanuric stage of CKD, there is hypervolemia , hyperhydration of the extra- and intracellular space, that is, a picture of water intoxication (edema of the brain, lungs), hyponatremia , hyperkalemia , hypocalcemia , which is associated with the development of osteodystrophy and osteomalacia. Violations of the acid-base state in the form of renal (azotemic) acidosis are also of significant importance.

GENERAL CHARACTERISTICS OF THE MAIN KIDNEY SYNDROMES AND DISEASES

Kidney diseases of various nature are observed in 1.5-2% of the population. They make up about 5.5-6% of the total morbidity, are characterized by a protracted course and high mortality.

The basis of the development of kidney diseases are pathological processes of different nature - inflammation, including allergic nature, typical disorders of local blood circulation, metabolic disorders, tumor degeneration, etc.

Different etiological factors and pathological processes often lead to similar morphological, functional and clinical manifestations of renal and extrarenal disorders. This is based on the similarity of direct mechanisms responsible for damage to kidney structures. The development of "major" clinical syndromes (acute and chronic kidney failure, nephrotic syndrome) in various nosological forms is related to this .

At the same time, some etiological factors under different conditions have an effect, which is characterized by a significant polymorphism of changes in the kidneys, probably, and differences in their pathogenesis. An example is diabetic nephropathy.

GLOMERULONEPHRITIS

Glomerulonephritis is most often a bilateral diffuse disease of the kidneys of an inflammatory nature. Various changes in glomeruli of nephrons are caused by a combination of exudative and proliferative processes that develop intracapillary . In the case of a severe course of the disease with the development of necrotic changes, the glomeruli are completely destroyed. The entire mass of the glomeruli of both kidneys is involved in the pathological process. Acute and chronic glomerulonephritis are distinguished .

Acute (diffuse) glomerulonephritis . Experimental models. In 1901, V. K. Lindeman in the laboratory of I. I. Mechnikov observed the main manifestations of nephritis in a rabbit after intravenous administration of nephrotoxic guinea pig serum, previously immunized with rabbit kidney suspension . Using a similar scheme, the Japanese scientist Masugi in 1933 reproduced the clinical picture of nephritis in a rabbit by injecting him with blood serum from ducks immunized with rabbit kidney

tissue . Another version of the jade model Masugi made according to the pattern rat — krill — rat.

In 1909, the Russian surgeon P. O. Herzen, trying to find out the mechanism of occurrence of "trench" nephritis (wartime nephritis), obtained his experimental model from a rabbit by cooling (freezing with chloroethyl) a kidney. At the same time, specific anti-renal antibodies were detected in the blood of experimental animals . A feature of the considered model was damage not only to the cooled, but also to the intact kidney. This model first suggested the possibility of an autoimmune nature of the mentioned disease. Italian scientists Mr. and Mrs. Kswelti (1945) recreated glomerulonephritis in rabbits by injecting into their abdominal cavity a cell suspension of kidney tissue and culture of streptococci. With sufficient reliability, acute glomerulonephritis is reproduced by introducing a foreign protein, serum, to animals. StabIau (1962) reproduced glomerulonephritis in sheep by immunizing them with basal membranes of glomeruli of human kidney nephron with complete adjuvant Freund . Neymann et al . (1965) reproduced experimental nephritis in rats by active immunization with suspension of homologous or autologous kidney with complete adjuvant Freund . Spontaneous occurrence of serological and morphological signs of autoimmune glomerulonephritis and other autoimmune diseases: systemic lupus erythematosus, autoimmune hemolytic anemia. Autologous 7-globulin, which is autoantibodies against renal autoantigens , was detected on the basal membrane of affected glomeruli . The onset of the disease is registered from the age of 3-5 months. Thus, two phases can be distinguished in the pathogenesis of experimental glomerulonephritis : heterologous , caused by the fixation of nephrotoxic antibodies (IgM , IgG) on the basal membrane of glomeruli of the nephron , and autologous , associated with the formation of complement-fixing antibodies to nephrotoxic globulin. Some authors suggest the possibility of a third, autoimmune , phase caused by antibodies against altered vascular glomeruli.

Etiology. Acute glomerulonephritis occurs against the background (or after) of any infection, mainly streptococcal. It is believed that group A hemolytic streptococcus (types 4, 12) is a specific " nephritogenic " strain. Other infections (viral, parasitic) also play a role. The etiological role in the occurrence of glomerulonephritis of cooling, burns, diffuse lesions of connective tissue (systemic lupus erythematosus, rheumatoid arthritis, nodular periarteritis), previous vaccination or treatment with heterologous sera has been clarified . Pathogenesis. Often, the absence of an infectious agent, such as streptococci, in the kidneys during the development of a diffuse inflammatory process in them, the presence of a latent period (1-3 weeks) in the course of the post-infectious glomerulonephritis , its occurrence in diseases of an autoimmune nature, serum sickness, after vaccination, in experimental modeling with the help of immunological intervention, the results of serological and immunofluorescent studies allow us to assume the allergic and autoallergic nature of the disease. Accordingly, two main mechanisms of glomerular damage are distinguished.

1. Damage to the glomerular basement membrane by antibodies to its antigens is nephrotoxic glomerulonephritis (differs in a rapidly progressing course).

The carrier of the antigenic properties of the basement membrane is a glycoprotein .

2. The development of the inflammatory process in the glomeruli as a result of fixation on the basal membrane and intramembrane immune complexes — immune complex glomerulonephritis . An exogenous (infectious or non-infectious origin) or

endogenous (tissue protein, DNA) substance acts as an antigen in this mechanism . Formed antibodies (IgM , IgG) directly interact with antigens in the blood serum, then in the form of immune complexes (antigen - antibody - complement) enter the glomeruli, being deposited on their basal membrane. Implementation of the damaging effect of immune complexes, as well as nephrotoxic antibodies, is carried out by induction of immune inflammation. In most cases (at least 80%), glomerulonephritis is immune-complex , including glomerulonephritis that develops after streptococcal infection, systemic lupus erythematosus, serum sickness, etc. Clinical and pathophysiological manifestations of acute glomerulonephritis reflect changes in renal, mainly glomerular , and extrarenal functions. The classic course of the disease is characterized by a rapid onset, oliguria , proteinuria, azotemia, arterial hypertension, edema (due to sodium retention, hypoproteinemia , hypervolemia , increased permeability of the capillary wall), hematuria, disorders of the central nervous system.

Chronic (diffuse) glomerulonephritis is a long-term progressive disease characterized by diffuse bilateral inflammation of the kidneys, heterogeneous in origin, clinical manifestations, and pathogenesis . Etiology. Chronic glomerulonephritis can occur as a consequence of an acute one, but mostly develops primarily. The following forms of chronic glomerulonephritis are distinguished : 1) infectious (poststreptococcal , with prolonged bacterial endocarditis, malaria, syphilis, tuberculosis and other infections); 2) non-infectious (serum, post-vaccination , medicinal, traumatic, poisoning with various poisons, cooling, renal vein thrombosis, diffuse connective tissue diseases — rheumatoid arthritis, systemic lupus erythematosus, hemorrhagic vasculitis, etc.); 3) separate (posteclamptic , radiation, hereditary, etc.). Pathogenesis. The immunological concept of the development of chronic glomerulonephritis is generally accepted . Together with the two main mechanisms, which are associated with the development of both acute and chronic glomerulonephritis , hypersensitivity of the delayed type is of some importance . According to the clinical features of the functionally compensated phase of chronic glomerulonephritis , four forms of the disease are distinguished.

1. The latent form (65% of all patients with chronic glomerulo -nephritis) is manifested (20-25%) by edema and transient hypertension.
2. The hypertensive form (32% of patients) is characterized by a persistent increase in blood pressure. Edema is noted in 1/3 of patients, hematuria in 2/3, cylinduria and leukocyturia in half , and proteinuria in all patients.
3. Nephrotic form (2-4% of patients), which is characterized by an edematous syndrome (in 2/3 of patients), significant proteinuria and cylindruria (in all patients), characteristic changes in the blood (hypoproteinemia , hyperlipidemia). 4. Mixed, or nephrotic-hypertensive , form (2.4% of patients), which is characterized by edema and hypertension (in all patients), changes in urine, as in the nephrotic form, however, unlike it, the absence of characteristic changes in of blood Violation of the glomerular-tubular balance in the functionally compensated phase of chronic glomerulonephritis is characterized by predominant changes in tubular functions in the form of isolated or combined syndromes (increased reabsorption of sodium ions and water in the proximal part of the tubules, decreased excretion of " osmotically free" water, concentration capacity, secretion of ammonia and hydrogen ions). The mass of functioning nephrons in most patients is preserved or slightly reduced. In the phase of decompensation due to significant sclerotic changes and the resulting

decrease in MDN, chronic glomerulonephritis manifests itself as a syndrome of chronic kidney failure.

NEPHROTIC SYNDROME

Nephrotic syndrome develops in pathological conditions of kidneys and other organs of different etiology, pathogenesis and morphogenesis. It is characterized by a combination of the following signs: edema, significant proteinuria and hypoproteinemia , dysproteinemia , hyperlipidemia . Etiology. Nephrotic syndrome is divided into primary and secondary by origin. Primary nephrotic syndrome is not associated with any previous kidney disease. Its main cause is a genetically determined metabolic defect (lipoid nephrosis) or transplacental transfer of specific isolated urinary syndrome — moderate antirenal antibodies from mother to fetus (congenital familial nephrosis). Secondary nephrotic syndrome is caused by some diseases of the kidneys (glomerulonephritis) or other organs (nephropathy of pregnant women, diabetes, amyloidosis, systemic lupus erythematosus, serum sickness, staphylococcal sepsis, etc.). It is also observed in case of poisoning by salts of heavy metals, widespread burns , radiation damage, in case of rejection of a kidney transplant, use of certain medicines (sulfanilamides, penicillin, corticosteroids), impaired blood supply to the kidneys. For experimental modeling of nephrotic syndrome, salts of heavy metals, puromycin , as well as immune effects (for example, introduction of a suspension from the tissue of a homologous kidney or anti-renal cytotoxic serum) are used. Pathogenesis. In most cases, the development of nephrotic syndrome is caused by immune mechanisms, mainly delayed type hypersensitivity . At the same time, antigens can be of both exogenous origin (bacterial, viral, parasitic, medicinal, food, compounds of heavy metals, etc.) and endogenous (DNA, denatured nucleoproteins, proteins of tumor origin, thyroglobulin). Antibodies formed in response to the arrival of antigens belong mainly to the IgM class . Damage to the glomeruli of the renal corpuscles is associated with deposition of amyloid, glyco- and lipoproteins, fibrinogen on the surface or in the basal membrane of the capillaries , with the activation of humoral and cellular mechanisms of the inflammatory reaction. As a result, the structural integrity of the basement membrane is lost, its composition and physicochemical properties change, and the permeability to blood plasma proteins increases sharply. In cases where the immune nature of the nephrotic syndrome has not been proven, the metabolic and physicochemical mechanism of development is the most likely . At the same time, nephrotic proteinuria is explained by a decrease in the permanent electric charge of the capillary wall, the disappearance of sialoprotein from it , which normally covers the endothelium and its processes with a thin layer. In places where the loss of anions and sialoproteins is maximal, polymorphonuclear leukocytes accumulate , whose lysosomal enzymes have a direct damaging effect on the basal membrane of capillaries. Proteinuria, in turn, causes secondary changes in nephron tubules and kidney stroma, as well as general changes in the body: hypoproteinemia and dysproteinemia (hypoalbuminemia , hyper-a2-globulinemia), edematous syndrome. A certain role in the occurrence of edema, in addition to hypoproteinemia and increased membrane permeability, is played by secondary hyperaldosteronism , which develops as a result of hypovolemia (the cause is the transfer of fluid into the tissues), a decrease in renal blood flow, and an increase in renin production. Hyperlipidemia characteristic of nephrotic syndrome is

characterized by an increase in the level of mainly triglycerides and cholesterol and is pathogenetically associated with disorders of protein metabolism, as well as inhibition of the lipolytic activity of blood plasma.

PYELONEPHRITIS

Pyelonephritis is an infectious -inflammatory disease in which the mucous membrane of the urinary tract and the parenchyma of the kidneys are involved in the process (simultaneously or sequentially) with the predominant damage to the interstitial tissue of the kidneys. Etiology and pathogenesis. The infection enters the kidneys by a hematogenous route or spreads upward through the urinary tract. The causative agents are mostly Escherichia coli, cocci. The occurrence of the disease, the transition of acute pyelonephritis to chronic contributes to various factors that lead to stasis of urine (narrowing, blockage of the ureters, adenoma of the prostate gland), disorders of urinary tract trophism, diseases and conditions that reduce the body's reactivity (diabetes, atherosclerosis, obesity, chronic intoxication etc). Pyelonephritis begins acutely and most often (with the exception of cases of complete recovery) through a latent, symptom-poor phase turns into a chronic form, which ends with shrinkage and kidney failure. Clinically, pyelonephritis is characterized by signs of a severe infectious process: intoxication (especially in the acute period); arterial hypertension (in 25% of cases in the initial stage and in 75% in the development stage); moderately manifested edematous syndrome and anemia; urinary syndrome (polyuria, in the late stage - oliguria , pollakiuria - frequent urination, hyposthenuria , in the final stage - isosthenuria , leukocyturia , hematuria, moderate - 5-10 g/l - proteinuria, cylindruria). Violation of the glomerular-tubular balance is characterized by the predominance of tubular dysfunctions over glomerular dysfunctions , especially in the initial stages of the disease (a kind of functional dissociation). This is evidenced by a decrease in the ability of the kidneys to concentrate urine due to a violation of the process of fluid reabsorption, early and severe tubular acidosis associated with a violation of acid and ammonogenesis , loss of salts, which is based on a sharp decrease in the tubular reabsorption of sodium and calcium ions. As a result, they may develop life-threatening violations of water-mineral metabolism and acid-base balance. The progression of pyelonephritis is accompanied by growths of the described disorders, a decrease in MDN and the transition of tubulointerstitial insufficiency into chronic kidney insufficiency.

DISORDERS OF NON-DIURETIC KIDNEY FUNCTIONS

Arterial hypertension develops as a result of a decrease in renal blood flow, mostly with acute or chronic damage to glomeruli of nephrons (focal and diffuse glomerulonephritis , chronic pyelonephritis,
diabetic glomerulosclerosis), in the case of narrowing or closing of the lumen of the renal arteries or their branches due to developmental abnormalities, atherosclerosis, thrombosis, embolism, compression by a scar or tumor. Anemia. In kidney diseases, which are accompanied by a violation of the excretory function of glomeruli of nephrons (acute and chronic glomerulonephritis , etc.), anemia is often observed. As a rule, it is normocytic , normochromic , hyporegenerative . Pathogenetically, the occurrence of this type of anemia is mainly associated with increased secretion of the inhibitor erythropoiesis and (or) a decrease in erythropoietin production against the background of increased secretion of the inhibitor erythropoiesis . The

consequence of the decrease or failure of the erythropoietic function of the juxtaglomerular apparatus of the kidneys is inhibition of DNA synthesis in erythropoietin-sensitive cells of the bone marrow, violation of their proliferation and differentiation, inhibition of maturation normocytes and release of reticulocytes from the bone marrow into the blood. An additional role in the development of renal anemia is played by inhibition of bone marrow functions by nitrogen-containing substances, hematuria, the presence of hemorrhagic diathesis, as well as iron deficiency caused by these factors and reduced reabsorption, loss of transferrin in the urine with significant proteinuria, and cyanocobalamin deficiency. Disorders of hemocoagulation . The study of blood coagulation and anticoagulation systems in kidney diseases (focal nephritis, diffuse acute and chronic glomerulonephritis) made it possible to establish, on the one hand, blood hypercoagulation and, on the other hand, a decrease in the activity of fibrinolysis. Hypocoagulation of blood with clinical manifestations of hemorrhagic syndrome develops only in the terminal stage of kidney failure . The main reasons for its development are a deficiency of some blood clotting factors (thromboplastin , proconvertin), thrombocytopenia , an increase in the level of blood plasma anticoagulants (heparin), activation of fibrinolysis.

Lecture No. 1 4

Topic: General characteristics of disorders of the endocrine system.
Neuroendocrine disorders. Peripheral disorders.

Purpose :

- To acquaint students with the main mechanisms and causes of disruption of the functional activity of the thyroid and parathyroid glands, the role of intoxication, infection, as well as quantitative changes in the content of individual trace elements in food and the surrounding environment in the etiology of endocrine diseases, the connection between the violation of hormonal regulation of phosphorus -calcium metabolism and pathology of the maxillofacial apparatus.
- The materials of the lecture are advertised for the formation of logical and professional thinking in the students, the doctor's responsibility for the state of the body of a patient with a disease of the endocrine system. The role of environmental factors (radiation pollution) in the development of endocrine pathology is emphasized. Ensuring that the recipients learn the leading value of domestic clinical and research schools in the development of problems of the pathophysiology of the endocrine system.

Basic concepts: Hyperthyroidism, hypothyroidism, Based's disease, Graves' disease , hyperparathyroidism , hypoparathyroidism .

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

In recent years, the frequency and prevalence of diseases of the endocrine system (including the thyroid and parathyroid glands) has increased significantly. This is connected, on the one hand, with the sharp deterioration of the ecological situation in Ukraine, and on the other hand, with the consequences of the accident at the Chernobyl gas station. We are talking about a possible mutation spillover into the gene pool of the entire population of Ukraine, and not just the 30-kilometer zone around Chernobyl, as a number of domestic and foreign scientists claimed a few years ago. Of all the factors that affect the thyroid gland, radioactive iodine-131 is in the first place. It can accumulate in it and cause its disruption.

Hypofunction of the thyroid gland. Hyperthyroidism is reproduced in animals by complete or partial removal of the gland, its destruction with the help of radioactive iodine, which selectively accumulates in the parenchyma of the gland, as well as by the introduction of thermostatic drugs that prevent the synthesis and release of thyroid hormones (metnlthiouracil , mercazolil , betazin , potassium perchlorate). The condition that occurs after thyroidectomy is called thyroid-induced cachexia. The consequences of thyroidectomy are more severe the earlier the operation is performed. In young dogs, rats, rabbits and other animals, sharp growth retardation, sexual underdevelopment, disorder of all types of metabolism, and trophic disorders are observed. As a result of the decrease in the level of oxidative processes, the

basic metabolism decreases by 25-40%, the body temperature decreases, there is a tendency to hyperglycemia and an increase in glucose tolerance. Due to a decrease in the breakdown of cholesterol and its utilization in tissues, the concentration of cholesterol in the blood increases by 2-3 times. Against this background, the effect of atherogenic factors increases. The results of radiological studies indicate inhibition of the incorporation of labeled amino acids into proteins. Retention of water in tissues is observed.

Thyroidectomized animals are sedentary. Disorders of the functions of the higher departments of the central nervous system are manifested in the absence of the formation of conditioned reflexes, the predominance of inhibition processes, and differentiation disorders. Etiological factors in the development of hyperthyroidism in humans are congenital defects in the biosynthesis of thyroid hormones; congenital hypoplasia or aplasia of the thyroid gland; autoimmune and infectious inflammatory processes in the gland; removal of a large amount of glandular epithelium during surgical intervention; damage to the gland by thermostatic drugs, radioactive iodine as a result of exceeding permissible therapeutic doses, as well as under the influence of ionizing radiation, etc. Most often, the cause of hyperthyroidism is insufficient intake of iodine and, possibly, cobalt. In the case of severe thyroid insufficiency (if the disease occurred in early childhood or is congenital), cretinism develops, in adults - myxedema (hyperthyroidism, which is accompanied by mucous swelling of the skin).
Disorders of mental activity, trophic, water-mineral, protein and lipid metabolism, growth and sexual development, thermoregulation and other body functions characteristic of hyperthyroidism reach an extreme degree in cretinism.
A decrease in metabolism, obesity, inactivity , and a decrease in body temperature are typical for myxedema. As a result of increased hydration of the skin and subcutaneous tissue and excessive accumulation of hydrophilic mucous substances in them, the patient's face becomes puffy, with poor facial expressions, thickened nose and lips. Brittle nails, hair loss and other trophic disorders are observed. Sexual function gradually fades, intelligence decreases, memory deteriorates, apathy, drowsiness appear, and in the late period of the disease - dementia.
Enlargement of the thyroid gland with iodine deficiency is known as endemic goiter. This disease is common in the Alps, Carpathians, Himalayas, Andes and other mountainous regions of the globe, where the soil and water contain little iodine. Iodine deficiency causes a decrease in the synthesis of thyroxine and triiodothyronine , as a result of which the production of thyrotropin in the pituitary gland slows down . This, in turn, causes hyperplasia of the thyroid gland, the mass of which sometimes reaches several kilograms.
The etiological role of iodine deficiency in the development of endemic goiter is confirmed by such an experiment. If a dog is fed with water that does not contain iodine during the first year and a half of its life, the mass of the thyroid gland reaches 100 g with a norm of 1 g. The most convincing evidence is the successful prevention of endemic goiter with iodine in the foci of its spread. As the experience of many endocrinologists shows, adding sodium or potassium iodide to drinking water or table salt prevents developmental diseases.
Hyperfunction of the thyroid gland.

An increase in the production of thyroid hormones (hyperthyroidism), a weakening of the strength of the connection between thyroxine and thyroxine-binding globulin, a violation of the metabolism of thyroid hormones, or an increase in the sensitivity of target tissues to their action lead to the development of thyrotoxicosis. Its most common manifestation is diffuse toxic goiter (Based's disease, Graves' disease). Diffuse toxic goiter is characterized by a typical symptom complex: enlargement of the thyroid gland, exophthalmos, increased basal metabolism, increased heat production, tachycardia, tremors, increased mental excitability. No and many other pathological phenomena are caused by the toxic effect of thyroxine and triiodothyronine , which are produced in excess.
The most important etiological factor of thyrotoxicosis in humans is mental trauma. Developmental diseases are promoted by infection, hypothermia, as well as physiological fluctuations in the functional activity of the gland associated with the menstrual cycle.
The notion of hyperproduction of thyrotropin as the leading pathogenetic link of diffuse toxic goiter are currently under review. The main importance is given to the violation of immune processes and the increase in sensitivity of adrenoceptorin lol catecholamines . In the blood of patients there is a long-acting stimulator of the thyroid gland (English Long acting thyroid stimulator - LATS) — an immunoglobulin of the IgO type (see the "Allergy" section). The pathogenic role of prostaglandins of the thyroid gland in disorders of its function has been proven. In the pathogenesis of thyrotoxicosis and its complications, antibodies circulating in the blood against brain tissue proteins, thyroglobulin , thyrotropin receptors , microsomal and other antigens are also important. Exophthalmos is caused by an exophthalmic factor, which has a pituitary origin and is similar in a number of features to thyrotropin . These factors act even after surgical treatment of patients and can cause hypogyrsotoxicity eiscephaloophthalmopathy or hypertension.

The main manifestations of thyrotoxicosis were studied in animals that were administered thyroid hormone preparations or added dried thyroid gland to food. At the same time, n dogs observed loss of body weight, increased activity of the heart and lungs, increased basic metabolism, body temperature, trophic disorders, diarrhea, vomiting. The sensitivity to hypoxia increased, the excitability of all links of the reflex bladder increased, motor activity increased.
The leading mechanism of the toxic effect of an excess of thyroxine and hrnhyudthyronine is an increase in the permeability of the mitochondrial membrane. Violation of the functional integration of mitochondria leads to the disconnection of oxidative phosphorylation , as a result of which energy accumulation in macroergic phosphate bonds of adenosine triphosphoric acid and other compounds decreases . The free energy of oxidation is released in the form of heat.
A negative nitrogen balance in thyrotoxicosis indicates the predominance of protein catabolism. As a result of increased breakdown of glycogen in the liver and muscle tissue, hyperglycemia is observed. The utilization of glucose by tissues is accelerated, the activity of hexokinase is increased.
An excess of thyroid hormones inhibits the transition of carbohydrates into fats, accelerates the breakdown of cholesterol and its utilization in tissues, intensifies the oxidation of fats in the liver, and also increases the sensitivity of adipose tissue to the lipolytic effect of adrenaline. As a result of the listed changes, the mobilization

of fat from the depot increased, which explains the weight loss of patients with thyrotoxicosis, hypocholesterolemia , and hypoxarctonemia .
Thyroid hormones disrupt the metabolism of the heart muscle. Dystrophic changes in the myocardium, violations of cardiac - ventricular conduction, overload of the left ventricle are revealed. The peroxidation of lipids in the membranes of cardiomyocytes , energy and plastic support of cardiac activity is disturbed . A " thyrotoxic " heart responds inadequately to cholinergic and adrenergic influences.
Violation of calcitonin secretion .
Some consequences of thyroidectomy are obviously caused by the loss of secretion of the protein hormone of the thyroid gland - calcitonin . The formation of calcitonin is also disturbed in hypofunction of the thyroid gland caused by gnreostatic substances and hyperthyroidism of endogenous and exogenous origin, sometimes excessive secretion of calcitonin is associated with tumors, then they originate from interfollicular C-cells of the thyroid gland, in which this hormone is synthesized.

Very little is known about the violation of calcitonin secretion in humans. Perhaps the origin of false hypoparathyroidism is associated with its increase — a disease in which, despite the normal functioning of the prostate glands, hypocalcism and other disorders of phosphorus -calcium metabolism are observed.

DISORDERS OF PARATHYROID GLAND FUNCTIONS

Hypofunction of parathyroid glands.
Loss of function of the parathyroid glands leads to the development of parathyroiditis Tegania . In the experiment, it is reproduced by removing glands from dogs and cats. One or two days after the operation, the guards become lethargic, refuse to eat, have thirst, a decrease in body temperature, and shortness of breath. As a result of a decrease in the concentration of calcium in the blood (from 2.25-2.99 to 1-1.25 mmol/l), the ratio of monovalent (La+, K) and divalent (Ca ?+, M£2') ions changes. The consequence of this is a sharp increase in neuromuscular excitability. Muscle stiffness appears, gait is disturbed. At the same time, multiple fibrillar contractions of the muscles of the whole body are observed, which are then joined by clonic attacks convulsions _ Clonic convulsions turn into tonic convulsions, opisthotonus develops (a sharp bending of the body with the head thrown back). Convulsive contractions can also spread to internal organs (pilorospasm , laryngospasm). During one of these attacks, the animal dies.
Against the background of hyiocalcism, the content of inorganic phosphorus in the blood increases. Violations of mineral metabolism are due to inhibition of bone tissue resorption, absorption of calcium in the intestines, and increased phosphate reabsorption in nephron tubules.
In the pathogenesis of paratnreopryvnoy tetany, certain importance is attached to the violation of the detoxification function of the liver. Feeding meat from dogs with parathyroid glands removed increases tetany due to insufficient elimination of products of nitrogenous metabolism, in particular, weakening of the ability of the liver to convert ammonia into urea.
In the case of additional parathyroid glands (in rabbits , rats) or preservation of a piece of the parathyroid gland during surgery, the animals develop chronic hypoparathyroidism , the clinical picture of which is known as parathreonopreptive

cachexia. It is characterized by weight loss, anorexia, increased neuromuscular excitability, dyspepsia and various trophic disorders.
Hypoparathyroidism in humans develops most often as a result of accidental damage or removal of the parathyroid glands during surgery on the thyroid gland. Relative hypofunction of the glands is observed during intensive growth, pregnancy, lactation and other conditions characterized by an increased need for calcium salts in the body.
Pathogenesis and clinical picture of hypoparathyroidism) in humans are close to those observed in the experiment. An increase in neuromuscular excitability is determined by the appearance of muscle contractions during stimulation of the motor nerves with a galvanic current of a certain strength, when the hand is pressed above the elbow or lightly tapped on the skin at the exit of the facial nerve in front of the external auditory canal.
Children in the first or second year of life, usually in combination with rickets, often experience spasmophilia — periodic muscle spasms that occur when the ambient temperature rises and other adverse effects occur. Especially dangerous is laryngospasm , which can cause asphyxiation and death.
Hyperfunction of parathyroid glands. As a result of the increased secretion of parathyroid hormone , the formation and activity of osteoclasts , which carry out bone resorption, increases, and their differentiation into osteoblasts, which take part in new formation of bone tissue, is inhibited. At the same time, the absorption of calcium in the intestines increases, the reabsorption of phosphates in the tubules of the nephrons decreases , the formation of soluble calcium salts in bone tissue and insoluble calcium phosphate in various organs, including the kidneys, increases.
Hyperparathyroidism in experimental animals is reproduced by the introduction of an extract of the parathyroid glands of animals or purified parathyroid under the influence of large doses of the hormone, the level of calcium in the blood reaches 4.99 mmol/l, the concentration of peorianic phosphorus decreases, and the excretion of phosphorus in the urine increases. Although parathyrin somewhat enhances tubular reabsorption of calcium ions, excretion; their excretion in urine increases due to significant hypercalcism . Dehydration of the body, vomiting, fever, acute kidney failure occur, as a result of which the animal dies.
Experimental chronic hyperparathyroidism differs from acute parathyroid intoxication . At the same time, there is progressive thinning of bone tissue (osteoporosis), deposition of calcium salts in the kidneys, lungs, heart, and other internal organs up to their complete calcification. The walls of blood vessels become hard and brittle, blood pressure rises. Animals die, as a rule, from uremia.
The origin of hyperparathyroidism in humans is associated with adenoma or hyperplasia of the parathyroid glands. Generalized fibrous osteodystrophy, which develops at the same time, is characterized by pain in muscles, bones and joints, softening of bones, and sharp deformation of the skeleton. Mineral components are washed out of the bone tissue and deposited in the muscles and internal organs (this phenomenon is figuratively called the movement of the skeleton into soft tissues). Nephrocalcinosis develops , narrowing of the lumen of nephron tubules and their blockage with stones (nephrolithiasis) and, as a result, severe kidney failure. As a result of deposits of calcium salts in the walls of main vessels, hemodynamics and blood supply to tissues are disturbed

Lecture No. 1 5

Topic: Pathophysiology of the nervous system. Causes and features of the development of pathological processes in the nervous system. **Pain.** Classification, etiology and pathogenesis.

Purpose :

- - To acquaint students with the main role of the nervous system in ensuring the unity of all body systems and its adaptation to changing environmental conditions. Emphasize that disorders of the nervous system are the basis for the development of many diseases - level 1
- The applicant must know the causes and mechanism of impaired function of neurons and nerve synapses of the sensitive and motor function of the nervous system - II level

To provide students with knowledge about the leading role of the nervous system in the development of a large number of somatic diseases - level III

- To provide students with the ability to create a model of "camphor epilepsy" in a rat and a frog and, using its example, to get acquainted with various forms of movement disorders in animals - IV level
- Emphasize the need for in-depth knowledge of the causes and mechanisms of development

diseases of the nervous system to understand not only the pathology of this system but also to recognize many somatic diseases .

- Draw attention to the huge contribution of domestic scientists (I.M. Sechenov , I.P. Pavlov, I.M. Bekhterev) in studying the problems of the pathophysiology of the nervous system; The role of H.M. Kryzhanivskyi in creating the concept of generator mechanisms of neuropathological syndromes.

Basic concepts : epilepsy , nerve synapse, neuron, trophic,

Plan and organizational structure of the lecture:

Greetings, verification of those present, announcement of the topic, purpose of the lesson, motivation of higher education seekers to study the topic.

Content of lecture material (lecture text)

Nervous trophism and dystrophic process.

Nervous trophism refers to the effect of nerves on tissue, which causes changes in metabolism in it in accordance with the needs at any given moment. Where does it mean, the pyrotrophic action of the nerves is closely related to their other functions (sensitive, motor, secretory) and together with them ensures the optimal function of each organ . The first evidence that nerves have a trophic function was obtained by the French scientist Majandy in 1824. In experiments with the cutting of the trigeminal nerve in rabbits , he discovered the formation of ulcers in the area of sensitive denervation (eye, lip). Subsequently, the neurogenic ulcer model was repeatedly reproduced, and not only in the area where the branches of the trigeminal nerve are located . Trophic disorders occur in any organ if its innervation is disturbed by interference with nerves (afferent, efferent, vegetative) or nerve centers. Medical practice also shows that nerve damage (trauma, inflammation) threatens the appearance of an ulcer or other disorders (edema, erosion, necrosis) in the corresponding area. Biochemical, structural and functional changes in

denervated tissues Experience shows that pathogenic effects on the peripheral nerve always lead to changes in metabolism (carbohydrates, lipids, proteins, nucleic acids, etc.) in the corresponding organ. These changes are not only quantitative, but also qualitative in nature. For example, myosin in denervated muscle loses its ATPase properties , and glycogen in its structure becomes simpler, more elementary. A reorganization of enzymatic processes is observed, for example, the isoenzyme spectrum of lactate dehydrogenase (LDH) changes towards the predominance of DISH, that is, those molecular forms of enzymes that are adapted to anaerobic conditions. The activity of succinate dehydrogenase enzyme decreases . The general tendency of metabolism is that it acquires an embryonic character, that is, glycolytic processes begin to dominate in it over oxidative ones. The power of the Krebs cycle weakens, the output of macroenergetics decreases , and the energy potential decreases. Significant morphological changes occur in the tissues of innervation disorders. If we are talking about the cornea, skin, or mucous membrane, then all stages of inflammation develop here in sequence. Elimination of infection, trauma factor , drying does not prevent the process, although it slows down its development. As a result, an ulcer is formed, which has no tendency to heal. The study of the fine structure showed changes in the organoids, in particular, a decrease in the number of mitochondria, lightening of their matrix. Obviously, this is related to a violation of oxidative phosphorylation and Ca2+ -accumulating ability of mitochondria, and at the same time, the energy capabilities of the cell. Mitotic activity decreases in denervated tissues. With regard to functional disorders, the consequences of denervation depend on the type of tissue. For example, when denervated, skeletal muscle loses its main function — the ability to contract. The heart muscle contracts even when all extracardiac nerves are cut. The salivary gland will secrete saliva, but the nature of the saliva will not depend on the type of food. Denervated tissue reacts to many humoral factors differently than normal tissue. It is primarily about mediators of the nervous system. V. Cannon (1937) established that skeletal muscles are deprived of sympathetic nerves in one case, and cholinergic nerves in the other , and respond to adrenaline and acetylcholine more strongly than normal. This is how the law of denervation — increased sensitivity of denervated structures — was discovered . In particular, this is due to the fact that cholinergic receptors , which are normally concentrated only in the area of neuromuscular synapses, appear on the entire surface of the myocyte membrane after denervation . The unusualness of the response of denervated structures lies not only in its strengthening, but also in its distortion, when, for example, instead of relaxing the muscles of the vessels, they contract, which can seriously affect the condition of the vessels, blood circulation, etc. An important question is whether there are special trophic nerves. At one time , Majhandi assumed that, along with sensitive, motor and secretory nerves, there are also special trophic ones that regulate tissue nutrition. Later I.P. In an experiment on animals, Pavlov (1883) found such a branch among the nerves that go to the heart, which, without spilling into the bloodstream, increased the force of heart contractions. He called this nerve enhancing and recognized it as purely trophic. Full and harmonious innervation of the organ , according to I.P. Pavlov, three types of nerves can be provided: functional, vasomotor (regulating the supply of nutrients) and trophic (determining the final disposal of these substances).

In principle, A.A. was of the same opinion. Orbely , who together with O.G. Ginetsynskyi in 1924, showed that an isolated (without blood circulation) muscle of a frog, very tired by long-term irritation of the motor nerve , begins to contract again if stimulation of the sympathetic nerve is started . The trophic function of the organ to action and its adaptation to future work, which is carried out thanks to motor nerve. The above, however, does not give grounds for asserting that trophic (sympathetic) nerves do not have any other effect on the tissue or that the motor nerve does not affect metabolism. O.D. Sneranskyi (1935) believed that all nerves affect metabolism, there are no non-trophic nerves, "a nerve is functional only because it is trophic."

Mechanisms of trophic influence of nerves.

There are two points of view regarding the influence of nerves. Some researchers believe that trophic is not an independent function of the nervous system. A nerve impulse, activating an organ (for example, a muscle), simultaneously changes the metabolism in the cell according to the scheme: mediator — activation of secondary mediators — activation of enzymes. Others believe that trophic cannot be reduced to the impulse (mediator) action of the nerve . New research has shown that the nerve has another function — a non-impulse one, which is ensured by the flow of axoplasm both in one and the other direction. This is necessary for feeding axons. However, it turned out that the substances that move along the processes of neurons penetrate through synapses and end up in cells that are interned (muscle, etc.). In addition, these substances specifically act on the effector cell. The experiment showed that when the nerve that feeds the red muscle grows into the white muscle after surgery, a radical change in metabolism takes place in it, it switches from the glycolytic to the oxidative metabolic pathway. So, the trophic action of the nervous system consists of two moments, impulse and non-impulse. The latter is related to "trophic substances, the nature of which is being clarified.

Pathogenesis of neurogenic dystrophy. Analyzing the process, one should be guided by the fact that the trophic function is carried out according to the principle of a reflex and it is necessary to evaluate the value of each link of the reflex, i.e. "contribution" to the mechanism of development of the dystrophic process. The sensitive nerve obviously plays a special role in this, since, firstly, the transmission of information to the nerve center from the denervation zone is interrupted ; secondly, a damaged sensitive nerve is a source of pathological information, including pain information; thirdly, it emanates centrifugal effects on the fabric. It has been proven, in particular, that the substance P enters the tissue from the axoplasm through sensitive nerves, which disrupts metabolism and microcirculation. The importance of nerve centers in the development of dystrophy is evidenced by the experiments of O.D. Speransky with selective damage to the centers of the hypothalamus. The consequence of this is the formation of trophic ulcers in various organs on the periphery.

The role of efferent nerves in dystrophy is that their function (motor, secretory) is distorted . Impulse activity, synthesis of mediators (adrenaline, serotonin, acetylcholine, etc.) stop, axonal transport of "trophic substances" is disrupted. The gene is involved in the process, the synthesis of enzymes is disrupted, the output of macroergs decreases , the exchange takes on a more primitive character. Transport functions of cell membranes change. An organ with disturbed innervation can become a source of autoantigens . The process is complicated by the fact that purely

neurotrophic changes are joined by a violation of blood and lymph circulation (microcirculation) with the development of hypoxia.
So, neurogenic dystrophy is a complex, multifactorial process that begins with the fact that the nervous system ceases to control the metabolism in tissues, and as a result, complex disorders of metabolism, structure and function occur (see fig .).

Pain

The concept of pain contains, firstly, a peculiar feeling and, secondly, a reaction to this feeling, which is characterized by a certain emotional coloring, reflex changes in the functions of internal organs, motor unconditional reflexes and volitional efforts aimed at getting rid of the pain factor . This reaction is similar in nature to the feeling of suffering that a person experiences when there is a threat to his life, and it is extremely individual, as it depends on factors, among which the degree of tissue damage, the upbringing of a person, and the emotional state at the time of inflicting a painful stimulus are of primary importance .
Observations show that under the action of the harmful factor, a person can experience two types of pain. If, for example, a hot match is touched to the skin, then at first there is a sensation similar to a prick - the "first" pain. This pain is clearly localized and quickly subsides. After some time, a diffuse burning "second" pain appears, which can last quite a long time. This dual nature of pain is observed when the skin and mucous membrane of some organs are damaged.
A significant place in the symptoms of various diseases is occupied by visceral pain, that is, pain that occurs in internal organs. This pain is difficult to localize, has a diffuse character, is accompanied by severe experiences, depression, and a change in the activity of the autonomic nervous system. Visceral pain is similar to "second" pain.
Studies conducted mainly on people during surgical interventions have shown that not all anatomical formations can be a source of pain . The organs of the abdominal cavity are not sensitive to the usual surgical effects (cutting, suturing), only the mesentery and parietal peritoneum are painful . However, all internal organs with non-striated muscle tissue react painfully to stretching, spasm or convulsive contraction.
Arteries are very sensitive to pain. Narrowing of the arteries or widening of the arteries causes sharp pain.
Lung tissue and visceral pleura are sensitive to painful irritation, the parietal pleura is very sensitive to it.
The results of operations on humans and animals showed that the heart muscle is apparently not sensitive to mechanical trauma (injection, cut). If one of the coronary arteries is pulled in the animal, a painful reaction occurs. The pericardium is very sensitive to pain. The question of which nerve formations are involved in the perception and conduct of pain is a difficult one. Regarding this, there are two fundamentally opposite points of view. According to one of them, pain is a specific, special feeling, and there are no special nervous devices that perceive exclusively painful stimuli. Any sensation based on irritation of certain receptors (temperature, tactile, etc.) can turn into pain if the strength of the irritation is large enough and exceeds a known limit, 3 from this point of view pain differs from others only quantitatively — pressure, heat can become painful if the stimulus that caused it has excessive force (intensity theory).

According to the second point of view, which is now widely accepted, there are special pain receptors, special afferent pathways that transmit pain stimuli, and special structures in the brain that process pain information (specificity theory). Studies show that the receptors of the skin and visible mucous membrane, which respond to painful stimuli, belong to two types of sensitive fibers of the anterolateral system — thin myelinated A5 with a conduction velocity of excitation of 5-50 m/s and unmyelinated C~ fibers with a conduction velocity of 0.6 -2 m/s. activity in A§ fibers causes a feeling of sharp pricking pain, while excitation of POVIAb- non-like C-fibers causes a burning sensation.

The question of the mechanism of activation of pain receptors has not been finally clarified. Some facts indicate that severe deformation of free nerve endings (for example, when tissue is compressed or stretched), a significant increase in skin temperature (above 45 °C) or a decrease in it (below 15 °C) are adequate stimuli for pain receptors, affect the permeability of their membrane for ions and cause the occurrence of an action potential. But it is also assumed that free nerve endings belonging to A8 or C fibers contain one or more specific substances that are released under the influence of damaging factors, interact with receptors on the outer surface of the membrane of nerve endings and cause their excitation. In the future, these substances are destroyed by the corresponding enzymes that surround the nerve endings, and the feeling of pain disappears. It is believed that receptor activators can be histamine , serotonin, bradykinin , somatostatin , substance P, prostaglandins , potassium ions. At the same time, not all of these substances are found in nerve endings, but many of them are formed in tissues when cells are damaged and inflammation develops, and with their accumulation is associated with the occurrence of pain.

thermal , etc.), which is the physiological basis for the state of increased pain sensitivity (hyperalgesia, hyperpathy) , which accompanies some pathological processes. An increase in the concentration of hydrogen ions can also be important in the mechanisms of activation of pain receptors.

The question of which central mechanisms are involved in the formation of pain sensation and complex reactions of the body in response to pain stimulation is being studied. Of the modern theories of pain, the gate theory proposed by Me is the most developed and recognized back and Wall . One of the main tenets of this theory is that the transmission of nerve impulses from afferent fibers to neurons of the spinal cord, which transmit signals to the brain, is regulated by the spinal gate mechanism — the system of neurons of the gelatinous substance (substantia gelatiriosa — SG). It is assumed that pain occurs with a high frequency of discharges in T neurons. Both thick myelin fibers (M), belonging to the lemniscal system, and thin fibers (V) and in the lateral ral end on the body of these neurons systems . In addition, the collaterals of those and other fibers form siantic connections with the neurons of the gelatinous substance. Outgrowths of SG neurons, in their turn , form axo-axonal sinans at the ends of M and V fibers and are able to inhibit the transmission of impulses from fibers of both types to T neurons, the SG neurons themselves, are excited by impulses, sud come from the fibers of the lemniscal system, and are inhibited when thin fibers are activated.

Therefore, 8C neurons can play the role of a gate that opens or closes the path of impulses that excite T neurons. The gate mechanism limits the transmission of nerve impulses to T neurons when afferent fibers of the lemniscal system are excited

("closes the gate") and, conversely, facilitates the passage of impulses to of T neurons in cases where the afferent flow through thin fibers ("opens the gate") increases.
When the excitation of T neurons exceeds a critical level, their impulse leads to the excitation of the action system. This system includes nervous structures that provide forms of behavior under the influence of a painful stimulus, motor, vegetative and endocrine reactions and where the sensations characteristic of pain are formed.
The function of the sninal portal mechanism is controlled by various parts of the brain, whose effects are transmitted to the neurons of the spinal cord by the fibers of the descending pathways. The central pain control system is activated by impulses that come from the thick fibers of the lemniscal system.
The gateway theory works to explain the nature of phantom pain and causalgia. Phantom pain occurs in people after limb amputation. For a long time, the patient can feel the amputated limb and strong, sometimes unbearable pain in it. During amputation, large nerve trunks with many thick nerve fibers are usually cut, and the channels for receiving impulses from the periphery are interrupted. Neurons in the spinal cord become less controlled and can fire in response to various unexpected stimuli.
Causalgia is a severe, unbearable pain that occurs when a somatic nerve is damaged . Any, even the slightest impact on the affected limb causes a sharp increase in pain. Causalgia occurs more often as a result of incomplete nerve transection , when most of the thick myelin fibers are damaged. At the same time, the flow of impulses to the neurons of the posterior horns of the spinal cord increases — "the gates open." Therefore, both with phantom pain and with causalgia, a generator of pathologically increased excitation appears in the spinal cord or higher, the formation of which causes the disinhibition of a group of neurons due to a violation of the external apparatus, which is localized in the damaged structure. The proposed theory makes it possible to explain the fact, known for a long time in medical practice, that pain noticeably subsides when relaxing procedures are applied - heating, rubbing, massage, mustard seeds, etc. All these methods increase the impulse in thick myelin fibers, and this reduces the excitation of neurons of the anterolateral system.
refipecpury) pain may occur . For example, heart disease causes pain in the area of the left scapula and in the innervation zone of the ulnar nerve of the left hand; in case of distension of the gall bladder, the pain is localized between the shoulder blades; when the stone passes through the ureters, the pain from the lower back spreads to the inguinal area. Reflex pain is explained by the fact that damage to internal organs causes excitation, which reaches the same neurons of the posterior horns of the spinal cord through the afferent fibers of the autonomic nerves, where the afferent fibers from the skin end. Increased afferent impulse from internal organs lowers the excitation threshold so that irritation of the corresponding skin area is perceived as pain.
Experimental and clinical observations indicate that many departments of the central nervous system are involved in the formation of pain sensation and the body's reaction to pain.
Through the spinal cord, motor and sympathetic reflexes are implemented, the primary processing of painful SIIs is also there. £1/11 in"
Various functions for processing pain information are performed by the reticular formation (reticular formation). These functions include: preparation and

transmission of pain information to the higher somatic and autonomic parts of the brain (thalamus, hypothalamus, limbic system, cortex), facilitation of protective segmental reflexes of the spinal cord and brain stem, involvement in the reflex response to pain stimuli of the autonomic nervous system, respiratory and vascular centers.

The thalamus provides an analysis of the quality of the pain sensation (intensity, localization, etc.). Pain information activates neurogenic and neurohumoral structures of the hypothalamus. This is accompanied by the development of vegetative, endocrine and emotional reactions aimed at restructuring all body systems under the influence of painful stimuli. Pain irritation, which comes from the outer coverings, as well as from some organs in case of injury, is accompanied by general excitement and activation of the sympathetic nervous system — increased breathing, increased blood pressure, tachycardia, hyperglycemia, etc. The pituitary - adrenal system is activated , all components of stress are observed. Excessive pain exposure can lead to the development of shock. Pain that comes from internal organs and is similar in nature to "second" pain, is most often accompanied by general depression and vagal effects — a decrease in blood pressure, hypoglycemia, etc.

The iambic system plays an important role in creating the emotional coloring of human behavior in response to painful stimulation.

The cerebellum, pyramidal and extrapyramidal systems carry out programming of motor components of behavior reactions when a pain sensation occurs.

Conscious components of behavior during pain are implemented with the participation of the cerebral cortex. Experimental studies of recent years have proven that the nervous system contains not only pain centers, the excitation of which leads to the formation of pain, but also structures, the activation of which can change the pain reaction in animals up to its complete disappearance. It has been shown, for example, that electrical stimulation or chemical irritation of some areas of the central gray matter, the pons, the amygdala, the gynocampus, the cerebellar nuclei , and the reticular formation of the midbrain causes clear analgesia. It is also known that human emotions affect the nature of the reaction-response to a painful stimulus: fear increases the reaction to pain, lowers the threshold of pain sensitivity, aggressiveness and rage, on the contrary, sharply reduce the reaction. These and other observations formed the idea that the body has antinociceptive systems that can suppress the perception of pain . There is evidence that there are four such systems in the brain: neuronal opiate , hormonal ossifying, neuronal non-opiate , hormonal non-opiate .

The neural opiate system is localized in the midbrain, medulla oblongata, and spinal cord. It has been proven that the central cerebellum , the nuclei of the suture, and the reticular formation contain the bodies and endings of epkephalinergic neurons. Some of these neurons send their axons to spinal cord neurons. In the posterior horns of the spinal cord, enkephalinergic neurons were also found , which distribute their endings on nerve conductors of sensitivity. The released enkephalin inhibits pain transmission through synapses to spinal cord neurons. The experiment showed that this system is activated when the animal is painfully stimulated.

The function of the hormonal system is to conduct afferent impulses from the spinal cord to the hypothalamus and. the pituitary gland with the release of corticoliberin , corticotropin and (3-linotron and well, from which a strong analgesic polypeptide

(3-endorphin) is formed. The latter, having entered the bloodstream, inhibits the activity of pain-sensing neurons in the spinal cord and thalamus and excites neurons of the central substance, which inhibit pain.

The neural neopathic system includes serotopinergic , adrenergic and dopaminergic neurons that form nuclei in the brainstem. Stimulation of the most important monoaminergic structures of the brain stem (nuclei of the suture, cyanosis, substantia nigra, central gray matter) causes pronounced analgesia . All these formations have a direct output to the pain-sensing neurons of the spinal cord, and under the influence of serotonin and norepinephrine released by them , there is a significant suppression of reflex pain reactions.

The hormonal neopiate system is associated mainly with the function of the hypothalamus and pituitary gland and their hormone vasopressin. It is known that dogs with genetically impaired synthesis of vasopressin have increased sensitivity to painful stimuli. Administration of vasopressin into the blood or into the ventricles of the brain causes deep and long-lasting analgesia in animals . In addition, vasopressinergic neurons of the hypothalamus send their axons to various structures of the brain and spinal cord, including neurons of the gelatinous substance, and can influence the function of the spinal portal mechanism and other analgesic systems. There is evidence that, in addition to vasopressin, other hormones of the hypothalamus - pituitary system, such as somatostatin and some other peptides, also have an antinociceptive effect .

All analgesic systems interact with each other, they provide an opportunity to manage pain reactions and reduce their negative consequences. When the function of these systems is disturbed, various pain syndromes may occur. Therefore, one of the effective ways of combating pain is the development of ways to activate antinocicepta - including systems (acupuncture, suggestions, use of pharmacological agents, etc.).

The meaning of pain for the body. Pain occurs so often in a person's everyday life that it has entered his consciousness as an inevitable companion of existence. However, it should be remembered that this phenomenon is not physiological, but pathological. Pain is caused by various factors, the only common property of which is the ability to damage body tissues. Like any pathological process, pain is contradictory in its content and has, on the one hand, protective and adaptive, and on the other - pathological significance. Depending on the nature of the pain, the cause, time and place of its occurrence, either protective or own pathological elements may prevail. The value of the protective properties of pain is enormous for human and animal life: it is a danger signal, informs about the development of a pathological process. However, having played the role of an informant, pain later itself becomes a component of the pathological process, sometimes very formidable

List of recommended literature (main, additional, electronic information resources):

Recommended Books

Main:

1. 1. Ataman O.V. Pathophysiology: General pathology. – Vinnytsia: New book, 2018. – Volume 1. - 584 p.
2. 2. Ataman O.V. Pathophysiology: Pathophysiology of organs and systems. – Vinnytsia: Nova kniga, 2019. – Vol. 2. – 448 p.
3. 3. Yu.V. Byts, G.M. Butenko, A.I. Gozhenko . Pathophysiology: a textbook / edited by M.N. Zaika , Yu.V. Bytsia, M.V. Crystal . - Kyiv: VSV "Medicine", 2015. - 752 p.
4. 4. Zaiko M.N., Byts Y.V., Kryshtal M.V. etc. Pathophysiology: a textbook / edited by M.N. Zaika , Yu.V. Bytsia, M.V. Crystal . – Kyiv: Medicine, 2017. - 736 c.

Additional:

1. 1. Ataman O.V. Pathological physiology in questions and answers. – Vinnytsia: New book - 2007. – 512 p.
2. 2. Zaiko M.N., Byts Yu.V., Butenko H.M. and others. Pathophysiology: a textbook / edited by M.N. Zaika , Yu.V. Bytsa . - K.: Medicine, 2008. - 704 p.
3. 3. Krishtal NV, Mikhnev VA, Zayko NN et al . Pathophysiology : Textbook / Ed . by NV Krishtal , VA Mikhnev : Textbook , the 3rd Edition . — Kyiv : AUS Medicine Publishing , 2019. - 656 p.
4. 4. Robbins and Cotran pathological basis of disease / Ed . by Vinay Kumar , Abul K. Abbas , Jon C. Aster : Textbook , the 9 th Edition . – Philadelphia : Elsevier Saunders , 2015. - 1392 p. 952

13. Electronic information resources

1. https://info.odmu.edu.ua/chair/pat_physiology/ - information resource of the department of general and clinical pathological physiology
2. http://moz.gov.ua – Ministry of Health of Ukraine
3. www.who.int - World Health Organization
4. www.dec.gov.ua/mtd/home/ - State Expert Center of the Ministry of Health of Ukraine
5. http://bma.org.uk - British Medical Association