GENERAL PATHOPHYSIOLOGY

Methodical instructions for the practical class for foreign students (majoring in «Medicine» and «Dentistry»)

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

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ЗАГАЛЬНА ПАТОФІЗІОЛОГІЯ

Методичні вказівки
для практичних занять з підготовки іноземних студентів
(спеціальність «Медицина» та «Стоматологія»)

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Topic 1. Subject and tasks of pathophysiology. Methods of pathophysiological research. Main stages of development of pathophysiology

Justification of the topic: Pathological physiology is a science that studies functional changes in the body of sick people and animals. It studies the most general patterns of occurrence, development, course and outcomes of diseases. The main method of learning of pathophysiology is an experiment, with the help of which certain types of disease models, disorders of organs and systems that are reproduced on animals in order to study the main patterns of the development of human diseases. Thus, the experiment is the main method of pathophysiological research.

Purpose of the lesson:

General – to clarify the subject and tasks of pathophysiology. Pathophysiological research methods. The main stages of the development of pathophysiology. Determination of the essence of the pathophysiological experiment, its features and significance in medicine

Specifically:

Know:

1. The essence of acute and chronic experiments, to evaluate their positive and negative sides, the advantages of the experiment compared to the observation method.

Be able to:

1. To characterize the main stages of the pathophysiological experiment and the main criteria for the selection of animals in the experiment.

Practical experience:

1. Draw up a plan for conducting a pathophysiological experiment and choose a species of laboratory animal in accordance with its purpose.
2. To evaluate the relationship between the experiment and the method of clinical observation.

Graphological structure of the topic "The subject and the tasks of pathophysiology. The metods of pathophysiology" is attached.

Material and methodical support from topics " The subject and the tasks of pathophysiology. The metods of pathophysiology".

1. Lectures;
2. Methodological developments for teachers;
3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational tasks to determine the final level of knowledge;
6. A set of KROK-1 tasks;
7. Tables and slides;
8. Mice, rats, rabbits, frogs;
9. Video films;
10. Syringes and other surgical instruments, straps, pneumograph, walls for fixing animals, tweezers, scissors.

Oriented map of students work on the topic "The subject and the tasks of pathophysiology. The metods of pathophysiology"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of knowledge	10	Control of theoretical training of students using a programmed method using constructive answers to cards questions	Tests, control, cards, questions	Study room
2.	Analysis of theoretical material	35	Analysis of the theoretical material is carried out on the basis of control questions of the topic and "Krok-1" tasks	Control questions of the topic, "KROK-1 tasks"	
3.	Conducting an experiment	30	Introduction and preparation for setting up the experiment Setting up the experiment	Mice, rats, rabbits, frogs, walls for fixing animals, tweezers, scissors, syringes and other surgical instruments, straps, pneumograph	
4.	The final stage of determining the level of knowledge and skills. Summing up	15	Determination of the initial level of formation of knowledge and skills	Solving situational tasks.	

Pathophysiology – is a science that studies the most general patterns of occurrence, development and consequences of pathological processes, typical pathological processes and diseases.

As a science, pathophysiology is a fundamental medical science; as an educational discipline – a theoretical medical subject, the main theoretical medical discipline.

Thus, pathological physiology is a science that studies functional changes in a diseased organism and establishes general laws of the origin, occurrence, development, course and consequences of diseases.

The main goal of pathophysiology – establishment of the most general regularities, laws according to which the pathological process, the disease, develops.

Tasks of pathophysiology:

1. Study of the most general questions of pathology, related to the treatment of philosophical aspects of medicine.

• Pathophysiology investigates and provides insight into the problems of general pathology, which are of fundamental methodological importance for understanding the origin and essence of the disease in general and its individual forms, the formation of a medical worldview or thinking. These include:

- general doctrine of disease,
- common etiology,
- general pathogenesis,
- the role of external and internal environmental factors in pathology.

In other words, pathophysiology reveals the laws of the disease. Thus, philosophy, dialectical materialism is the methodological (worldview) basis

of pathophysiology. In addition, using dialectical materialism as a method, pathophysiology plays a leading role among the medical sciences in combating unscientific and reactionary concepts in medicine. It is not by chance that pathophysiology is called the "philosophy of medicine."

2. Study of the general laws of the origin, occurrence, development, course and consequences of diseases.

3. Development of principles of therapy based on the study of general patterns in various diseases and pathological processes.

4. ***Experimental development of therapy methods***, which are then tested in the clinic, and in the case of successful testing – implemented in clinical practice.

5. On the basis of theoretical and practical knowledge, promoting the formation of the doctor's thinking, that is, not only transferring modern knowledge to the student, but also teaching him to use this knowledge in order to be able to build a chain of researched phenomena into a logical system.

Components of pathophysiology

General pathology

General pathology is divided into general nosology and typical pathological processes. The content of general nosology corresponds exactly to the first task of pathophysiology. Typical pathological processes are those that are characterized by the preservation of the main general laws of their development regardless of the form of expression and are the basis of many diseases. These include inflammation, fever, tumor growth, allergy, hypoxia, etc.

Pathophysiology of organs and systems

Pathological physiology of organs and systems – in the same way as general pathology, studies the general laws of various diseases and pathological processes, but at the level of individual organs and systems, in other words – the general laws of the functioning of organs and systems in various pathologies. General patterns of disorders of the functions of the blood, circulation, breathing, digestion, urination, endocrine and nervous systems are studied here.

Clinical pathophysiology

Clinical pathophysiology is still more developed as a science. Naturally, the main tasks of clinical pathophysiology are the same as experimental ones. The differences are in the object of research and, accordingly, in the methods. While the object of experimental pathophysiology is a laboratory animal, the object of clinical pathophysiology is a sick person. Accordingly, the main method of traditional pathophysiology is an experiment, and the methods of clinical pathophysiology are harmless functional research methods used in clinical practice for the purpose of diagnosis.

Clinical pathophysiology has the advantage over the experimental one that it receives data about the nature of the disease that can be directly used in the clinic. On the other hand, the possibility of research on humans is limited by ethical considerations. A specific task of clinical pathophysiology is to test the methods developed in the experiment in the clinic. A fundamental feature of clinical pathophysiology stems from the modulation of human biological (physiological) processes by social factors.

***Tasks of clinical pathophysiology*:**

- studying and analysis of the nature and severity of body function disorders at each stage of the disease;
- identification of the relationship between pathogenesis and its clinical manifestations (symptoms);
- detection of the degree of influence of the pathological process on the affected organ or tissue, as well as on other organs and systems of the patient's body;
- the ability to use methods of functional laboratory diagnostics to assess the degree of organ and system dysfunction and to choose a pathogenetically based treatment;
- evaluate specific and non-specific reactivity of the patient, taking in account its features when choosing optimal methods of treatment for a specific patient;
- development of new recommendations for prevention, diagnosis and treatment of diseases.

Methods of pathophysiology

Pathophysiologists use the method of modeling pathological processes and diseases in several of its varieties.

The following basic techniques are used to study pathological processes:

Exclusion method -removal or damage of this or that organ (surgical, pharmacological, physical, mechanical). This technique has been used for a long time. With its help, for example, it was possible to establish that diabetes and its development are related to the dysfunction of the islet apparatus of the pancreas. Removal of one of the paired organs (kidney) made it possible to study the compensatory and plastic capabilities of the remaining organ.

Irritation method – through various influences, the functions of various organs are changed. Irritation of the vagus nerve causes bradycardia, sympathetic nerves - narrowing of arteries.

The "turn on" method – introduction of various substances into the body (hormones, enzymes, extracts from tissues, biologically active substances, etc.). Then, the obtained results are compared with the results of similar effects in certain human diseases. For example, when allergic mediators are introduced, symptoms of anaphylactic shock are observed.

The method of comparative pathology – study in a comparative "evolutionary" aspect of various pathological processes (fever, inflammation, hypoxia). Correct scientific analysis of human reactions to pathogenic influence requires more complete knowledge of the ways and forms of their formation in the evolution of the animal world. I. I. Mechnikov brilliantly revealed the significance of this method when studying inflammation and immunity to infectious processes.

Method of isolated bodies – establishing the nature and degree of damage to a specific organ (heart, lungs) and its contribution to the development of insufficient blood circulation, breathing, etc.

The method of parabiontosis – onnection of two animals (parabiontosis) through the circulatory and lymphatic systems to study mutual humoral influences (hormones and other metabolites).

Tissue culture method – isolation and cultivation of cellular elements of various organs and tissues – widely used to study the role of individual cellular elements in the regulation of hematopoiesis and immunopoiesis, mechanisms of cell malignancy, establishment of mechanisms of cyto-damaging action of various pharmacological drugs.

It is important to emphasize that pathophysiology does not have specific methods of experimental research and uses methodological techniques developed in various branches of natural science.

CONCEPTS AND CATEGORIES OF NOSOLOGY

General nosology (disease doctrine)(from the Greek nosos - disease), refers to the oldest problems of medicine. The main categories of nosology are "health", "diseases", "predisease", "norm", "etiology", "pathogenesis" and others. Health and illness, as a rule, alternate and pass from one to the other, often without discernible boundaries. It is important for a doctor to know the general criteria that would enable him to unmistakably distinguish health from illness.

"Health" and "disease" are the most general categories of medicine.

"Health is a state of complete physical, spiritual and social well-being, and not only the absence of disease and physical defects" (WHO)

Basic health criteria*:*

- balance of the organism and the external environment;
- compliance of structure and function;
- the body's ability to maintain homeostasis;
- full participation in work.

To make a diagnosis of "health", the doctor examines the patient and compares the obtained data with the norm.

Norm - ***is characteristic of the majority of the population, the most typical value of a particular parameter***. From a clinical point of view,**norm** is a relative category that characterizes the optimal parameter for a person in each specific situation.

Pathophysiologists consider the relativity of the norm in three aspects:

1. *Historical relativity of the norm and some specific norms*. Different generations have their own parameters of functioning – constants that are characteristic for most of the people may be different in the process of evolutionary development (acceleration of physical development parameters of children in the 60s-80s of the 20th century).

2. *Geographical relativity of the norm*. External conditions in different regions of our planet are not the same, which implies different parameters of the body's functioning. (hemoglobin content in the blood of highlanders is higher than that of the inhabitants of the plains).

3. *Situational relativity of the norm.* The most important type of norm from the point of view of pathophysiology and clinical medicine (with a large amount of physical activity in a healthy person, indicators of vital activity of the organism go beyond the statistical norm – pregnancy, stress, fatigue, etc.).

All this emphasizes that the medical norm is not a typical, static standard, but a changing optimum. The concept of norm includes the body's ability to adapt to certain influences of the external environment and actively change it for its own purposes, which is due to various adaptive mechanisms.

In most observations, the disease does not appear immediately, but develops through the pre-disease stage (pre-morbid stage).

Pre-disease – ***this is a decrease in the functional activity of some adaptive mechanisms of the body, which leads to a decrease in its adaptation capabilities.***

Pre-disease should be considered as an opportunity for the body to get sick as a result of insufficient adaptation mechanisms under the influence of adverse factors. At some points, the pre-disease does not turn into the disease (this mainly applies to its first period). For one reason or another (reduction in intensity or complete cessation of action of the pathogenic agent, mobilization of additional mechanisms of adaptation, etc.), this state of the body can once again return to the category of "health".

Disease – is a special type of suffering caused by damage to the body and its individual systems by various damaging factors, characterized by a violation of the system of regulation and adaptation and a decrease in working capacity (WHO). Disease is the unity and struggle of two opposite processes: injury and protection.

The main criteria of the disease:

- occurrence of disease under the influence of pathogenic agents;
- insufficient adaptation to the external environment;
- impairment of vital activity and working capacity.

Despite the variety of diseases, some common pathological changes are found in them, namely: disorders of general and regional blood circulation, inflammation, fever, hypoxia, necrosis, dystrophy, etc.

Depending on their properties and features, they are distinguished: pathological process, pathological condition, pathological reaction.

Pathological process- this is a dynamic state of pathological and protective-adaptive reactions that occur in the body under the influence of a pathogenic factor at different levels, which manifests itself in morphological, metabolic and functional disorders.

Pathological processes are: violation of peripheral blood circulation and microcirculation, inflammation, hypoxia, necrosis, starvation, wound and infectious process, tumors, etc. Some pathological processes are called typical.

A typical pathological process – is a pathological process that occurs in the form of permanent connections or combinations that were formed and consolidated in the process of evolution, which develops according to general laws, regardless of its causes, localization and type of living organism.

Pathological condition – this is a permanent deviation of the structure and function of an organ or tissue from the norm, has a biologically negative meaning for the body and almost without changes over time.

We can distinguish:

1) *pathological conditions caused by genetic defects and malformations of intrauterine development* – polydactylia (the presence of additional fingers on the upper or lower extremities), congenital clubfoot, "rabbit lip", etc.;

2) *pathological conditions caused by previously experienced pathological processes and disease* – blindness after an eye injury, the development of a hump after tuberculosis of the spine, false joints, loss of a limb or part of it, etc.

Pathological reaction – this is most often and short-term, unusual reaction of the body to some influence, which is not accompanied by a long-term and pronounced violation of the regulation of body functions and work capacity.

In clinical practice, a number of other terms are used that reflect certain features of the development and course of various human diseases.

"Remission" (from the Latin Remissio – reduction, weakening)

Remission is a temporary improvement in the patient's condition, characterized by slowing down or stopping the progression of the disease. Clinically, this is expressed by the weakening, partial reversal of development or complete disappearance of the manifestations of the disease.

Remission can be a characteristic period of the development of a number of diseases, but it is not recovery, it is again replaced by exacerbation (relapse). In those cases when it is impossible to establish the cause, they say about the spontaneous remission that has arisen.

"Relapse" (from the Latin Recidivus - restored)

Relapse – recovery or strengthening of manifestations of the disease after its temporary disappearance, weakening or termination (remission).

For some diseases, both infectious and non-infectious, the probability of recurrence is high. These include: malaria, brucellosis, gout, rheumatism, schizophrenia, etc. The development of a relapse may repeat the primary clinic of the disease, but it is not rare and differs in its manifestations.

Relapse and remission are two interrelated concepts. A recurrent course of the disease always implies the presence of remission. Therefore, the causes and mechanism of relapses are often the same as in remissions, but with a minor sign (discontinuation or inadequate treatment, reduced immunity, nutritional disorders, etc.). Some diseases have their own, specific mechanisms of recurrence (malignant tumors).

"Latent course" (from Latin Lateens – hidden, invisible)

The term itself speaks for itself – it is an outwardly invisible course of the disease (malaria, toxoplasmosis, rheumatism).

"Complication" (from the Latin Complication – complication)

A complication is any pathological pro-process attached to the main disease, which is not mandatory for this disease, but owes its occurrence to it. The occurrence of complications is explained either by the unity of the causative agent, or by disorders developed during the main disease.

Complications to one degree or another contribute to the deterioration of the main disease. They often acquire the main importance in the life of the patient and can even be the cause of his death (ulcer disease – ulcer breakthrough – peritonitis – death of the patient).

"Aggravation" (from the Latin Exacerbation – exacerbation, flash)

Exacerbation is a stage of the course of the disease, characterized by an increase in existing symptoms or the appearance of new ones. For example, the course of hypertensive disease can be exacerbated by the development of a hypertensive crisis.

Forms and periods (stages) of disease development

There is a great variety of forms of occurrence, course and results of the disease. Each disease has its own specific features, which depend on the pathogenicity and duration of action of the causative factor, the state of the body at the time of its action.

Typical forms of disease development reflecting the duration of disease development:

- Lightning form – from several minutes to several hours.
- The most acute form – up to 4 days.
- Acute form – about 5–14 days.
- Subacute form – 15–40 days.
- Chronic form – lasts for months and years.

According to the nature of the clinical manifestations of the disease, the following are distinguished:

- The typical course – the clinic of the disease is characteristic of this nosological form.
- Atypical course – the clinic of the disease is characterized by a deviation from the usual course and can manifest itself in the form of:
  - erased form (silent or weakly expressed symptom complex);
  - abortive form (shortened course, rapid disappearance of symptoms and sudden recovery);
  - lightning form (rapid development and severe course of the disease).

Periods (stages) of disease development

Latent stage (incubation, in relation to infectious pathology). It lasts from the moment of exposure to the causative factor until the appearance of the first symptoms of the disease. All the events that take place during this period mainly correspond to "pre-disease".

Prodromal stage lasts from the first signs of the disease to the full manifestation of its symptoms. For example, bark is characterized by the appearance of Bielsky-Koplyk-Filatov spots, for mountain sickness – unmotivated euphoria, motor excitability.

The stage of severe manifestations (or the onset of the disease) is characterized by the full development of the clinical picture.

The outcome of the disease. The following types of disease outcomes are observed:

- ✓ recovery (complete and incomplete);

- ✓ transition to a chronic form;
- ✓ death.

Recovery

Full recovery- this is a state characterized by the complete restoration of the body's normal vital activity after an illness. Its adaptive capabilities are completely restored, that is, the state of the organism corresponds to the definition of the concept of "health".

It must be remembered that complete recovery does not always mean a return to the original state (the formation of connective tissue instead of muscle after an abscess, appendectomy).

Incomplete recovery characterized by insufficient restoration of body functions, preservation of individual functional abnormalities after the end of the disease. The adaptation capabilities of these people are reduced.

The transition to a chronic form

The transition to a chronic form is characterized by a slow course of the disease with long periods of remission (months, years). The chronicity of the disease is determined by the characteristics of the pathogenic agent (virulence of the pathogen, duration of its presence, etc.) and the reactivity of the organism.

Death – this is not an instantaneous action: the cessation of vital functions occurs gradually, several stages of the body's death are distinguished: preagony, agony, clinical and biological death. Preagony, agony, and clinical death are classified as terminal states.

Terminal states – these are reverse fading of the body's functions that preceded biological death, when its adaptation mechanisms are unable to eliminate the effects of the etiological factor. Without assistance to a person during this period, biological death usually occurs.

Preagony (preagonal state) is characterized by the development of inhibition in the central nervous system, sometimes with disturbance of the bulbar centers. Consciousness is usually preserved, but may be dimmed, confused, eye reflexes are adequate. Blood pressure is reduced, shortness of breath is noted. The duration of agony is different (hours, days) and it ends very often with the onset of a terminal pause (stopping breathing and a acute slowing of cardiac activity, up to its temporary cessation). The duration of the pause is from a few seconds to 3–4 minutes.

Agony (from the Greek agonia – struggle) – develops after the terminal pause. Its main symptom is the appearance after a pause (apnea) of the first independent breath. Breathing gradually intensifies, and then weakens and stops ("gasping" – breathing from English Gasping – convulsive, spasmodic). Similar changes occur with hemodynamic indicators. Consciousness is absent, eye reflexes and reaction to external stimuli are not determined. Periods of appearance and cessation of activity of vital functions (breathing, cardiovascular system) can be repeated several times, but the average duration of agony is 2–4 minutes, although in some cases it can be observed for several hours. At the last stages of its development, blood pressure drops to almost zero, heart sounds are almost undetectable, pupil dilation and corneal clouding are noted.

Clinical death develops after cessation of breathing and cardiac activity. Continues until the onset of irreversible processes in the higher departments of the central nervous system. At this stage, the organism as a whole has not yet died – energy substrates are stored in its tissues and cells, and metabolic processes continue. With certain medical effects (resuscitation measures), it is possible to restore vital activity, up to the initial level.

The average duration of clinical death is 3–4 minutes, a maximum of 5–6 minutes. Its duration is determined for each person individually and depends on the duration of dying, age, environmental temperature, etc.

Biological death – this is no longer a terminal state, it is characterized by irreversible changes in the body and is the final stage of its individual existence. The conclusion about the onset of biological death is made on the basis of the presence of its absolute signs – corpse cooling, the appearance of corpse spots on the skin, corpse tanning, etc..

Setting up the experiment.
Discussion of results and formulation of conclusions

Acquaintance with the components of the experiment and the requirements for them.

1. Selection of research objects. Laboratory animals. Humane treatment of animals is a necessary condition of a scientific experiment.

2. Preparation of animals for the experiment. Methods of anesthetizing animals (general and local anesthesia). Methods of complete anesthetization of the animal (decerebration of the frog, anesthesia, curettage). Methods of partial restriction of animal movement (tying, machines for fixing animals). Accustoming animals to the laboratory environment.

3. Methods of taking blood from different animals (taking blood from surface vessels, from internal vessels in angiostomized animals). Injections under the skin, in the abdominal cavity, in the vein of a dog, rabbit, guinea pig, frog.

4. Methods of graphic registration of heart contractions, blood pressure, breathing. Bloodless methods of determining blood pressure.

5. Experimental surgical operations. Asepsis and antiseptics. Surgical instruments.

6. Peculiarities of experimental study of pathological processes at different levels of integration. Methods of molecular pathology.

7. Critical transfer of experimental data to the clinic.

Discussion of the results of the experiment:

In the introduction, it should be noted, that the experiment is the most important means of studying the laws of nature, which is of great importance for pathophysiology. The experiment makes it possible to reproduce many pathological processes under the simplest conditions. It makes it possible to dissect complex pathological phenomena into simpler ones. In the experiment, it is possible to study the general patterns and dynamics of the development of pathological processes. The significance of the experiment lies in the fact that it makes it possible to carry out such effects that are unacceptable on a

person, to trace the dynamics of the pathological process in its entirety, to investigate its pathogenesis more deeply, and to carry out tests of new means.

Formulation of conclusions on the experiment:

1. The data obtained in the experiment cannot be mechanically transferred to a person:

- human physiological processes are strongly modulated by social factors;
- physiological processes in humans and different animal species may differ. However, "only after passing through the fire of experiment, medicine will become what it should be, that is, conscious, and therefore, always and fully expediently acting" (I.P. Pavlov).

2. An acute experiment, an experiment on isolated organs – a method of analytical research. The Pavlovian stage in the development of the experimental method is characterized by the introduction of a chronic experiment as a method necessary "to obtain impeccable analytical data in many cases, and synthetically almost always" (I. P. Pavlov).

Tasks for independent work on the topic "The subject and the tasks of pathophysiology. The metods of pathophysiology".

It is necessary to draw up a plan for conducting a pathophysiological experiment and choose a species of laboratory animal in accordance with its purpose. To evaluate the relationship between the experiment and the method of clinical observation. Analysis of mistakes with an explanation of the correct answers.

List of questions and works to be studied:

1. Definition of the term "pathophysiology".
2. Subject, methods and tasks of pathophysiology.
3. The main features and tasks of the pathophysiological experiment.
4. Correlation of the clinical observation method with the pathophysiological experiment.
5. Is an experiment on a person possible?
6. The main stages of the pathophysiological experiment.
7. Name the famous founders of the scientific experiment method.
8. Specify the role of various scientists in the development of experimental pathology and medicine.

List of practical skills that must be mastered:

1. Methods of conducting a pathophysiological experiment;
2. Choose a type of laboratory animal according to its purpose;
3. Evaluate the correlation of the experiment with the method of clinical observation.

Situational tasks KROK-1 to determine the final level of knowledge

1. Patient D., 34 years old, complains of pain in the gums of the upper jaw, bleeding, slight loosening of the teeth. Diagnosed with periodontitis. What is a typical pathological process in this case?

A. Caries. B. Bleeding. C. Inflammation. D. Pain. E. Redness.

2. A 10-year-old child suffered several attacks of rheumatism. During his clinical examination, it was established that there were inflammatory phenomena in the joints and there were signs of mitral valve insufficiency. Which of the pathological phenomena in this patient can be attributed to the concept of "disease"?

A. Rheumatism. *D. Inflammation of the joints.*
B. Mitral valve defect. *E. Insufficiency of the mitral valve.*

3. A patient was admitted to the infectious department with complaints of pain in the right hypochondrium, general weakness, yellowness of the skin, discolored stool. Objectively: the sclera and skin are jaundiced, t – 39 °C, the liver is enlarged, the stool is acholic. A diagnosis of "hepatitis" was made. What stage of the disease does this correspond to?

A. The outcome of the disease. *D. Prodromal period.*
B. Incubation period. *E. The outbreak of the disease.*
C. Latent period.

4. Patient Zh., 5 years old, became acutely ill with an increase in body temperature to 38.2 °C, complained of pain when swallowing. In the oral cavity, a bright red rash, redness of the gums in the area of the front teeth of the upper jaw. What nosological concept characterizes the patient's condition?

A. Relapse of the disease. *D. Pathological reaction.*
B. Exacerbation of the disease. *E. Period of remission.*
C. The outbreak of the disease.

5. The patient was admitted to the hospital for the first time with a diagnosis of gastric ulcer. Currently, he complains of pain in the epigastric region, heartburn, nausea, tarry stool. How can such a patient's condition be characterized?

A. Complications. *C. Remission.* *E. Pathological condition.*
B. Relapse. *D. Pathological reaction.*

6. The patient consulted a doctor because of a furuncle (inflammation of a hair follicle) in the back area. The patient has no fever or signs of intoxication. This is most likely:

A. Disease. *C. Pathological reaction.* *E. –.*
B. Pathological condition. *D. Pathological process.*

7. A woman who had her teeth treated for caries agreed to a tooth extraction due to complications. Which of the pathological phenomena in women can be attributed to the concept of "pathological condition"?

A. Increase in temperature. *C. Swelling.* *E. Absence of a tooth.*
B. Redness. *D. Edema.*

8. During a dental examination, a 37-year-old patient was found to be missing 1 left upper premolar. According to the patient, the tooth was removed two years ago as a result of periodontal disease. What phenomenon is observed in the patient?

A. Pathological process. *C. Pathological condition.* *E. Complications.*
B. Pathological reaction. *D. Chronic process.*

9. In a patient with peptic ulcer, after the treatment, digestion normalized, pains disappeared, mood improved, but after a few weeks pains in the epigastrium, heartburn, acid belching appeared again. How should this course of the disease be characterized?

A. Prodromal period. *C. Latent period.* *E. Complications.*
B. Period of remission. *D. Relapse.*

10. A patient with pneumonia is prescribed complex treatment: etiotropic, pathogenetic, symptomatic. Etiotropic means of pharmacocorrection include drugs affecting:

A. The reason for the development of the disease
B. The cause and conditions of disease development
C. Conditions that will contribute to the development of the disease
D. Causal relationships
E. Function of the diseased organ

Standards of correct answers to the task КROK-1

1	2	3	4	5	6	7	8	9	10
C	*A*	*E*	*C*	*A*	*D*	*E*	*C*	*D*	*A*

Recommendations for registration of work results

1. Written answer to test tasks (initial level of knowledge).

2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.

3. Protocol for solving situational tasks with an explanation of the correct answers.

LITERATURE

Main

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Topic 2. Pathogenic effect of physical factors (ionizing radiation and thermal factors)

Justification of the topic: The primary (direct) effect of ionizing radiation on living tissue is manifested by the ionization and excitation of atoms and molecules and the formation of free radicals that have high chemical activity. Free radicals cause chain chemical reactions as a result of which DNA structures and enzymes are damaged and lipid radiotoxins are formed. The latter, in turn, suppress of the synthesis of nucleic acids, the activity of enzymes, increase the permeability of biomembranes (indirect effect of ionizing radiation). As a result, metabolic disorders, functional and structural damage to cells, organs and body systems occur. First of all, pathological changes occur in organs and tissues with high proliferative activity – lymphoid, hematopoietic, epithelium of the gastrointestinal tract, gonads. Distant effects of ionizing radiation on the body include mutations in germ and somatic cells. The former may manifest themselves in subsequent generations as the development of hereditary diseases, the latter as malignant tumors (leukemia, cancer) many years after exposure.

The effect of high and low temperature (T°) on the body as one of the pathogenic factors of the external environment requires careful study. Overheating (hyperthermia) or hypothermia, which develops under the influence of high or low T° in production, in certain climatic zones, is a common pathological process that leads to the development of pronounced pathological changes in the system of thermoregulation and general metabolism of the body, and, as a result, can lead to serious disorders of the functioning of the cardiovascular and nervous systems. In addition, the local effect of high T°, which leads to burns and burn disease, and low T°, which causes frostbite, is no less relevant.

Studying in an experiment on animals the effect of high and low T° environmental temperature allows to reveal the mechanisms of development of hyper- and hypothermia.

Purpose of the lesson:

General – to characterize the pathogenic effect of ionizing radiation on the body, to characterize local and general manifestations of radiation damage, the main mechanisms of their development in order to further develop the ability to rationally apply prevention and pathogenetic treatment of radiation sickness.

To characterize the essence of disorders that occur in the human body under the influence of high and low T°, to use knowledge of the mechanisms of these disorders in practice in the diagnosis and treatment of overheating and hypothermia.

Specifically:

Know:

1. Mechanisms of local and general reactions that occur during irradiation.
2. Identify the main manifestations of radiation damage, explain the mechanism of local and general action of ionizing radiation on the body.

3. To characterize the stages of overheating, the main phenomena of overheating and their mechanisms. Define the concept of heat stroke and solar stroke.

4. To characterize the stages of hypothermia, the main manifestations of hypothermia and their mechanisms. Define the concepts of natural and artificial hypothermia.

5. Describe the concept of defrosting. Describe the degrees of frostbite.

Be able to:

1. Interpret the concepts of "ionizing radiation", "free radicals", "lipid peroxidation", "radiolysis of water", "radiation disease".

2. Explain the mechanism of local and general reactions that occur during irradiation.

3. Identify the main manifestations of radiation damage, explain the mechanism of local and general action of ionizing radiation on the body.

4. Describe the stages of overheating, the main phenomena of overheating and their mechanisms, concepts of thermal and solar shock, burns.

5. Describe the stages of hypothermia, the main manifestations of hypothermia and their mechanisms, the concept of frostbite. Describe the degrees of frostbite.

Practical experience:

1. Describe ionizing radiation, its types and properties.

2. Interpret the processes of free radical oxidation in the norm.

3. Explain the mechanisms of heat exchange between the body and the external environment.

4. Explain the useful adaptive meaning of compensatory reactions that develop when the T° of the environment increases, when the T° of the environment decreases.

The graphological structure of the topic "Pathogenic effect of physical factors. (ionizing radiation and thermal factors)" is attached.

Material and methodological support of the topic "Pathogenic effect of physical factors. (ionizing radiation and thermal factors)":

1. Lectures;
2. Methodical guidelines for teachers;
3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational tasks to determine the final level of knowledge;
6. A set of KROK-1 tasks;
7. A set of diagrams and tables (presentation);
8. Video films;
9. For the experiment (experimental animals – mice; tripod, thermometer, kettle, glass rod, tubs with ice and water).

Oriented map of students work on the topic "Pathogenic effect of physical factors (ionizing radiation and thermal factors)"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of knowledge	10	Control of theoretical training of students using a programmed method using constructive answers to card questions	Test control, card questions	Study room
2	Analysis of theoretical material	35	Analysis of the theoretical material is carried out on the basis of control questions of the topic and "Krok-1" tasks	Control questions of the topic, tasks "Krok-1"	
3	Conducting an experiment	30.	Introduction and preparation for setting up the experiment. Setting up the experiment	Mice, tripod, thermo-meter, kettle, glass rod, tubs with ice and water	
4	The final stage of determining the level of knowledge and skills. Summing up	15	Determination of the initial level of formation of knowledge and skills.	Solving situational tasks	

Ionizing radiation (radiation) – types of radiant energy that, falling into certain environments or penetrating through them, cause ionization in them. In a narrower sense, ionizing radiation does not include ultraviolet radiation and radiation in the visible range of light, which in some cases can also be ionizing. Radiation in the microwave and radio ranges is not ionizing, since its energy is not enough to ionize atoms and molecules in the ground state.

The following types of ionizing radiation are most significant:

- Short-wave electromagnetic radiation (flow of high-energy photons).
- X-ray radiation.
- Gamma radiation.
- Particle flows:

Beta-particles (electrons and positrons), alpha-particles (helium-4 atomic nuclei), neutrons, protons, other ions, fission fragments (heavy ions resulting from nuclear fission).

Impact of ionizing radiation on the body

The main effect of all ionizing radiation on the body is reduced to the ionization of the tissues of those organs and systems that are exposed to radiation. When working with products that have ionizing radiation, the ways of the latter's influence can be twofold: with the help of external and internal radiation.

External radiation may occur when working on accelerators, X-ray machines and other installations emitting neutrons and X-rays, as well as when working with closed radioactive sources.

When exposed to external rays with significant penetrating power, ionization occurs not only on the irradiated surface of the skin and other coverings, but also in deeper tissues, organs and systems. The period of direct external exposure to ionizing radiation – exposure – is determined by the exposure time.

Internal radiation occurs when radioactive substances enter the body, which can happen when vapors, gases and aerosols of radioactive substances are inhaled, entering the bloodstream (in cases of contamination of skin and mucous membranes damaged by them). Internal radiation is more dangerous.

Direct and indirect action of ionizing radiation

The first mechanism includes damage to the target molecule as a result of direct interaction of radiation with this molecule, that is, as a result of direct radiation action.

The second mechanism includes by damage to the target molecule by active products formed from other molecules as a result of their direct interaction with radiation.

Among them there are both radicals and non-radical products. The hydroxyl radical is a powerful oxidizer and is considered the most chemically active product of water radiolysis. The hydrated electron also has high reactivity, however, already as a reducing agent. H_2O_2, although not a radical, is a very unstable compound and is a source of radical products. In the presence of Fe^{2+} ions, H_2O_2 decomposes to form OH^- (Fenton's reaction).

The products of H_2O radiolysis can diffuse from the place of formation to the vital molecules of the cell and cause their modification, i.e. damage.

During H_2O radiolysis, there is a shift in the acid-base state, changes in oxidation-reduction processes, which lead to metabolic disorders in the body. Radiolysis products actively react with protein molecules, often forming toxic compounds. Extremely harmful to the body and reactive peroxide compounds are formed, which trigger a whole chain of successive biochemical reactions and gradually lead to the destruction of cell membranes (cell walls and other structures).

RADIATION DISEASE

Radiation disease – a disease that occurs as a result of exposure to various types of ionizing radiation and is characterized by a symptom complex that depends on the type of radiation, its dose, the localization of the source of radioactive substances, the distribution of the dose over time and the human body.

Radiation sickness can develop as a result of short-term irradiation with significant doses, and as a result of chronic exposure to ionizing radiation.

Acute radiation disease (ARD) – a disease that occurs with external, relatively uniform irradiation in a dose of more than 1Gy (100 rads) for a short time.

Chronic radiation disease (CRD)develops as a result of long-term continuous or fractionated irradiation of the body in doses of 0.1-0.5 cGy/day with a total dose exceeding 0.7-1 Gy.

ACUTE RADIATION DISEASE

Depending on the radiation dose, there are 4 clinical forms of ARD:

Typical (bone marrow) form

This is the only form of ARD that has periods and degrees of severity.

Degrees of severity of the bone marrow form of ARD depends from uniform irradiation in a person, depending on the absorbed dose of radiation:

- Light (1–2 Gy).
- Medium (2–4 Gy).
- Heavy (4–6 Gy).
- Extremely heavy (more than 6 Gy).

Periods of the bone marrow form of GPH:

- Initial (primary reaction).
- "Imagined well-being" (hidden).
- Manifestational.
- Restoration.

Initial period (primary reaction period)

It starts from the moment of exposure to radiation and lasts from several hours to 34 days, the duration depends on the dose.

*Indicators of primary reaction are*increased T°, nausea, vomiting (from single to multiple and uncontrollable), especially after taking liquid, lack of appetite, feeling of heaviness in the head, headache, general weakness, drowsiness, shock-like state, drop in blood pressure (BP), short-term loss of consciousness , diarrhea Neutrophilic leukocytosis and lymphopenia are observed in the peripheral blood on the first day after irradiation.

We can distinguish four syndromes in the formation of the primary reaction, which are intertwined:

1. *Astheno-hypodynamic*, manifested by headache, dizziness, sharp weakness, irritability, insomnia, feeling of fear, excitement.
2. *Gastrointestinal*, which is characterized by vomiting, nausea, loss of appetite, salivation, less often – diarrhea. This syndrome is centrogenic and depends little on damage to the digestive organs themselves. Pathogenetically, it is associated with the formation of radiotoxins as a result of the direct harmful effect of radiation and their influence on the regulatory structures of the central nervous system. Therefore, clinically, the initial reaction is very similar to the picture of acute poisoning.
3. *Cardiovascular* – decrease in blood pressure, tachycardia, arrhythmia, shortness of breath.
4. *Hematological* – there is a short-term leukocytosis with a shift of the leukocyte formula to the left, lymphopenia, which reaches a maximum 72 hours after irradiation.

Hidden period (imaginary well-being)

The duration depends on the dose: it can last 30 days (with doses of 1–2 Gy) or be absent at all (with doses of more than 10 Gy).

It is characterized by the absence of clinically visible signs of the disease (including the improvement of the patient's well-being), although a number of clinical signs are observed in this phase as well, for example: lymphopenia, oropharyngeal syndrome, hair loss (when exposed to doses of at least 4 Gy), thrombocytopenia and neutrophilic leukopenia, depression early stages of spermatogenesis, etc.

Inflammatory period

Depending on the dose, irradiation may occur at 57 weeks (with doses of 1–2 Gy) or already on the 12th day after irradiation (with doses of more than 20 Gy).

The main clinical syndromes of the acute period of GPH:

Hematological syndrome.It is manifested by pancytopenia, that is, a decrease in the content of all formed elements in the blood. Since the lifespan of different blood cells is not the same, the content of short-lived formed elements – lymphocytes, neutrophils, and much later – erythrocytes – decreases first. Thus, lymphocytes disappear from the blood the earliest. Lymphocytopenia can be detected already in the period of imaginary well-being. Then the content of granulocytes decreases (neutropenia), then platelets (thrombocytopenia) and, finally, erythrocytes (anemia).

Causes of pancytopenia -lesions of the central nervous system, natural death of mature formed elements contained in the blood.

Hemorrhagic syndrome.First of all, hemorrhages appear on the mucous membranes (MM) of the oral cavity, then a petechial rash appears on the skin of the inguinal region, inner surfaces of the thighs, lower legs, and forearms, hemorrhages in the subcutaneous tissue. In severe cases, nasal and intestinal bleeding, as well as hematuria, occur. When examining the fundus – congestion with small hemorrhages. Hemorrhages in the brain or meninges are accompanied by the appearance of focal neurological symptoms; into the lung tissue – hemoptysis; in the gastrointestinal tract – tarry feces.

Asthenic syndrome

It includes a complex set of clinical signs arising as a result of functional disorders of the central nervous system (general weakness, dizziness, fainting, drowsiness during the day, insomnia at night, etc.).

Oropharyngeal syndrome

In this syndrome, the pathological process is usually determined by damage to the tonsils, mucous membranes of the pharynx, nasal passages, and tongue.

Gastrointestinal syndrome

It is manifested by gastric and intestinal dyspepsia as a result of the development of toxic-septic gastroenterocolitis. Hemorrhagic gastroenterocolitis often occurs against the background of toxemia.

Syndrome of cardiovascular disorders

Manifestations: a feeling of palpitations, pains in the heart region of a different nature, increased pulse, expansion of the borders of the heart, deafness of heart sounds, systolic murmur over the apex, a decrease in blood pressure up to collapse, on the ECG: a decrease in the voltage of the waves, widening of the ventricular complex (QRS), flattening of the T waves and P, displacement of the S-T interval.

Recovery period

It starts 45–50 days after irradiation.

It usually begins with signs of normalization of hematopoiesis. Single myeloblasts, promyelocytes, myelocytes, monocytes, and reticulocytes appear in the peripheral blood, and then the number of leukocytes, platelets, and

reticulocytes increases rapidly (several days). All signs of its regeneration are observed when examining the RBM: the number of blast forms and myelokaryocytes increases. Simultaneously with the regeneration of hematopoiesis and an increase in the number of neutrophils, the body temperature decreases to normal values, the general well-being of the patient improves. Bleeding disappears. Necrotic masses are rejected and shallow erosions on the skin and MM are healed. From 2-5 months. the function of sweat and sebaceous glands of the skin is normalized, hair growth is restored. For a long time, phenomena of asthenia, dysfunction of the central nervous system remain,

Restoration of altered functions is slow and is characterized (especially in severe forms of ARD) by the fact that, along with regeneration, increased exhaustion and functional insufficiency of regulatory processes remain in damaged organs for a long time, especially in the cardiovascular system and nervous system.

With a positive result of ARD the recovery period lasts a total of 3–6 months, sometimes up to 1 year, full recovery, depending on the severity of radiation sickness, can be delayed for 1–3 years.

Radiation sickness of the 1st century. The recovery period occurs by the end of the 2-nd month after irradiation. Full recovery and restoration of working capacity is noted.

Radiation sickness of the II century Recovery begins with the appearance of signs of activation of hematopoiesis. Body temperature decreases, general well-being improves.

Radiation sickness of the III century. With a positive ending, a long period of recovery occurs, during which the recovery of the functional state of individual organs and systems takes place at different rates and times. Hematopoiesis is restored violently and in a short period of time. Moreover, within a few days, the RBM transforms from a depleted to a hyperplastic one. In the peripheral blood, neutrophilic leukocytosis develops with a shift of the leukocyte formula to the left.

Intestinal form

It develops with an irradiation dose of 10–20 Gy. With the intestinal form, a severe and long-lasting (up to 3–4 days) primary reaction occurs 5–10 minutes after exposure.

Manifestations:

- There is an increase in T° of the body, erythema of the skin, from the first day – uncontrollable vomiting, diarrhea.
- In the first week, a short latent period is possible, when the stool can temporarily normalize.
- From 6–8 days – sharp deterioration: severe enteritis, dehydration, bleeding, infectious complications.
- A clinical picture of necrotic enteropathy develops, clinically manifested by an increase in T° of the body (often up to +40 °C), liquid or mushy stools, abdominal distension.

- When palpating the abdominal cavity, there are usually sounds of splashing and grumbling in the ileocecal region.
- Necrotic enteropathy in severe cases can be complicated by intussusception, intestinal perforation and the development of peritonitis.
- As a result of atony of the stomach, food masses can linger in it for a long time.
- Absorption processes in the intestines are disrupted, body weight progressively decreases.
- The number of leukocytes in the blood drops dramatically.
- Hemorrhages in the intestinal tract and infectious complications aggravate the condition of affected patients to an even greater extent.
- Death usually occurs in 8–12 days from the predominant intestinal damage, although such post-radiation changes as agranulocytosis and thrombocytopenia, as well as hemorrhages in various organs and tissues, along with the phenomena of bacteremia, will inevitably accompany these lesions.

Toxemic (vascular) form

It develops with an irradiation dose of 20–80 Gy. The pathogenetic basis of this form, along with the manifestations of severe intestinal damage, are pronounced signs of vascular damage, general intoxication of the body due to profound changes in metabolism, and breakdown of intestinal tissues. This leads to impaired kidney function, which manifests itself in oliguria, an increase in residual nitrogen and urea in the blood. Intoxication causes a drop in vascular tone (especially arterioles and venules), resulting in sharp hypotension. In this form, the primary reaction is pronounced.

Manifestations:

- The hidden period is absent or short.
- Collapse is possible immediately after exposure.
- General intoxication, hemodynamic disturbances, weakness, headache, tachycardia, oliguria, azotemia increase on the 2–4th day.
- From 3–5 days – general brain disorders and meningeal symptoms (brain swelling).
- Joining the infection increases intoxication and the victims quickly die.
- Death occurs in the first 4–7 days after injury, as a result of increasing intoxication with tissue metabolites, sometimes – from the development of agranulocytosis.

Cerebral form

At a dose of more than 80 Gy. possible death of the victim in the first two days (fluctuations – from a few minutes and hours to 3 days) with a clinical picture of severe cerebrovascular disorders: psychomotor agitation, convulsions, ataxia, respiratory and circulatory disorders.

- The leading one is convulsive-hyperkinetic syndrome.
- Immediately after exposure to ionizing radiation, a pronounced and violent primary reaction develops: exhausting vomiting, diarrhea and the so-called early transitory incapacity, which manifests itself as a short-term (for 20–30 minutes) loss of consciousness.

- The initial reaction is quickly replaced by depression or, on the contrary, increased motor excitability, convulsions.
- Then the phenomena of ataxia and uncoordinated movements appear, there is progressive arterial hypotension, collapse, coma and death from paralysis of the respiratory center.

Overheating – this is a pathological condition caused by the accumulation of heat in the body due to the insufficiency of thermoregulation mechanisms at a significant increase in T° of the external environment or increased heat production with a sharp limitation of heat transfer at normal T° of the air.

Long-term effect of high T° of the environment on the body leads to general overheating of the body (heat stroke). In unadapted people, heatstroke can develop at an air temperature above 45–47 °C already after 4–6 hours.

Causes of overheating

Normal life activity is possible under the condition of maintaining a constant body temperature due to the balance between heat generation and heat release.

At high T° of the air, the constancy of the body temperature is maintained mainly due to the function of the skin, through which heat transfer is carried out by: radiation, conduction of heat, evaporation of sweat.

When T° of the surrounding air is equal to T° of the body, heat transfer is carried out only due to sweating.

Factors contributing to overheating: heavy physical exertion, lack of wind, insufficient water consumption, overeating, obesity, infections.

Pathogenesis of overheating

1. As the air temperature increases, sweating and evaporation increase. At T° above 35°C, a person loses about 5 liters of sweat per day, which corresponds to the return of almost 3000 kcal of heat.
2. Staying in an environment with high T° leads to acceleration of metabolic processes in the body, which, with a decrease in heat output, contributes to the progressive development of general overheating.
3. Accumulation in the body during overheating of excess heat leads to disruption of all exchange processes (first of all, protein and water-salt exchanges are disturbed).
4. The body loses water and salts, protein denaturation occurs.
5. With a significant water deficit, blood thickens, hypoxia increases, blood circulation worsens.
6. The central nervous system is most sensitive to overheating, so the symptoms of its damage prevail in the clinical picture of overheating.
7. Morphological changes in general overheating are non-specific and are reduced to perfusion of internal organs, not sharply expressed thickening of blood, perivascular hemorrhages, phenomena of pulmonary edema and brain edema.
8. An increase in T° of the body to 42 °C and above is considered critical. Death occurs from paralysis of the respiratory center.

Periods in the development of overheating:

Compensation period. Given the relative lack of heat transfer through the skin, other ways of heat transfer are mobilized:

- ✓ expansion of peripheral vessels,
- ✓ acceleration of blood flow,
- ✓ increased sweating,
- ✓ increased breathing (disruption of the respiratory center warmed by blood),
- ✓ reduction of heat production

Arousal period, when the T° of the body begins to rise, it manifests itself in anxiety, rapid and shallow breathing, acceleration of the pulse (tachycardia 130–140 beats per minute), increased metabolism, increased reflex activity, convulsive twitching.

Depression period -violation of water-electrolyte exchange, thickening of blood and increase in its viscosity (contributes to the development of heart failure), decrease in vegetative functions (breathing and blood pressure), disappearance of reflexes, clonic convulsions, comatose state.

Death occurs from cessation of breathing during exhalation and cessation of heart activity in systole.

Heat stroke is a pathological condition associated with the maximum accumulation of heat in the body. The peculiarity of heat stroke is the rapid achievement of life-threatening T° (rectal) values of 42–43 °C.

Heat stroke is an extreme variant of decompensation of thermoregulation mechanisms in case of heat damage as a result of rapid exhaustion and failure of adaptive processes characteristic of the compensation stage in hyperthermia. Lethality in case of heat stroke reaches 30 %.

The causes of heatstroke are the action of the heat factor of high intensity, the low efficiency of the body's adaptation mechanisms to the increased T° of the external environment.

Pathogenesis of heat stroke

Overheating of the body after a short-term compensation stage quickly leads to a breakdown of thermoregulation mechanisms and an intensive increase in T° of the body, acute progressive intoxication develops, heart failure increases, and breathing stops.

Intoxication of the body during heat stroke(as well as at the stage of decompensation of hyperthermia) – an essential and natural link of its pathogenesis. The degree of intoxication correlates with the increase in T° of the body. The important role of intoxication in the pathogenesis of heat stroke is evidenced by the delayed death of the victims: most of them die a few hours after the cessation of excessive heat, when the T° of the body approaches the normal range.

Sunstroke – a condition resulting from severe overheating of the head by direct sunlight.

Along with others, the infrared part of solar radiation, i.e. radiant heat, has the greatest pathogenic effect. The latter, unlike convection and conduction heat, simultaneously warms both the surface and deep tissues of the body. In addition, infrared radiation, acting on the whole body, intensively warms the GM tissue, in which the neurons of the thermoregulation center are located. In this regard, sunstroke develops, changes rapidly and threatens with a fatal outcome.

Pathogenesis of sunstroke

The pathogenesis of sunstroke is a combination of the mechanisms of hyperthermia and sunstroke itself. Various lesions of the central nervous system are leading.

Increasing arterial hyperemia of brain. *Reasons:*

✓ An increase in T° of the brain under the influence of infrared radiation of sunlight.

✓ BASs formed directly in brain tissue: kinins, adenosine, acetylcholine, etc.

The long-term effect of heat and various vasodilators reduces the neuro- and myogenic tone of the arteriole walls. Arterial hyperemia leads to increased tissue blood flow. For the brain, which is in the closed space of the bony skull, this means its compression.

Increase (in conditions of arterial hyperemia) of lymphoid formation and the filling of lymphatic vessels with an excess of lymph leads to an increase in compression of the GM substance.

Progressive venous hyperemia of the brain. Its cause is compression of the brain, including venous vessels and sinuses located in it. Venous hyperemia leads to the development of hypoxia of the brain, edema of the brain and small focal hemorrhage in the brain. As a result, focal symptoms appear in the form of various neurogenic disorders of sensitivity, movement and vegetative functions. Growing disorders of metabolism, energy supply and plastic processes in brain neurons. This potentiates the decompensation of thermoregulation mechanisms, disorders of the functions of the cardiovascular system, breathing, endocrine glands, blood, other systems and organs. With severe changes in the brain, the victim faints, a coma develops.

Thermal burn – damage to tissues when their temperature increases to 45–50 ^{o}C and above as a result of the action of hot liquids, steam, flame, heated solid bodies.

Classification of burns

Superficial burns*:*

I degree – persistent hyperemia and infiltration of the skin;

II degree – peeling of the epidermis and formation of blisters;

III A degree – partial necrosis of the skin with preservation of deep layers of the dermis.

Deep burns*:*

III B degree – death of all skin structures (epidermis and dermis);

IV degree – necrosis of the skin and deep tissue layers.

Leading pathophysiological factors in thermal injuries:

- stronger pain impulse from the lesion;
- a powerful sympathoadrenal reaction accompanied by spasm of capillaries in the microcirculation system;
- hypovolemia and secondary erythremia as a result of a shock reaction and increased fluid loss through damaged skin.

Hypothermia – a pathological condition caused by a drop in the body's internal T° to the level of < 35 °C due to the effect on the body of low T° of the external environment and/or a significant decrease in heat production in it.

Causes of hypothermia:

1. Low T° of the external environment (water, air, etc.) is the most common reason.
2. Enhanced heat output while maintaining a normal (average) level of heat production.
3. Reduction of heat production with normal heat transfer.
4. Increased heat output in combination with low intensity of heat production.

Exogenous factors leading to the development of hypothermia:

- Low T° of the surrounding air.
- Increased humidity.
- High heat capacity of the environment (for example, when immersed in cold water).
- Low PaO_2 in the surrounding air (for example, in highland conditions). Under these conditions, O_2 consumption and the ability to produce high T° during physical activity will be reduced, increasing the likelihood of developing hypothermia.

Pathogenesis of hypothermia

Hypothermia compensation stage

It is characterized by the activation of emergency adaptive reactions aimed at reducing heat transfer and increasing heat production.

1. Activation of emergency adaptive reactions.

The mechanism of development of the hypothermia compensation stage includes:

A decrease in the efficiency of heat transfer is achieved due to the reduction and cessation of sweating, narrowing of the arterial vessels of the skin and muscles, due to which blood circulation in them is significantly reduced.

Activation of heat production due to increased blood flow in internal organs and increased muscle contractile thermogenesis.

Inclusion of a stressor reaction (excited state of the victim, increased electrical activity of thermoregulation centers, increased secretion of liberins in hypothalamus neurons, ACTH and TSH in pituitary adenocytes, CA in the medulla of the adrenal glands, and corticosteroids in their cortex, thyroid hormones in the thyroid gland).

Due to the complex of these changes, T° of the body decreases, but still does not go beyond the lower limit of the norm. The body's temperature homeostasis is maintained.

2. The above-mentioned changes significantly modify the function of the body's organs and physiological systems: tachycardia develops, blood pressure and cardiac output increase, breathing rate increases, and the number of erythrocytes in the blood increases.

3. These and some other changes create conditions for the activation of metabolic reactions, which is evidenced by a decrease in the content of glycogen in the liver and muscles, an increase in glucose and free fatty acids in the blood, and an increase in the consumption of O_2 by tissues. Intensification of metabolic processes is combined with increased release of energy in the form of heat and prevents the body from cooling down.

4. If the causative factor continues to operate, compensatory responses may become insufficient. At the same time, the temperature of not only the covering tissues of the body, but also its internal organs, including the brain, decreases. The latter leads to disorders of the central mechanisms of thermoregulation, discoordination and ineffectiveness of heat production processes – their decompensation develops.

Hypothermia decompensation stage.

The stage of decompensation (maladaptation) of thermoregulation processes is the result of a disruption of the central mechanisms of heat exchange regulation. Body temperature falls below the normal level and continues to decrease further. The body's temperature homeostasis is disturbed - the body becomes poikilothermic.

The reason for the development of the decompensation stage: increasing suppression of activity of cortical and subcortical structures of brain, including centers of thermoregulation. The latter determines the inefficiency of heat production reactions and the continuous loss of heat by the body.

Pathogenesis of the hypothermia decompensation stage:

Violation of mechanisms of neuroendocrine regulation of metabolism and functioning of tissues, organs and their systems.

Disorganization of tissue and organ functions.

Suppression of metabolic processes in tissues.

The degree of functional and metabolic disorders directly depends on the degree and duration of the decrease in T° of the body.

Direct causes of death in deep hypothermia: cessation of cardiac activity, respiratory arrest. Both the first and the second are to a greater extent the result of cold depression of the vascular and respiratory bulbar centers. The reason for stopping the contractile function of the heart is the development of fibrillation (more often) or its asystole (less often).

The death of the body in hypothermia occurs, as a rule, when the rectal temperature drops below 25–20 °C. Those who died in conditions of hypothermia show signs of venous congestion of the vessels of internal organs, brain and spinal cord; small- and large-focal hemorrhage in them; pulmonary edema; depletion of glycogen reserves in the liver, skeletal muscles, myocardium.

Depending on the time of death of a person under the influence of cold, there are three types of cooling that cause hypothermia:

♦**acute**, in which a person dies within the first 60 minutes. (when staying in water at T° from 0 °C to +10 °C or under the influence of wet cold wind).

♦ **subacute**, in which death occurs before the end of the fourth hour of being in conditions of cold, damp air and wind.

♦ **slow**, when death occurs after the fourth hour of exposure to cold air (wind), even with clothing or protection of the body from the wind.

Classification of hypothermia:

1. Mild degree – basal temperature of 33–35 °C.
2. Moderate degree - basal temperature of 28–32 °C.
3. Severe degree - basal temperature < 28 °C.

Artificial lowering of T° of the body (hibernation), which is achieved under anesthesia with the help of physical effects, is used in medicine (cardio- and neurosurgery) in order to reduce the body's need for O_2 and prevent temporary ischemia of the brain.

Frostbite (*lat. – congelatio***)** – damage to body tissues under the influence of cold.

Often, frostbite is accompanied by general hypothermia of the body and especially often affects such parts of the body as: auricles, nose, insufficiently protected limbs, primarily fingers and toes. Frostbite differs from "cold burns" in that they occur as a result of direct contact with extremely cold substances, such as dry ice or liquid nitrogen. Most often, frostbite occurs in cold winter time at an ambient temperature below -20…-10 °C. If you stay outdoors for a long time, especially with high humidity and strong wind, you can get frostbite in autumn and spring at an air temperature above 0 °C.

Etiology of frostbite.

The direct cause of frostbite is the effect of low T° on the human body. The human body has a thermoregulation system that prevents thermal damage to tissues, but under the influence of a number of external factors, the effectiveness of thermoregulation decreases and frostbite occurs.

The factors causing frostbite can be divided into the following main groups:

1. **Weather conditions.**Frostbite is caused by humidity and wind. Most often, the occurrence of such injuries is possible with positive air temperature, with strong wind and high humidity. Wind and high humidity increase heat transfer, reduce the heat-insulating properties of clothes and shoes.
2. **The state of thermal insulation of the extremities.**Tight shoes, prolonged immobility, the need to constantly hold any object in the hands reduce the efficiency of microcirculation, and as a result, contribute to the occurrence of cold lesions.
3. **General condition of the body.**A weakened body produces less heat and, as a result, is more prone to cold injury. There are many reasons that increase a person's vulnerability to cold: injuries, blood loss, lack of food, fatigue, stress, smoking, alcohol intoxication.
4. **Various disorders of blood supply.**The development of frostbite is largely facilitated by obliterating diseases of the extremities, various systemic diseases affect capillaries and larger vessels. Also, tissues with low vascularity, for example, scar tissue, are more prone to frostbite.

Pathogenesis of frostbite.

Under the influence of cold, complex changes occur in the tissues, the nature of which depends on the level and duration of the decrease in T°. When T° is below -30 °C, the main importance in defrosting is the harmful effect of cold directly on tissues, and cell death occurs. Under the influence of T° up to -10…-20 °C, at which most frostbites occur, vascular changes in the form of spasm of small blood vessels are of leading importance. As a result, the blood flow slows down, the action of tissue enzymes stops, and the supply of oxygen to the tissues is significantly reduced.

Conditionally, it is possible to distinguish two large groups of causes of the formation of necrosis during frostbite. These are local and systemic factors.

Local factors. There are two reasons for the death of cells in the focus of frostbite: direct traumatizing effect of cold, disruption of metabolic processes in tissues and organs due to a decrease in their T°.

Direct cold damage to tissues is relatively rare in contact frostbite. Most often, metabolic changes lead to cell death. As a result, ischemia begins to build up in the cooled parts of the body. Microcirculation disorders play a leading role in the pathogenesis of local lesions. Tissues are left without an adequate supply of O_2 and nutrients, as a result of which massive cell death develops, which leads to the emergence of foci of necrosis.

System factors. System impacting factors can be conditionally divided into 2 groups:

The first group - this is the absorption into the blood of the products of autolysis of cells during necrosis of frostbite foci. In general, the clinic and pathogenesis are similar to burn disease.

The second group – general cooling of the body. This factor begins to act at a body temperature below +34 °C. All exchange processes slow down, metabolism is disturbed. In connection with hypothermia, the process of dying with general hypothermia has a number of characteristic features. The tissue's need for O_2 is reduced, due to which the dying process is significantly extended in time. When warming, a pronounced "oxygen deficiency of tissues" is revealed, which causes a sharp increase in hypoxia and deterioration of the patient's condition. The transition to a state of clinical death is observed at T° +24 °C due to a malfunction of the respiratory center in the medulla oblongata. The duration of clinical death, during which successful resuscitation of the patient is possible, exceeds the usual 5–6 minutes.

Setting up the experiment.
Discussion the results and formulation the conclusions

Experiment No 1. The effect of elevated temperature.

1. Place the mouse in the bank.
2. To study the initial state of the animal: behavior, color of visible skin, number of respiratory movements per minute.
3. Place the jar with the mouse in a bath with water, temperature 38 ^{o}C.
4. In the future, increase the water temperature by 10 (up to 45 ^{o}C), and monitor changes in the animal's condition. When studying the condition of the animal, pay attention to the following: behavior, breathing, coat color, etc. after 5 minutes.
5. Describe the results according to the attached scheme.

After immersing the can with the mouse in water, a slight reddening of the visible integuments and some increased breathing is noted. In the future, the phenomena of hyperemia intensify, breathing becomes more frequent, anxiety appears, which is increasingly intensified. A state of excitement is observed, which is replaced by increasingly growing depression. Then the

animal lies at the bottom of the can, severe shortness of breath, cyanosis, clonic convulsions, and death are noted.

Experiment No 2. Effect of low temperature.

1. Place the jar with the mouse in the ice bath.

2. Pay attention to the following: behavior, breathing, color of visible skin.

3. 5 minutes after immersing the jar with the mouse in ice, note a slight paleness of the visible integuments and a slightly accelerated breathing.

4**.** Describe the results according to the attached scheme.

In the future, pay attention to the appearance of hyperemia, a sharp increase in breathing, and the appearance of anxiety, which is increasing more and more. To observe a state of excitement, which will be replaced by an increasingly growing depression. Record the position of the animal lying on the bottom of the jar, note severe shortness of breath, cyanosis, clonic convulsions, death.

Discussion of the results of the experiment

1. For hyperthermia - pay attention to the initial changes in the state of the body, which are an adaptive reaction aimed at maintaining a constant body temperature. These changes are manifested in shortness of breath, flushing and increased sweating. The mechanism is explained by a reflex reaction from exteroceptors on the surface of the body.

Initial changes constitute the first stage – compensation. In the future, these adaptive mechanisms turn out to be insufficient, the body temperature rises and overheating occurs. At the same time, the normal relationship between the physical and chemical regulation of the body is disturbed, the metabolism increases, which further contributes to the increase in body temperature. The nervous system is affected by the following effects: the flow of impulses from extero- and interoreceptors, high blood temperature, unoxidized metabolic products, loss of salts and water by the body. All this excites the nervous system. The normal regulation of functions is disturbed, which leads to an even sharper increase in breathing, impaired blood circulation, impaired water and other types of metabolism. This is the second stage of overheating – excitement. Then comes a state of depression. Breathing is uneven, sharp cyanosis. Seizures occur, which explain overexcitation in the central nervous system, which are replaced by paralysis of the centers. This is the third stage of overheating.

When discussing the mechanisms of the observed phenomena, emphasize the presence of not only quantitative, but also qualitative changes in the body.

2. For hypothermia – pay attention to the initial changes in the state of the body, which are an adaptive reaction aimed at maintaining a constant body temperature. These changes manifest in shortness of breath, pallor, and decreased sweating. The mechanism is explained by a reflex reaction from extrareceptors on the surface of the body.

The initial changes are the first stage of hypothermia – compensation. In the future, these adaptive mechanisms turn out to be insufficient, the body temperature decreases, hypothermia actually occurs. At the same time, the normal relationship between physical and chemical regulation of heat is

disturbed. Increasing heat production and reducing heat output only by physical mechanisms becomes insufficient.

Metabolism increases, neurohumoral mechanisms of body protection against cold are activated. The nervous system is influenced by impulses from extra- and intrareceptors, transforms them and sends afferent impulses to muscles, adrenal cortex, hypothalamic-pituitary system. The normal regulation of functions is disturbed, which leads to an even sharper increase in breathing, impaired blood circulation, impaired energy and other types of metabolism. The second, short-term stage of hypothermia comes – the stage of excitement, which is replaced by a longer stage of depression. Breathing is uneven, sharp cyanosis. Convulsions appear, which are explained by overexcitation of the central nervous system, which are replaced by paralysis of the center. When discussing the mechanisms of the observed phenomena, emphasize the presence of not only quantitative, but also qualitative changes in the body.

Formulation of conclusions based on the experiment

For hyperthermia:

1. The cause of the observed phenomena is an increase in the ambient temperature.

2. Conditions that contribute to overheating – humidity, physical exertion, lack of air movement, reduced reactivity of the body.

3. The initial increase in the temperature of the environment does not cause pronounced changes in the animal's condition. This is achieved due to an increase in heat transfer and a decrease in heat production. Further increase in ambient temperature – overstrain of compensatory mechanisms, body temperature rises. A stage of excitement is developing, which is replaced by depression.

For hypothermia:

1. The reason for the observed phenomena is the low temperature of the environment.

2. Conditions that contribute to hypothermia are high humidity.

3. The effect of low temperature is accompanied by the inclusion of compensatory reactions aimed at maintaining normal body temperature. It consists in changing thermoregulation in the direction of: – increasing heat production – limiting heat output. In the future, the compensatory mechanisms become insufficient and the body temperature decreases. At the same time, the function of the central nervous system is suppressed, which is manifested by a violation of the vasomotor center. This leads to paralysis of blood vessels and rapid loss of body heat.

Tasks for independent work

It is necessary to characterize ionizing radiation, its types and properties, to explain the useful adaptive meaning of compensatory reactions that develop when the T° of the environment increases and when the T° of the environment decreases. Be able to explain the mechanisms of occurrence. Analyze the errors with an explanation of the correct answers.

List of questions and works to be studied:

1. What types of ionizing radiation can have a pathogenic effect on the body?
2. What is the pathogenesis of general and local effects of ionizing radiation on the body?
3. What is the essence of the direct damaging effect of ionizing radiation on cells?
4. What is the essence of the indirect progressive effect of ionizing radiation on cells?
5. What determines the radiosensitivity of tissues to the action of ionizing radiation?
6. What is radiation sickness? Name the forms and stages of acute radiation sickness.
7. What syndromes are most characteristic of the period of the advanced clinical picture of ARD? What is their pathogenesis?
8. Name the most important long-term effects of ionizing radiation on the body.
9. What factors contribute to the development of radiation injuries and prevent them?
10. What protective and compensatory mechanisms in cells are aimed at preventing and eliminating radiation damage?
11. The concept of hyperthermia.
12. The cause and conditions of overheating.
13. Stages of overheating. The main phenomena of overheating and their mechanisms.
14. Heat and sunstroke.
15. Burn. Burn disease.
16. The concept of hypothermia. Reason and conditions of cooling.
17. Cooling stages. Compensatory reactions to the action of low T° of the environment and their mechanisms. The main phenomena of cooling and their mechanisms.
18. Natural and artificial hypothermia.
19. Frostbite.

List of practical skills that must be mastered:

1. Interpret the processes of free radical oxidation in the norm;
2. To evaluate the results of the study of lipid peroxidation;
3. Explain the mechanisms of heat exchange between the body and the external environment;
4. Explain the useful adaptive meaning of compensatory reactions that develop when the temperature of the environment increases;
5. Explain the useful adaptive meaning of compensatory reactions that develop when the temperature of the environment decreases;

Situational tasks KROK-1 to determine the final level of knowledge

1. When studying the comparative radiosensitivity of tissues, it was found that their sensitivity to the action of ionizing radiation is not the same. Indicate which of the listed tissues is the most radiosensitive?

A. Cartilaginous. *C. Bone.* *E. Nervous.*
B. Hematopoietic. *D. Muscular.*

2. During the accident on the nuclear submarine, the submariners were irradiated. The primary ionization of which molecules is most important in the development of radiation sickness?

A. Water. *C. Lipids.* *E. Enzymes.*
B. Structural proteins. *D. Nucleic acids.*

3. During the period of acute radiation sickness, the patient experienced leukopenia, thrombocytopenia, autoinfection, autointoxication, bleeding, and increased body temperature. What form of radiation sickness is this picture characteristic of?

A. Bone marrow. *C. Toxemic.* *E. Hemorrhagic.*
B. Intestinal. *D. Cerebral.*

4. The liquidator of the consequences of the accident at the nuclear power plant developed a hemorrhagic syndrome during the course of acute radiation sickness. What is most important in the pathogenesis of this syndrome?

A. Increasing the activity of the factors of the blood clotting system.
B. Decreased activity of blood coagulation factors.
C. Violation of the structure of the vessel wall.
D. Increase in the activity of fibrinolysis factors.
E. Thrombocytopenia.

5. In a rabbit after irradiation, the third period of the bone-marrow form of ARD is observed. Damage to which tissue is leading in the pathogenesis of disorders in this case?

A. Bone. *C. Nervous.* *E. Glandular epithelium.*
B. Hematopoietic. *D. Epithelium of gonads.*

6. A nuclear power plant worker was taken to the clinic after a single exposure with complaints of weakness, headache, increased T°, diarrhea. In the blood analysis – leukocytosis with lymphopenia. What is the most likely stage of radiation sickness?

A. The period of primary reactions. *D. Latent period.*
B. A period of imaginary well-being. *E. Prodromal period.*
C. The period of the developed clinical picture.

7. When working with radioactive substances, the employee received a total radiation dose of 4 Gy as a result of the accident. Complains of headache, nausea, dizziness. What changes in blood composition can be expected in a patient 10 hours after exposure?

A. Lymphocytosis. *C. Agranulocytosis.* *E. Neutropenia.*
B. Leukopenia. *D. Neutrophil leukocytosis.*

8. An employee of a "hot" workshop was taken to the hospital before the end of the working day, complaining of headache, dizziness, nausea, and general weakness. Objectively: consciousness is preserved, the skin is hyperemic, dry, hot to the touch. Heart rate - 130/min. Breathing is frequent, shallow. What violation of thermoregulation processes most likely occurred in a person in this situation?

A. *A decrease in heat production without a change in heat output.*
B. *Enhancement of heat transfer and heat production.*
C. *Reduction of heat transfer.*
D. *Increasing heat production without changing heat output.*
E. *Increasing heat transfer and reducing heat production.*

9. A patient with large burns of the skin of the body has signs of severe intoxication. For which stage of burn disease is this characteristic?

A. Burn infection. *C. Burn exhaustion.* *E. Terminal.*
B. Burn shock. *D. Burn toxemia.*

10. A 25-year-old man's body temperature rose to 39 °C after a long stay in the sun with high air humidity. What pathological process is observed in this case?

A. Burn disease. *D. Non-infectious fever.*
B. Hyperthermia. *E. Hypothermia.*

Standarts of correct answers to the KROK-1 task

1	2	3	4	5	6	7	8	9	10
B	*A*	*A*	*E*	*B*	*A*	*D*	*C*	*D*	*B*

Recommendations for registration of work results

1. Written answer to test tasks (initial level of knowledge).
2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.
3. Protocol for solving situational tasks with an explanation of the correct answers.

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Topic 3. Pathology of reactivity. Barriers. Violation of phagocytosis

Justification of the topic: The concept of reactivity has firmly entered practical medicine and contributes to the assessment of the patient's condition. The emergence, development, course and outcome of the disease are determined, first of all, by the state of reactivity as the ability to respond to changes in the body's vital activity to various environmental influences. Any pathological process to one degree or another changes the body's reactivity, at the same time, a change in reactivity that has exceeded physiological limits can become the basis of the development of the disease.

The barrier function of the organism developed in the process of evolution, it is the adaptation of the organism to environmental conditions. The penetration of pathogenic agents into the body is hindered, first of all, by anatomical and physiological formations of non-specific protection, which protect the body or its individual parts from the pathogenic effects of the environment and ensure the preservation of homeostasis. Barrier permeability changes during pathological processes.

Purpose of the lesson:

General -to study the influence of environmental factors on the body's reactivity. To be able to characterize external and internal barriers under the influence of environmental factors. To study the essence of the processes of the phagocytic reaction, its mechanisms and place in the body's immune system, to evaluate its biological significance.

Specifically:

Know:

1. The influence of environmental factors on the body's reactivity.
2. To be able to characterize external and internal barriers under the influence of environmental factors.
3. To study the essence of the processes of the phagocytic reaction, its mechanisms and place in the body's immune system, to evaluate its biological significance.

Be able to:

1. Explain the general regularities of the functioning of the body, its individual organs and systems.
2. Explain the features of barrier devices.
3. To characterize phagocytosis as a biological phenomenon.
4. To characterize the main properties of tissue macrophages.

Practical experience:

To find out the general regularities of the functioning of the body, the peculiarities of barrier devices, the main properties of leukocytes, to characterize phagocytosis as a biological phenomenon and the main properties of tissue macrophages.

The graphological structure is added from the topic "The pathology of reactivity. Biological barriers. Violation of phagocytosis"

Material and methodological support of the topic "The pathology of reactivity. Biological barriers. Violation of phagocytosis":

1. Lectures;
2. Methodical guidelines for teachers;
3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational tasks to determine the final level of knowledge;
6. A set of KROK-1 tasks;
7. A set of diagrams and tables (presentation);
8. Video films;
9. For the experiment (experimental animals – rabbit, mouse, frog, pneumograph, kymograph, ammonia, thin rubber probes, 10 % magnesium sulfate solution, syringes, tweezers, scissors, 10 % trypan blue solution, ether).

Oriented map of students work on the subject:
"The pathology of reactivity. Biological barriers. Violation of phagocytosis"

No	Stage of lesson	Academic time	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of knowledge	10	Control of theoretical training of students using a programmed method using constructive answers to ticket questions	Test control, card questions	Study room
2	Solving educational tasks on the following topics: 2.1 Analysis of theoretical material 2.2 Conducting the experiment	70	Analysis of the theoretical material is carried out on the basis of control questions of the topic and tasks "Step 1". Introduction and preparation for setting up the experiment. Setting up the experiment	Control questions of the topic, task "Krok-1". Rabbit, pneumograph, kymograph, ammonia. Frog, thin rubber probes, 10 % magnesium sulfate solution, syringes, tweezers. Mouse, syringes, scissors, 10 % trypan blue solution, ether	Study room
3	The final stage of determining the level of knowledge and skills. Summing up	10	Determination of the initial level of formation of knowledge and skills	Solving situational tasks	Study room

Reactivity – the ability of the organism to respond to the effects of internal and environmental factors by changing its vital activity.

Specific mechanisms of reactivity can be implemented at the following levels: molecular, cellular, tissue, organ, system, organism as a whole.

Types of reactivity

Reactivity is formed in the process of evolutionary development of specific, hereditary qualities of the organism. In addition to species properties, it also reflects group (typical) and individual characteristics of the response of

individual organisms. Therefore, biological (species, primary), group (typical) and individual reactivity are distinguished.

Species (biological) reactivity

Species reactivity is protective and adaptive changes that occur under the influence of environmental influences (irritations) that are normal (adequate) for each species of animal.

Species reactivity is also called primary, as it is determined by species (biological) features. It is aimed at preserving the species as a whole and each individual separately.

Group (typical) reactivity

Group reactivity is the reactivity of certain groups of individuals within one species, united by any feature (type of constitution, blood group, etc.), the main features of the response of all representatives of this group to the influence of environmental factors. Allocate age, gender and constitutional group reactivity.

Age reactivity

Each period of the ontogenetic development of the human body is characterized by its own, special type of response to external and internal stimuli. Different age groups react differently to the same stimulus.

Sexual reactivity

There is a significant number of observations that reflect the difference in reactivity between female and male organisms.

The reactivity of men is characterized by wide individual diversity and a more diverse range of variability. Female reactivity, with a more "narrow" response, contributes to greater stability in relation to a significant number of exogenous factors. Therefore, the course of diseases (somatic, infectious) in women is manifested by a smaller variation of symptoms and frequent manifestation of typical forms. Men are characterized by a significant polymorphism of clinical signs – from erased, asymptomatic, to extremely severe cases of the same pathology. As a result, the total mortality of men is higher than that of women in almost all age groups.

Constitutional reactivity is determined by relatively stable morphofunctional features of the organism, which are determined by heredity and long-term influence of environmental factors.

Individual reactivity depends on hereditary, constitutional properties, age, sex, and environmental influences. It is determined primarily by the type of VND, functional features of the nervous system, endocrine glands, immune system, other organs and tissues.

Specific (immunological) reactivity is expressed in the ability of the immune system to respond to antigenic stimuli. It provides immunity (immunity) to infectious diseases, reactions of biological incompatibility of tissues, increased sensitivity.

Non-specific (non-immunological) reactivity manifests itself during the action of environmental factors on the body. It is implemented using such mechanisms as stress, a change in the functional state of the nervous system, parabiosis, phagocytosis, biological barriers.

Specific and nonspecific reactivity can be physiological and pathological.

Physiological reactivity is a response adequate to the nature and intensity of the impact, which has an adaptive nature.

Pathological reactivity is an organism's reaction, inadequate to the degree of severity and nature of changes in life activity, which leads to a decrease in its adaptive capabilities.

According to the forms of manifestation, reactivity is distinguished as increased (hyperergy), decreased (hyperergy, anergy), perverse (dysergy).

1. Hyperergy – the predominance of excitation processes, which causes a more violent course of inflammation, a high intensity of the manifestation of symptoms of diseases with pronounced changes in the function of organs and systems.
2. Hypergia (anergia) – predominance of inhibition processes, which leads to a sluggish, asymptomatic course of inflammatory diseases.
3. Positive hypergia is a decrease in the external manifestations of reactions associated with the development of active defense reactions.
4. Negative hypergia – a decrease in the external manifestations of the reaction with suppression, damage, exhaustion of the mechanisms that regulate the body's reactivity (slow wound healing after a long and severe infection).
5. Dysergia – an atypical, perverted reaction to the action of any factors. Examples:

Atypical reaction of the patient to any medicinal product.

Perverted reaction to the effect of cold (dilation of blood vessels and increased sweating).

Factors affecting the body's reactivity

1. Age.
2. Sex.
3. Heredity.
4. Constitution.
5. Functional state of nervous system.
6. Functional state of the endocrine system.
7. Functional state of the immune system.
8. The state of the connective tissue.
9. Environmental factors (climate, type of food, social conditions, action of mechanical, physical, chemical, biological factors, etc.).

Resistance – resistance of the body to the action of pathogenic factors.

In the process of evolution, the organism developed certain adaptive mechanisms to ensure its existence in the conditions of constant interaction with the environment, various factors of which could cause not only disruption of vital activity, but also death in the absence or imperfection of these mechanisms.

The concept of "reactivity" is closely related to the concept of "resistance". Reactivity is a general designation of resistance mechanisms, and resistance is an expression of reactivity as an active, protective, adaptive act, and is a qualitative indicator of reactivity.

Biological barriers

Barrier devices are physiological mechanisms of non-specific protection of the body against the action of pathogenic agents.

Biological barriers – these are specialized tissue structures that protect the body or its individual parts from the pathogenic influence of the environment and ensure the maintenance of homeostasis.

Barrier systems of the body are specialized organs and tissues or certain of their structures that affect the penetration of cells, macro- and micromolecules. Barrier systems are divided into internal (histohematic, membranes of cells and cell organelles) and external (skin and mucose tissue).

External barriers: the skin and its appendages, as well as mucose tissue with the glands present in them.

Internal barriers: 1) barrier organs and 2) histohematal barriers separating blood and tissues.

Barrier organs: liver, kidneys, spleen, lymph nodes, placenta.

Histogematic barriers – barriers of formation between blood and organs.

The functional characteristics of barriers depend on the biological and morphological characteristics of individual organs and tissues. A feature of each internal barrier is its selective permeability.

Currently, the following are distinguished:

1. ***Non-specialized histohematic barrier*** (properly histohematic barrier) – a barrier between blood and extracellular fluid.

2. ***Specialized histogematic barriers*** – barriers between blood and organ tissues:

– *hematoencephalic* – barrier between blood and brain tissues;

– *hematoplacental* – the barrier between the mother's blood and the body of the fetus;

– *hematoophthalmic* – barrier between blood and eye tissues and fluids;

– *hematothyroid* – barrier between blood and thyroid tissue;

– *hematotesticular* – the barrier between the blood and the tissue of the spermatic cord.

1. Non-specialized histohematic barrier – blood capillaries of vessels, the wall of which consists of endothelium and basement membrane (consisting of collagen fibers and glycosaminoglycans). Capillary walls separate blood plasma (approximately 3.5 L) and intercellular (interstitial) fluid (approximately 10.5 L).

Blood capillaries are the main structural element of internal barriers. The endothelium of capillaries, like the basement membrane in various organs, has morphological features characteristic of each organ. They are the morphological basis of the selective permeability of barriers.

Differences in the mechanisms of implementation of the barrier function depend on the structural features of the main substance (non-cellular formations that fill the space between cells). The main substance forms a membrane that envelops macromolecules of fibrillar proteins designed in the form of protofibrils, which constitutes the supporting core of fibrous structures. The basement membrane of capillaries is located directly under the endothelium, which includes a large number of neutral mucopolysaccharides. The basal membrane,

the main amorphous substance and fibers make up the barrier mechanism, in which the main reactive and labile link is the main substance.

2. Specialized histogematic barriers – hematoencephalic, hematoophthalmic, hematothyroid, hematocochlear, hematopleural, hematosynovial, hematotesticular, hematofollicular, placental, etc.

The barrier function is based on the following mechanisms:

- Dialysis.
- Ultrafiltration.
- Osmosis.
- Metabolic activity of cells included in the structure of the barrier.

The intensity of transport through the barrier depends on the needs of the organ, the state of hemodynamics, nervous and humoral influences, various influences of the internal and external environment.

The functional state of histohematal barriers can change with changes in sleep and wakefulness, starvation, overfatigue, trauma, exposure to chemicals (including drugs), ultrasound, electromagnetic waves, and radiation.

The permeability of histohematic barriers changes during pathological processes. Increased permeability increases the sensitivity of organs to intoxication and poisons, enhances tumor growth. A violation of the barrier function is associated with the possibility of autoimmune damage to organs and tissues.

Barriers of isolating type protect parenchymatous cells from contact with serum and xenogenic proteins. Restriction mechanisms:

The microstructure of the vascular wall, through which proteins almost do not penetrate – blood-brain barrier vessels, large arteries, aorta, muscle-type vessels (arterioles).

Functioning of auxiliary cells of the organ, which, even in the presence of permeability of blood vessels for proteins, isolate parenchymal cells on the pathways of extravascular transport of proteins (hematoencephalic, hematoneuronal, hematotesticular, hematoophthalmic).

Barriers of partially isolating type ensure the penetration of serum and xenogenic proteins from blood vessels into the interstitium (vascular plexuses of ventricles of GM, end lobes of salivary glands, bile capillaries of the liver, reticular and glomerular zones of the adrenal glands).

Barriers of the non-isolating type permeable to serum and xenogenic proteins according to the permeability coefficient, concentration and species specificity (cardiomyocytes, skeletal muscle fibers, medulla of adrenal glands, adipocytes).

Blood-brain barrier (BBB) – it is a set of physiological mechanisms and corresponding anatomical formations in the central nervous system (CNS), which participate in the regulation of the composition of the cerebrospinal fluid (CSF).

The hematoencephalic barrier regulates the penetration from the blood into the brain of BASs, metabolites, and chemicals that affect the sensitive structures of the brain, prevents the entry of foreign substances, microorganisms, and toxins into the brain.

The following are emphasized as basic provisions in the conceptions of the BBB:

1. Penetration of substances into the brain is carried out mainly not through the cerebrospinal tract, but through the circulatory system at the capillary-nerve cell level.

2. BBB is to a greater extent not an anatomical formation, but a functional concept that characterizes a certain physiological mechanism. Like any physiological mechanism existing in the body, the BBB is under the regulatory influence of the nervous and humoral systems;

Among the main factors that affect the BBB, the main one is the level of activity and metabolism of nervous tissue.

The main function that characterizes the BBB is the permeability of the cell wall. The necessary level of physiological permeability, adequate to the functional state of the body, determines the dynamics of the entry of physiologically active substances into the nerve cells of the brain.

BBB permeability depends on 1) the functional state of the body, 2) the content of mediators, hormones, and ions in the blood. An increase in their concentration in the blood leads to a decrease in the permeability of the BBB for these substances.

The functional scheme of the BBB includes, along with the histohematal barrier (HBB), neuroglia and the system of cerebrospinal fluid spaces. HHB has a dual function: regulatory and protective.

*Regulatory function*ensures relative constancy of physical and physicochemical properties, chemical composition, physiological activity of the organ's intercellular environment, depending on its functional state.

Protective function HHB consists in the protection of organs from the entry of foreign or toxic substances of endo- and exogenous nature.

Histological structure of BBB:

The main component of the BBB, which provides its functions, is the wall of the capillary of the brain.

Mechanisms of substance penetration into brain cells:

– through the cerebrospinal fluid, which serves as an intermediate link between the blood and the nerve or glial cell, which performs a nutritional function (the so-called cerebrospinal fluid pathway);

– through the capillary wall.

The functioning of the BBB:

Processes underlying the operation of the BBB:

Dialysis.

Ultrafiltration.

Osmosis.

Change in electrical properties.

Solubility in lipids.

Tissue affinity.

Metabolic activity of cellular elements.

Hematoplacental barrie rregulates the flow of various substances, including medicines, from the mother's blood to the fetus and back.

Functionally, but not morphologically, the placental barrier is similar to the blood-brain barrier, but differs from it in that it participates in the metabolism of two organisms that have significant independence. The morphological basis of the placental barrier is the epithelial cover of the villi of the placenta, which is in contact with the epitheliocytes of the capillaries located in them. The hematofollicular barrier is formed by the cells of the inner theca of the maturing follicle and the follicular epithelium. The trophic needs of the maturing egg are provided by granuloma cells, since there is no direct contact between the follicular fluid and the egg. Follicles that undergo atresia do not have a hematofollicular barrier.

Hematotesticular barrier form the walls of blood vessels that have a solid endothelium, their own shell of the seminiferous tubules, Sertoli cells, interstitium and the protein shell of the testicles. These structures ensure high selectivity of the penetration of substances into the seminiferous tubules and isolate the spermatogenic epithelium from the body's own immune system. When the blood-testicular barrier is damaged (injury, high temperature, infections – viral parotitis, tuberculosis), auto-Ags are formed, which induce the synthesis of the corresponding auto-Ats, which cause testicular cell damage and spermatogenesis.

Damage and disruption of barrier function precedes the development of any pathological process. Not only the method of exposure of the pathogenic factor and the extent of damage is important for the pathogenesis of the disease, but also the ability of various barriers localized within intact tissues to participate in the development of protective and compensatory reactions.

Disorders of phagocytosis and the system of mononuclear phagocytes

Phagocytosis – the process of absorption and digestion of microbes and animal cells by various connective tissue cells – phagocytes.

The doctrine of phagocytosis was created by the outstanding scientist-embryologist, zoologist and pathologist I. I. Mechnikov, who should be considered the first in the doctrine not only of phagocytosis, but also of immunity. In 1908, he received the Nobel Prize in Physiology for the creation of the cellular theory of immunity.

Phagocytosis is an important part of the body's non-specific resistance. It ensures the development of pre-immune and immune responses, removes immune complexes from the bloodstream, preventing immune complex diseases. During phagocytosis, its executors implement a complex set of protective and adaptive mechanisms, which include not only a cytotoxic or bactericidal effect on the object of phagocytosis, but also the secretion of inflammatory mediators (exocytosis), activation of the energy metabolism of phagocytes.

Cells capable of phagocytosis are called phagocytes. The process of phagocytosis is carried out with the participation of the following cells:

1. *Polymorphonuclear phagocytes* (mainly neutrophils).

2. *System of mononuclear phagocytes*. This system includes monocytes and cells that are their derivatives:

- connective tissue macrophages,
- Kupffer cells in the liver,
- alveolar macrophages of the lungs,
- macrophages of the central nervous system,
- free and fixed spleen macrophages,
- macrophages of serous cavities,
- osteoclasts,
- microglial cells of the central nervous system.

3. The ability to phagocytosis is characteristic of eosinophils and basophils, but this type of activity is not the main one for them.

4. Platelets can participate in phagocytosis.

5. Some prolymphocytes are capable of phagocytosis, but mature lymphoid cells are not phagocytes.

Episodically, other cells that do not belong to the blood system (nerve and epithelial cells) can phagocytose.

"Professional" phagocytes.

Monocytes and tissue macrophages belong to "professional" phagocytes, that is, to the system of mononuclear phagocytes (the former name is the reticuloendothelial system). These cells are characterized by a high capacity for phagocytosis and pinocytosis. On their membranes there are receptors for fixation of Ab, due to which they are able to carry out immune phagocytosis both with fixation of complement and without it.

Mechanisms of phagocytosis disruption and their consequences

Violation of the process of phagocytosis can be the result of a violation of the processes that occur in the phagocytes themselves, or be the result of a violation of opsonization processes. In some cases, the very objects of phagocytosis make the process of phagocytosis impossible.

1. Violation of the phagocyte system. These violations may be related to:

– with impaired phagocyte motility (occurs with "lazy leukocyte" syndrome, impaired energy supply of cells, with Chediak-Higashi syndrome),

– with a violation of the adhesiveness of phagocytes (occurs with congenital or acquired pathology of phagocyte receptors to Ig and complement components, with a violation of the adhesive glycoprotein of membranes),

– with impaired endocytosis (occurs in the same syndromes as impaired phagocyte motility),

– with a violation of bactericidal properties, which may be associated with the pathology of lysosomes or the insufficiency of their enzymes (incomplete phagocytosis takes place).

2. Violation of opsonization systems. It occurs when there is a lack of substances that perform the function of opsonins. This is observed in immunodeficiencies, disorders of the complement system, etc.

3. Disorders of phagocytosis associated with the object of phagocytosis. A number of objects of phagocytosis (for example, mycobacterium tuberculosis, dust particles) cannot be digested by phagocytes due to the presence of protective mechanisms in these objects against phagocyte systems (in mycobacterium tuberculosis), or due to the lack of appropriate neutralization mechanisms in phagocytes (for particles dust). As a result of their inability to cope with these pathogenic agents, they begin to release lysosomal enzymes into the location of the pathogenic agents, which leads to the development of chronic inflammation, stimulation of fibroblasts and the development of sclerosis.

The system of phagocytes and diseases associated with disorders of its functions

Violation of chemotaxis of phagocytes

Violations of phagocyte mobility are found in many patients with recurrent severe infections. This may be the result of a defect in the cells themselves, the presence of chemotaxis inhibitors in the blood, or a lack of chemotaxis factors. In some patients, the basis of neutropenia may be a violation of the mobility of neutrophils. With the so-called in the syndrome of "lazy leukocytes" unchanged neutrophils are present in the central nervous system, but their voluntary migration and chemotaxis are reduced. Probably, the defect consists in a violation of the ability to migrate from the red bone marrow into the vascular bed.

Causes of chemotaxis disorders:

1. Cellular defects

Chediak-Higashi syndrome.
Panhypogammaglobulinemia.
Neutropenia.
IgE-hyperimmunoglobulinemia (Job's syndrome).
IgA-hyperimmunoglobulinemia.
Chronic kidney failure.
Enteropathic acrodermatitis.
Leukosis.
Kartagener's syndrome.
Schwachmann's syndrome.
Ichthyosis
Down syndrome (trisomy 21).
Measles.
Severe course of eczema on the background of infections.

2. Circulating inhibitors

Wiskott-Aldrich syndrome.
Rheumatoid arthritis.
Hodgkin's disease (lymphogranulomatosis).
IgA myeloma.
Chronic candidiasis of the skin and mucose tissue.
Periodontitis.
Bone marrow transplant.
Cirrhosis.

3. Insufficient production of chemotactic factors

Absence of the C5 component of complement.
Anomaly of the Hageman factor.
Systemic lupus erythematosus.
Violation of the activation of the C3 component of complement system.
Insufficiency of Ig.

Setting up the experiment. Discussion the results and formulation the conclusions

Experiment No. 1: study of the barrier function of the mucous membranes of the respiratory tract.

1. Fix the rabbit. Put a pneumograph on the chest, connect it with a rubber tube to the capsule Moray and record the output breath.
2. Bring a cotton ball soaked in ammonia to the external respiratory tract of the animal, record changes in breathing. Repeat the effect on the respiratory tract with ammonia. Pay attention to the duration of the breath stop after each subsequent irritation. Draw a pneumogram.

Experiment No 2: study of the barrier properties of the skin.

1. In the experiment, take two frogs of the same mass, study the initial state.
2. Administrate 2–3 ml of 10 % magnesium sulfate solution, one into the spinal lymphatic bag, and the other into the stomach (using a syringe and probe).
3. Monitor the condition of the animals for 30 minutes. The first observation should be carried out 7–10 minutes after the injection of magnesium sulfate.
4. Pay attention to changes in reflex activity (rollover, corneal, pain reflexes) characteristic of magnesium sulfate intoxication.
5. Enter the results in the table.

Time	Frog No1	Frog No2
	2–3 ml of magnesium sulfate is injected into the dorsal lymphatic bag	2–3 ml of magnesium sulfate is injected into the stomach

Experiment No. 3: study of the blood-brain barrier.

1. Inject to the mice under the skin of 0.5–1 ml of 10 % trypan blue solution.
2. After 40 minutes kill the animal with ether.
3. Open the chest, abdominal cavity, skull.
4. Compare the intensity of staining of internal organs and the brain.

Discussion of the results of the experiment

Experiment 1. Short-term respiratory arrest was observed during inhalation of ammonia vapors. During repeated inhalations of ammonia vapors, the breath holding time is shortened.

Experiment 2. After the introduction of 3.0 ml of magnesium sulfate solution into the spinal lymphatic bag, after 30 minutes there is a decrease in mobility, weakening of reflexes, and respiratory disorders. The condition of the second frog, to which magnesium sulfate was injected into the stomach, did not change.

Experiment 3. 30 minutes after the injection of 0.5–1.0 ml of 1 % solution of trypan blue under the skin of a rat, an intense blue staining of all organs is revealed during an autopsy, while the brain tissue is not stained.

Formulation of conclusions based on the experiment

1. Due to the presence of a large number of receptors of the nervous system in the mucous membrane, reflexes of a protective nature can occur here. In the case of sudden entry of irritating gases or vapors into the respiratory tract, there is a reflex delay of breathing, as a result of which the entry of the harmful agent into the body stops.

2. With regard to many substances, the mucous membrane of the stomach and intestines has limited permeability. Some substances are absorbed by the mucous membrane in small amounts, for example, magnesium sulfate. Therefore, in this experiment, no noticeable signs of poisoning were detected after the introduction of magnesium sulfate into the digestive tract of animals. The second animal, to which magnesium sulfate was injected under the skin, soon showed signs of poisoning, which increased all the time.

3. The function of the blood-brain barrier is performed by the endothelium of the brain capillaries, as well as the meninges, the ependyma of the ventricles, and the choroid plexus.

Tasks for independent work

It is necessary to find out the general regularities of the functioning of the organism, the peculiarities of barrier devices, the main properties of leukocytes, to characterize phagocytosis as a biological phenomenon. Be able to explain the mechanism of occurrence. Analyze the errors with an explanation of the correct answers

List of questions and works to be studied:

1. Concept of reactivity.
2. Types and mechanisms of reactivity.
3. The importance of endogenous factors in the formation of pathological reactivity.
4. The influence of exogenous factors on the development of pathological reactivity. Mechanisms of changes in sensitivity to hypoxia under conditions of hypothermia. Value for the clinic.
5. The concept of barrier devices of the body. External and internal barriers.
6. Mechanisms providing the barrier role of the skin and mucous membranes.
7. Mechanisms providing the barrier role of blood, bone marrow, spleen, lymph nodes, liver, kidneys.
8. Histohematic barriers, the barrier role of cell membranes and cell organelles.
9. Significance of violation of the body's barrier functions in pathology.
10. The concept of phagocytosis.
11. Phagocytic theory of I.I. Mechnikova.
12. Classification of phagocytes, its principles.
13. Stages of phagocytosis, their mechanisms. Regulation of phagocytosis.

14. Pinocytosis and ultramicrophagocytosis.
15. Disorders of phagocytosis and their role in pathology.
16. Concept of the systemmononuclear phagocytes.
17. Principles of uniting cellular elements into the system of mononuclear phagocytes, its structure and functions.
18. Rolemononuclear phagocytes in specific immunological reactions.

List of practical skills that must be mastered:

Characterize the general regularities of the functioning of the organism, the peculiarities of barrier devices, the main properties of leukocytes, phagocytosis as a biological phenomenon and the main properties of tissue macrophages.

Situational tasks KROR-1 to determine the final level of knowledge

1. Non-specific factors protecting the oral cavity from the penetration of pathogenic microorganisms play an important role in the general system of physiological resistance of the body. Which of the components in the oral cavity is the most important factor of non-specific protection?

A. β-lysine. *C. Complement.* *E. Properdin.*
B. Phagocytosis. *D. Lysozyme.*

2. The periodontist needs to evaluate the patient's factors of non-specific resistance of saliva and secretions of the mucous membranes of the oral cavity. What factor of non-specific resistance should be studied in the researched material in the first place?

A. Complement. *C. Lysozyme.* *E. Interferon.*
B. Secretory IgA. *D. Properdin.*

3. In patients with chronic granulomatosis, saprophytes cause serious diseases. What mechanisms cause the manifestations of this disease?

A. Gammaglobulin deficiency in the blood.
B. Violation of phagocytosis.
C. Absence of the thymus gland.
D. Deficiency of the T-lymphocyte system.
E. Disorders in the complement system.

4. In a practical session, students studied a stained blood smear of a mouse with bacteria phagocytosed by leukocytes. What organelle completes the digestion of these bacteria?

A. Ribosomes. *C. Lysosomes.* *E. Mitochondria.*
B. Golgi apparatus. *D. Granular endoplasmic reticulum.*

5. When examining patients with periodontitis, the degree of periodontal tissue damage was noted to depend on the amount of lysozyme in saliva and gingival fluid. What is the indicator of the body's protection under investigation?

A. Non-specific resistance. *C. Cellular immunity.* *E. Humoral immunity.*
B. Autoreactivity. *D. Tolerance.*

6. As a result of the viral process in the submaxillary salivary glands, significant sclerosis of their parenchyma occurred and the production of biologically active hormonal substances decreased. Because of this, regeneration of CO in the oral cavity was disturbed. The reason for this is insufficient content in saliva:

A. Mumps. *D. Growth factorepithelium.*
B. Thymocyte-transforming factor. *E. Insulin-like factor.*
C. Lysozyme.

7. In the experiment, a significant number of stem cells of the ChKM were destroyed in a certain way. Renewal of which cell populations in the composition of loose connective tissue will be inhibited?

A. Fibroblasts. *C. Macrophages.* *E. Pericytes.*
B. Pigment cells. *D. Lipocytes.*

8. A 15-year-old girl has a history of frequent purulent diseases. In the blood - leukopenia, neutropenia, impaired formation of lysosomes, incomplete phagocytosis. What is the most likely diagnosis?

A. Chronic granulomatosis. *D. Chediak-Higashi syndrome.*
B. Complement deficiency. *E. Alder's disease.*
C. Thymus hypoplasia.

Standards of correct answers to the task KROK-1

1	2	3	4	5	6	7	8
D	*C*	*B*	*C*	*A*	*D*	*C*	*D*

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Topic 4. Immunological reactivity disorders

Justification of the topic: Immunological reactivity provides the body's response to an antigenic stimulus, it provides control over the individual antigenic composition of the body, inactivation, removal of foreign antigens from the body, i.e. immunity. One of the disorders of immunity are immunodepressive and immunodeficient states, which significantly affect the development and course of diseases.

Purpose of the lesson:

General – to be able to characterize the regularities of immunodepressive and immunodeficient states.

Specific:

Know:

1. Immunodepressive and immunodeficient states, types of immunodeficient states
2. To determine the cause, mechanism of development and manifestations of acquired immunodeficiency syndrome

Be able to:

1. To characterize the structure of the immunocompetent system.
2. Explain the functions of individual cells of the immunocompetent system.
3. To analyze the mechanisms of immunological reactivity.
4. To analyze the mechanisms of high- and low-dose immunological tolerance.
5. To explain disorders leading to acquired insufficiency of the immune system – immunodepressive states.

Practical experience:

To justify the mechanisms of immunological reactivity, immunological tolerance, to explain the disorders leading to the acquired insufficiency of the immune system – immunodepressive states.

Graphological structure on the topic: Disorders of immunological reactivity

Material and methodological support:

1. Lectures;
2. Methodological developments for teachers;
3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational tasks to determine the final level of knowledge;
6. A set of "KROK-1" tasks;
7. A set of diagrams and tables (presentation);
8. Video films;

Oriented map of students work on the topic "Disorders of immunological reactivity"

No	Stage of lesson	Academic time	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of knowledge	10	Control of theoretical training of students using a programmed method using constructive answers to card questions	Test control, card questions.	Study room

No	Stage of lesson	Academic time	Educational guide		Place holding a class
			Educational tools	Equipment	
2	Solving educational tasks on the following topics: 2.1 Analysis of theoretical material	10 45	Analysis of the theoretical material is carried out on the basis of control questions of the topic and “Krok-1” tasks	Topic control questions, "Krok-1" tasks.	Study room
2	The final stage of determining the level of knowledge and skills. Summing up	25	Determination of the initial level of formation of knowledge and skills	Solving situational tasks	Study room

The biological significance of the system of immunobiological surveillance (IBN) consists in the control (surveillance) of the individual and homogeneous cellular and molecular composition of the organism. Detection of a carrier of foreign genetic or antigenic information is accompanied by its inactivation, destruction and, as a rule, elimination. At the same time, the cells of the name system are able to store the "memory" of this agent. Repeated contact of such an agent with the cells of the immune system is accompanied by the development of an effective response, which is formed with the participation of both specific (immune) and non-specific defense mechanisms.

Immune system – a complex of organs and tissues that contain immunocompetent cells and ensures the antigenic individuality and homogeneity of the organism by detecting and, as a rule, destroying and eliminating foreign antigens from it.

The substrate for the development of the immune response are the organs, tissues and cells functionally united in the immune system. The immune system consists of central and peripheral organs.

To the central (primary) organs belong the red bone marrow and the thymus gland. There is an antigen-independent distribution and maturation of lymphocytes, which later migrate to the peripheral organs of the immune system.

To peripheral (secondary) organs include the spleen, lymph nodes, tonsils, lymphoid elements. Both antigen-independent and antigen-dependent proliferation and differentiation of lymphocytes occur in these organs. As a rule, mature lymphocytes first come into contact with Ag precisely in the peripheral lymphoid organs.

Immunocompetent cells

Immunocompetent cells include T- and B-lymphocytes, NK-cells and antigen-presenting cells.

T-lymphocytes develop in the thymus from precursor cells; B-lymphocytes differentiate in the fetal liver and the red bone marrow of an adult organism; NK cells are formed from precursors of lymphoid cells in the BM.

Lymphocytes, like other leukocytes, express a large number of different molecules on their surface, with the help of which monoclonal antibodies identify their belonging to a specific cell population. Most often, for this

purpose, differentiating antigens (CD), which are specific cell markers, are detected. Among them, 1) linear cell markers, 2) maturation markers and 3) activation markers are distinguished.

B-lymphocytes. This subsystem is formed by different clones of B-lymphocytes. They mature in the BM, as well as possibly in peyer's plaques, tonsils, certain areas of the spleen and LN. B-lymphocytes originate from hematopoietic stem cells of the BM.

B-lymphocytes are the effector links of the humoral immune response. The B-lymphocyte membrane has an Ag receptor – IgM monomer. From RBM lymphocytes migrate to thymus-independent zones of lymphoid organs. The life span of most B-lymphocytes does not exceed 10 days, unless they are activated by Ag.

Mature B lymphocytes (plasma cells) produce antibodies – Ig of all known classes (IgG, IgM, IgA, IgD, IgE).

Antibodies (Ab) – these are proteins (immunoglobulins – Ig), which are synthesized under the influence of antigens and specifically interact with them.

T-lymphocytes. The T-lymphocyte subsystem is represented by various clones of T-lymphocytes. Their proliferation and differentiation occurs under the control of the thymus gland. T-cells, like B-lymphocytes, develop from the stem cells of the central nervous system. From here, in the form of precursor cells, T-lymphocytes enter the thymus with the blood, where their antigen-independent maturation occurs.

The main functions of T-lymphocytes

✓ Cytotoxicity (killer function) – the ability to destroy (kill) cells that carry antigens on their surface.

✓ Cooperative (helper) function - the ability to ensure the interaction of different subpopulations of T-lymphocytes, B-lymphocytes and macrophages.

✓ Synthetic function (secretory) – formation of biologically active substances - lymphokines.

✓ Suppressive function – suppression of excessive immune response, participation of T-lymphocytes in the formation of immunological tolerance.

Accordingly, specialized subpopulations of T-lymphocytes distinguish the specified functions: T-killers, T-helpers, T-suppressors, T-producers of lymphokines.

T-lymphocytes recognize Ag that has been previously processed and presented on the surface of antigen-presenting cells.

T-lymphocytes (thymus-dependent) are responsible for the cellular immune response, and also help to respond to Ag B-lymphocytes in the humoral immune response.

NK cells (natural (natural) killers) make up to 15% of all blood lymphocytes. They do not have surface determinants characteristic of T- and B-lymphocytes, they do not have a T-lymphocyte receptor. NK cells recognize and destroy tumor and virus-infected cells; defect of NK cells is the cause of chronic infections.

Antigen presenting cells present mainly in the skin, LN, spleen and thymus.

These include:

- macrophages, monocytes;
- dendritic cells,
- follicular progenitor cells of the LN and spleen,
- Langerhans cells,
- M cells in the lymphatic follicles of the digestive tract,
- epithelial cells of the thymus gland.

These cells a) capture, process and present Ag on their surface to other immunocompetent cells (T-helpers), 2) produce IL-1 and other cytokines, 3) secrete prostaglandin E2, which inhibits the immune response. Phagocytic and cytolytic activity of macrophages is enhanced by γ-IFN.

Antigen presentation- a process in which phagocytes move parts of absorbed material back to their surface and "give" them to other cells of the immune system – T-helpers.

In the mechanism of antigen recognition, there are two stages that are closely related to each other.

The first stage consists in phagocytosis and digestion of Ag.

At the second stage polypeptides, soluble Ag (serum albumins) and corpuscular bacterial Ag accumulate in phagolysosomes of macrophages. Then these peptides bind to glycoproteins of the major histocompatibility complex (MHC) of the cell, which carry out a return to the surface of the phagocyte, where they can be "presented" to T-helper lymphocytes.

Interaction of cells during the immune response

The immune response is possible as a result of the activation of lymphocyte clones and consists of two phases. In the first phase, Ag activates those lymphocytes that recognize it. In the second phase, these lymphocytes coordinate an immune response aimed at eliminating Ag.

Humoral immune response. In the humoral immune response, the effector cells are B-lymphocytes, antigen-presenting cells. Antibody formation is regulated by T-helpers and T-suppressors.

The macrophage absorbs Ag that has invaded the body and process it – splitting it into fragments. Ag fragments are exposed on the cell surface together with the MHC molecule. The MHC class II Ag-molecule complex is presented to the T-helper, which recognizes the MHC class II Ag-molecule complex on the surface of the antigen-presenting cell, which stimulates IL-1 secretion. Activated IL-1 T-helper synthesizes IL-2 and IL-2 receptors, through which the agonist stimulates the proliferation of T-helpers and cytotoxic T-lymphocytes. The biological meaning of this process lies in the accumulation of such a number of T-helpers that will ensure the formation of the required number of plasma cells in the lymphoid organs capable of producing antibodies against this Ag.

B-lymphocyte activation involves the direct interaction of Ag with Ig on the B-cell surface. Recognition by the T-helper receptor of the complex MHC class II Ag molecule on the surface of the B-lymphocyte leads to the

secretion of IL-2, IL-4, IL-5 and γ-IFN from the T-helper. Under their influence, the B-cell is activated and proliferates, forming a clone.

The activated B-lymphocyte differentiates into a plasma cell: the number of ribosomes increases, the granular endoplasmic reticulum and the Golgi complex become more pronounced.

The plasma cell synthesizes immunoglobulins (Ig). IL-6, secreted by activated T-helpers, stimulates the secretion of Ig. A part of mature B-lymphocytes after Ag-dependent differentiation circulates in the body as memory cells.

Cellular immune response. In the cellular immune response, effector cells are cytotoxic T-lymphocytes, the activity of which is regulated by T-helpers and T-suppressors. The specific effect of T-killer is manifested only as a result of close contact between it and the target cell, which is achieved due to the interaction of Ag on the surface of the victim with T-killer receptors.

System of factors of non-specific protection of the body

In addition to immunocompetent cells, cellular and humoral factors (constitutional factors) of the body's non-specific defense system also participate in the reactions of detection and elimination of foreign molecular and cellular structures. These include phagocytic cells, complement system factors, kinins, interferon, lysozyme, acute phase proteins and some others (see the topic "Pathology of reactivity").

Immunological reactivity – the ability of the organism to respond to the action of Ag by the formation of At and a complex of cellular reactions specific to this Ag.

Immune mechanisms are the central biological mechanism of reactivity and resistance, the main biological meaning of which is the maintenance of antigenic homeostasis. Immunological reactivity provides protection of the body against infectious agents, and also determines various types of non-infectious immunological processes.

Mechanisms of immunological reactivity:

- ***Humoral type of immune response*** aimed at extracellular bacteria and viruses. The effector link is Ab (Ig), which are products of the activity of mature B-lymphocytes (plasma cells).
- ***Cellular type of immune response***aimed at protection against intracellular infections and mycoses, intracellular parasites and tumor cells. The effector link is immune T-lymphocytes that carry specific receptors for this Ag.

IMMUNOPATHOLOGICAL CONDITIONS

Like any body system, the immune system is prone to pathological process. The branch of theoretical and practical medicine that studies patterns of immune system disorders that underlie various pathological processes and diseases is called immunopathology.

The basis of immunopathology is the inability of the immune system to ensure the antigenic homeostasis of the body (recognize "own" and "foreign"), to perform its normal protective functions ("own" not to be touched, "foreign" to be destroyed).

Immunodeficiency states, pathological tolerance, "graft versus host" reactions are the result of a defect or disruption of one or more links of the immune system, which normally provide an effective immune response.

Etiology of immunopathological conditions

Immunopathological conditions can be primary or secondary.

1. **The cause of primary violations –** inherited or congenital defect of the genetic program of immunocompetent cells, as well as cells that provide non-specific protection of the body.

2. **The reason for secondary violations –** disorders arising after birth at various stages of an individual's ontogenesis. They develop as a result of damage to the cells of the IBN system, which had a normal genetic program, under the influence of factors of a different nature:

- *Physical*.
- *Chemical*.
- *Biological*.

Pathogenesis of immunopathological conditions complex and has several development options.

• **Hyporegenerative**. It consists in inhibiting the proliferation of stem hematopoietic and/or polypotent, as well as other proliferating progenitor cells of the immune system.

• **Disregulatory**. Caused by disorders of the differentiation of antigen-presenting cells and/or T- and/or B-lymphocytes, as well as the cooperation of these cells.

Reasons

1. Change in the ratio of the number and/or effects of different categories of immunocompetent cells.

2. Violation of the content, number or sensitivity of receptors to them on the membranes of immunocytes, which leads to immunodeficiency and pathological tolerance.

• **Destructive (cytolytic)**. It consists in massive destruction of immunocytes.

Reasons

Defect of the immunocytes themselves.

Effect of cytolytic agents on immunocompetent cells. With massive destruction of immunocytes, leukopenia and various immunopathological conditions develop.

Immunodeficiency states (IDS) – persistent or temporary changes in the immune status caused by a defect in one or more mechanisms of the immune response to antigenic influences.

As a rule, the basis of the development of IDS is the absence or deficiency of cells of the immune system and/or disorders of their functions. This determines the high frequency of development of various infectious, parasitic, tumor and allergic diseases in IDS. On the other hand, debilitating diseases often develop IDS.

IDS and immunodeficiencies are typical forms of pathology of the IBN system, which are characterized by a decrease in the efficiency or inability of the body's immune system to carry out reactions of destruction and elimination of foreign antigens.

Risk factors of immunodeficiency

- Adverse family history.
- Almost all bad habits.
- Aging.

Types of immunodeficiencies

Primary inherited and congenital (genetic) defects of the immune system.

Secondary – immune deficiency develops as a result of endo- and exogenous effects on the normal immune system (for example, about 90 % of all viral infections are accompanied by transient immunodepression)

Primary immunodeficiency states

According to the WHO nomenclature, primary immunological deficiency is understood as the genetically determined inability of the body to implement one or another link of the immune response.

According to the classification proposed by the WHO, depending on the predominant damage to the B- and T-links of the immune system, the following primary specific IDS are distinguished:

1. Combined with simultaneous (in the same or varying degrees of severity) damage to the cellular (T) and humoral (B) links of the immune system.
2. With predominant damage to the cellular (T) link of the immune system.
3. With predominant damage to the humoral (B) link of the immune system.

1. Combined T- and B-immunodeficiency

Severe combined T- and B-immunodeficiency is characterized by the occurrence of a defect in immunocompetent structures at the earliest stages of the body's development. A simultaneous and pronounced decrease in T- and B-lymphocytes, plasma cells is characteristic. It is clinically manifested by a sharp decrease in the body's reactivity and resistance to the action of various pathogenic factors (viruses, bacteria, fungi).

Swiss type of agammaglobulinemia

It is inherited according to the autosomal recessive type. Sex-linked and sporadic forms are possible. The mechanism of immunodeficiency is based on a genetic defect at the level of the enzymes adenosine deaminase and purine nucleotide phosphorylase, which leads to disruption of adenosine metabolism. As a result, the production of hypoxanthine is blocked and ATP accumulates excessively in the tissues, which blocks the maturation of T cells.

The pathogenesis of the disease is due to a deficiency mainly of T-lymphocytes and to a lesser extent of B-lymphocytes when their maturation and functional activity (the ability to transform into plasma cells) is impaired.

Manifestations of the disease observed already in the first weeks of life:

Severe recurrent inflammatory processes of viral, bacterial, parasitic and fungal etiology.

Hypoplasia of the thymus and lymphoid tissue, especially LN.

Lymphocytopenia, hypogammaglobulinemia.

A decrease in the level of Ig in blood serum (traces of IgG, absent IgM and IgA).

Without treatment, children die in the first 2 years of life. The only effective method of treatment is transplantation of BM.

Louis-Bar syndrome (ataxia-telangiectasia)

The first signs of the disease appear in the period from 5 months to 3–5 years. It is inherited according to the autosomal recessive type. The disease is associated with a defect in the kinases involved in the regulation of the cell cycle. The defect is localized in chromosome 11q22.

It is characterized by a decrease in the number and maturation characteristics of T- and B-lymphocytes. Among T-lymphocytes, the T-helper subpopulation is mainly affected. Insufficiency of B-lymphocytes is manifested by a decrease in the level of Ig.

Manifestations of the disease:

1. Neurological disorders (ataxia, incoordination, speech disorders, slurred speech, nystagmus) are manifestations of congenital cerebellar atrophy.
2. Damage to small vessels: telangiectasias (local expansion of blood vessels) of the skin.
3. Mental disorders (mental retardation).
4. Endocrine pathology (disruption of adrenal glands, gonads, etc.).
5. Recurrent viral, bacterial, parasitic and fungal diseases.
6. Hypoplasia of the thymus gland.
7. Lesions of the musculoskeletal system: development of kyphosis, scoliosis, kyphoscoliosis, chest deformation.
8. Lymphocytopenia.
9. A significant decrease in the level of Ig, especially IdA, IgE, IgG isotypes.
10. Frequent development of tumors (especially in the lymphoid system).
11. Patients die from the progression of infections and malignant neoplasms. Life expectancy rarely reaches 20–30 years.

Wiskott-Aldrich syndrome

The disease is sex-linked (X-linked type of disease). Characteristic violation of activation of CD4+ and CD8+ – cells, production of IgG to capsular bacteria (patients do not produce antibodies to polysaccharides). Immediately after birth, the damage to the T-system is not manifested, but over time, the number of lymphocytes in the T-zones of the LN progressively decreases and the reactions of cellular immunity are suppressed. Despite the normal number of B-lymphocytes, the production of natural antibodies and the production of antibodies for immunization with polysaccharide antigens are acutely suppressed.

Manifestations of the disease:

- Skin damage (eczema).
- Recurrent inflammatory processes of viral, bacterial, parasitic and fungal etiology.
- Hemorrhagic syndrome due to thrombocytopenia (petechial rash, bleeding).
- A decrease in IgM in the blood with a normal content of IgG and an increased content of IdA and IgE. The development of malignant neoplasms (in approximately 10% of cases).
- Life expectancy of children does not exceed 10 years.

2. Immunodeficiencies with a predominant violation of the T-system of lymphocytes

The group of T-cell immunodeficiencies includes:

- ✓ DiGeorgi syndrome.
- ✓ Nezelof's syndrome.
- ✓ Chronic mucocutaneous candidiasis.

IDS with a predominant violation of the T-lymphocyte system is accompanied by a decrease in cellular immunity due to a pronounced decrease in the number and functional activity of T-lymphocytes (killers). Hypoplasia of the thymus is revealed.

The genetic block of reproduction and differentiation is possible in any period of T-lymphocyte genesis. Clinically, T-lymphocytic IDS is manifested by the development of viral and fungal infections of the skin, nails, scalp, disorders of the bronchopulmonary apparatus, intestines, and genitals. Often the first signs of immunodeficiency are thrush, complications after BCG vaccination, severe forms of infections caused by the herpes simplex virus of the 1st and 2nd serotypes and the varicella-shingles virus.

2 forms of T-type immunological deficiency are quite fully described – Di Giorgi syndrome and Nezelof syndrome.

DiGeorgi syndrome

It develops as a result of defects in embryonic development (violation of the formation of the 3rd and 4th parapharyngeal gill pockets in the embryonic period). Possible deletion of chromosome 22. It is characterized by a violation of the differentiation of precursor cells of T-lymphocytes into T0-lymphocytes, due to which the reactions of cellular immunity are acutely suppressed (immune response of the cellular type is impossible); humoral immune response is reduced, but preserved.

Manifestations of the disease:

1. Facial defects (low-lying ears, split along the middle line of the face ("wolf's mouth"), underdeveloped jaw, hypertelorism, etc.).
2. Congenital pathology of the heart and main vessels.
3. Hypocalcemic convulsions (appear 1–2 days after birth).
4. Hypoplasia of the thymus and parathyroid glands.
5. Increased susceptibility to infections.

6. A decrease in the content of T cells in the blood (CD3+, CD4+, CD8+) and their functional activity.

7. Suppression of delayed-type hypersensitivity reactions (HST) (in particular, transplant rejection) while maintaining humoral immunity.

8. Normal B-cell immunity.

9. Microscopically: there are no thymus-dependent zones of the LV and spleen.

Nezelof's syndrome

Characteristic aplasia of the thymus gland without aplasia of the parathyroid glands. The genetic defect is transmitted according to the autosomal recessive type. The transformation of T0-lymphocytes into T1-lymphocytes is disturbed, as a result of which the cellular mechanisms of the immune response cannot be carried out. Reactions of humoral immunity can be preserved.

Manifestations of the disease

From the neonatal period, recurrent infectious processes (of viral and fungal etiology).

Lymphocytosis

3. Immunodeficiencies with a predominant violation of the B-system of lymphocytes

Diseases are characterized by a normal level, but reduced functional activity of B-lymphocytes, a reduced number of plasma cells and Ab. Against the background of acutely suppressed humoral immunity, normal cellular immunity is observed.

In patients, the frequent development of purulent infections, autoimmune processes and a slight decrease in resistance to viruses and fungi are noted.

Clinical forms of predominant B-system deficiency of lymphocytes – Bruton's agammaglobulinemia, Job's syndrome, selective deficiency of IgG isotypes, or IgA, or IgM.

Bruton's agammaglobulinemia (Bruton's disease)

The disease is linked to the X-chromosome and has a recessive type of inheritance. Only boys who have a set of sex chromosomes XY are sick.

Dysgammaglobulinemia

In these conditions, there is a decrease in the blood of one or two classes of Id with a normal or increased content of others. The development of pathology is associated with a violation of the mechanisms of control over the synthesis of Id and the switching of their products from one class to another. Variants of selective Ig deficiency:

- Selective deficiency of IdA
- Selective deficiency of IdM
- Selective IgG deficiency (IgG2 and IgG4)
- Selective IgE deficiency
- At deficiency in normo- or hypergammaglobulinemia.

Among the specified selective Ig deficiencies, IdA deficiency is the most common (1/500–1/700 people). There are data on family cases.

Selective IgA Deficiency. The condition develops due to the inability of B-lymphocytes to differentiate into IgA-secreting cells. It is transmitted as an autosomal recessive, sometimes dominant trait. It is diagnosed in children older than 1 year, if the concentration of IgA in the blood serum is below 5 mg% with a sufficient level of other classes of Ig and the absence of signs of other IDS (for example, ataxia-telangiectasia). Manifested by various symptoms; in some cases it can be asymptomatic. Frequent manifestations are recurrent infections of the respiratory tract, urogenital tract, and intestines. A low level of IgA determines susceptibility to allergies.

Selective IgM Deficiency. From an early age, recurrent infections of various localization (staphylococcal pyoderma, meningococcal septicemia, ulcerative colitis with prolonged diarrhea). Meningococcal infection in individuals with IDM deficiency is often fatal.

Selective Deficiency of IgG. Defficiency of one or more subclasses of IgG. At the same time, the concentration of IgA and IgM is within the normal range or slightly increased. With IgG deficiency, respiratory and bronchopulmonary infections are observed, often caused by pneumococci and influenza.

Secondary immunological deficiency

Secondary (acquired) immunodeficiencies (ID) – violations of the body's immune protection occurring in the postnatal period as a result of external or internal factors, not related to the primary damage to the genetic apparatus.

Acquired ID is extremely diverse, accompanied by damage to both the T and B immune systems, and often both systems.

Causes of secondary immunodeficiency:

- Transient ID in newborns and the elderly.
- Insufficiency of nutrition, digestion, as well as intestinal absorption.
- Severe inflammatory processes.
- Infections (measles, rubella, leprosy, etc.).
- Tumors
- Loss of serum proteins.
- Hypoxia.
- Hypothyroidism.
- Uremia (chronic kidney failure).

Principles of ID therapy and prevention

General tactics of treatment of ID

Treatment is determined by the type of ID.

In case of severe pathology of T cells, transplantation of BM is indicated.

In case of IgG insufficiency – intravenous administration of solutions containing Ig.

Live vaccines should not be given to ID patients and their family members.

Transfusion of fresh blood and blood products is contraindicated in cellular ID.

Ig and plasma should not be administered to patients with selective IgA deficiency.

Intramuscular injections should be avoided with thrombocytopenia.

Prescribing antibiotics before surgical or dental interventions.

Drug therapy of ID

In almost all forms, the appointment is necessary:

- antibiotics (for the prevention and immediate treatment of infections),
- immunostimulants.

With humoral and combined ID – replacement therapy with immunoglobulins.

In case of insufficiency of adenosine deaminase – replacement therapy with an enzyme conjugated with polyethylene glycol. Gene therapy (corrected T-lymphocytes of the patient) is also carried out.

Complications of ID

- Autoimmune diseases.
- Development of serum sickness during treatment with Y-globulin.
- Development of malignant neoplasms.
- Severe infections.
- Graft-versus-host reaction (usually as a result of blood transfusion in patients with severe combined ID).

Prevention of IS. Medical and genetic counseling is necessary for primary ID.

Tasks for independent work

It is necessary to substantiate the mechanisms of immunological reactivity. Explain the mechanisms that enable the body to produce antibodies against all antigens that are present in nature and created artificially. Analyze the errors with an explanation of the correct answers

List of questions and works to be studied:

1. The concept of immunity and immunological reactivity.
2. Physiological and pathological immunological reactivity.
3. Specific and non-specific, cellular and humoral mechanisms of immunological reactivity (immune reactions).
4. The concept of immunodeficiency and immunodepressive conditions.
5. Classification of immunodeficiency states. Features of individual species.
6. Immunodeficiencies associated with a violation of T-lymphocytes.
7. Immunodeficiencies associated with B-lymphocyte disorders.
8. Combined immunodeficiency states.
9. Etiology, pathogenesis of acquired immunodeficiency syndrome (AIDS).
10. Immunological tolerance.
11. Pathophysiological basis of transplantation of organs and tissues.

List of practical skills that must be mastered:

Mechanisms of immunological reactivity, to analyze the mechanisms of protection of the mucous membrane of the oral cavity, mechanisms of high- and low-dose immunological tolerance, to explain disorders leading to acquired insufficiency of the immune system - immunodepressive states.

Situational tasks KROK-1 to determine the final level of knowledge

1. In a patient with clinical signs of primary ID, a violation of the function of antigen presentation to immunocompetent cells was found. The defect in the structures of which cells is possible?

A. Fibroblasts. *C. Macrophages, monocytes.* *E. 0-lymphocytes.*
B. T-lymphocytes. *D. B-lymphocytes.*

2. For the diagnosis of generalized herpetic infection, blood serum was examined in order to detect specific Ab of a certain class. Which type indicates the acute stage of a viral infection?

A. Ig M. *B. IgA.* *C. Ig E.* *D. Ig G.* *E. Ig D.*

3. In the second year of his life, the boy often began to suffer from respiratory diseases, stomatitis, pustular lesions of the skin. Even small injuries to the skin (gums) are complicated by long-term inflammation. It was established that the blood of the child is practically devoid of Ig of all classes. A decrease in the functional activity of which cell population underlies the described syndrome?

A. NK lymphocytes. *C. Neutrophils.* *E. T-lymphocytes.*
B. B-lymphocytes. *D. Macrophages.*

4. During the examination of a patient who has been taking glucocorticoids for a long time, lymphopenia was found. How can the functional state of the patient's immune system be characterized?

A. Secondary immunodeficiency. *D. Tolerance to autoantigens.*
B. Primary immunodeficiency. *E. Anaphylaxis .*
C. Congenital immunodeficiency.

5. When examining the state of the immune system of a patient with chronic fungal lesions of the skin, a violation of cellular immunity was revealed. The decrease of which indicators is the most characteristic in this case?

A. Immunoglobulins G. *C. T-lymphocytes.* *E. Plasma cells.*
B. Immunoglobulins E. *D. B-lymphocytes.*

6. A two-year-old child was diagnosed with hypoplasia of the thymus. Which indicator of the state of the immune system is most characteristic of this immunodeficiency?

A. Decrease in the number of B-lymphocytes.
B. Deficiency of T and B lymphocytes.
C. Decrease in the number of T-lymphocytes.
D. Absence of plasma cells.
E. Decrease in immunoglobulins M.

7. The patient has DiGeorgi syndrome, which is based on hypoplasia of the thymus gland. What form of immune pathology does this disease belong to?

A. Congenital B-lymphocyte deficiency.
B. Purchased B-lymphocyte deficiency.
C. Aquired deficiency of T-lymphocytes.
D. Congenital deficiency of T-lymphocytes.
E. Immunodepression in the T-lymphocyte system.

8. Mice with no hair cover (i.e., nude) did not have cellular reactions of the delayed type. For this pathology, the most probable are:

A. Absence of the thymus gland.

B. Absence of gammaglobulins in the blood.

C. Disorders of hematopoiesis.

D. Phagocytosis defect.

E. Deficiency of components of the complement system.

9. When registering a child for school, a Mantoux test was performed to resolve the issue of the need for revaccination, which turned out to be negative. What does this test result indicate?

A. Absence of cellular immunity to tuberculosis.

B. Absence of Ab to tuberculosis bacteria.

C. Presence of cellular immunity to tuberculosis.

D. Lack of antitoxic immunity to tuberculosis.

E. The presence of At to tuberculosis bacteria.

10. The patient's blood test revealed signs of HIV infection. Damage to which immunocompetent cells is characteristic of AIDS?

A. T-helpers. *C. B-lymphocytes.* *E. Neutrophils.*

B. T-killers. *D. Macrophages.*

Standarts of correct answers to the KROK-1 task

1	2	3	4	5	6	7	8	9	10
C	*A*	*B*	*A*	*C*	*C*	*D*	*A*	*A*	*A*

Recommendations for registration of work results

1. Written answer to test tasks (initial level of knowledge).

2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.

3.. Protocol for solving situational tasks with an explanation of the correct answers.

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Topic 5. Allergy

Justification of the topic: Currently, humanity is experiencing a rapid increase in the frequency of allergic reactions. Among the reasons for this, it is possible to note improper nutrition, uncontrolled use of drugs, especially antibiotics. An important factor that determines the growth of allergic diseases is the development of the chemical industry, the production of synthetic materials, paints, solvents and other chemical compounds. Along with the increase in cases of allergic diseases caused by various allergens from the external environment, allergic diseases caused by endogenous allergens are currently attracting the attention of doctors. Modern ideas about the mechanisms of various allergic reactions were formed mainly on the basis of experimental studies of anaphylaxis and allergy.

Purpose of the lesson:

General – to clarify the causes and mechanisms of allergic reactions in humans and animals.

Specific:

Know:

1. Classification, causes, stages of allergic reactions, mechanisms of their development. 2. Prevalence of allergens in everyday life, at work, in medicine, the need for their regulation.

Be able to:

1. To explain the dialectical relationship between immunity and allergy as two sides of the same process based on immunological reactivity.

Practical experience:

1. To substantiate the relationship between immunity and allergy, the relationship of allergy to reactivity

2. In the experiment, reproduce the degranulation of basophilic granulocytes (tissue basophils) as one of the mechanisms of allergic reactions.

A graph of the logical structure of the topic "Allergy" is attached.

Material and methodological support:

1. Lectures;
2. Methodological developments for teachers;
3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational tasks to determine the final level of knowledge;
6. A set of KROK-1 tasks;
7. A set of diagrams and tables (presentation);
8. Video films;
9. For the experiment (experimental animals – rabbits; microscopes, histological preparations).

Oriented map of students work on the topic "Allergy"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of he initial level of knowledge	10	Control of theoretical training of students using a programmed method using constructive answers to card questions	Test control, card questions.	Study room
2	Solving educational tasks on the following topics: 2.1 Analysis of theoretical material. 2.2. Conducting an experiment	 45 25	Analysis of the theoretical material is carried out on the basis of control questions of the topic and "Krok-1" tasks. Introduction and preparation for setting up the experiment. Setting up the experiment	 Topic control questions, "Krok 1" tasks. Microscopes, histological drugs, rabbits	Study room
3	The final stage of determining the level of knowledge and skills. Summing up	10	Determination of the initial level of formation of knowledge and skills	Solving situational tasks	Study room

Allergy – this is a qualitatively changed reaction of the body to the action of substances of an antigenic nature, which causes various structural and functional disorders.

Allergic reactions are based on an immunological mechanism, and they are highly specific reactions.

Etiology of allergy

Ag that caused an allergy is called an allergen. Depending on the structure, allergens are complete and incomplete (haptens).

Hapten becomes an antigen only after connecting with proteins of body tissues.

By their nature, allergens are most often:

- proteins,
- protein-polysaccharide or protein-lipoid complexes (serum, tissue, bacterial allergens),
- complex compounds of a non-protein nature (polysaccharides, polysaccharide-lipoid complexes – house dust allergen, bacterial allergens),
- simple chemicals, including individual elements (bromine, iodine, chromium, nickel).

Classification of allergens

According to A.D. Ado (1970), exoallergens and endoallergens are distinguished depending on the origin.

Endogenous allergensare divided into:

1. ***Natural (primary).***

- Brain tissue.
- Lens tissue.
- Tissue of the gonads.
- Tissue of the thyroid gland.

2. *Acquired (secondary).*

• *Non-infectious:* cold, burn and radiation allergens (induce the formation of allergens in the body from body molecules by denaturing protein and other macromolecules and releasing new determinant groups).

• *Infectious*:

➢ Simple

➢ Complex (tissue-microbe, tissue-toxin, virus-induced), formed under the influence of infection.

Exogenous allergens are divided into:

1. *Infectious*: bacterial, viral, fungal (causing agents of tuberculosis, toxoplasmosis, brucellosis, measles, influenza, herpes, infectious hepatitis, candida, trichophytes, epidermophytes, actinomycetes, etc.).

2. *Non-infectious*:

Plant (pollen, plant sap).

Medicinal (vaccines, serums, antibiotics, sulfonamides, vitamins, insulin, preparations of arsenic, iodine, mercury, etc.).

Food (of animal and vegetable origin - cow's milk, eggs, meat, fish, citrus fruits, strawberries, chocolate, etc.).

Household (inorganic and organic substances of microbial origin – household dust, library dust, wool and dander of domestic animals, fluff of domestic birds, poisons of hymenoptera, bed mites, fish food, detergents, etc.).

Simple chemicals (ursol, benzene, formalin, etc.).

Stages of allergic reactions

Regardless of the type of allergic reaction, 3 stages can be distinguished in its development:

1. Stage of immune reactions (immunological). It includes:

Primary contact of the organism with Ag (sensitizing contact).

The period of sensitization (production and accumulation of specific At or sensitized T-lymphocytes).

Interaction of Ag with Ab.

Sensitization happens:

1) active – in the case of Ag immunization, when the own immune system is activated in response;

2) passive – in a non-immunized organism when blood serum is injected into it, which includes Ag, or cell suspensions with sensitized lymphocytes, obtained from a donor actively sensitized by this Ag.

In the immunological phase, two key points of allergy are determined – the type and form of the future allergic reaction.

2. Stage of biochemical reactions (biochemical, pathochemical)

The biochemical (pathochemical) stage consists in the fact that in response to the interaction of Ag with Ab or Ag with sensitized T-lymphocytes, the activation of target cells and biochemical factors of liquid environments (plasma, tissue fluid) occurs with the release or formation of biologically active substances (BAS) - allergy mediators. The first mediators of allergy involve other effector cells, other humoral factors with the formation of secondary mediators.

3. Stage of functional and structural changes (pathophysiological)

The pathophysiological stage is characterized by the appearance of clinical symptoms of allergy. Clinical manifestations of allergy are the result of pharmacological effects of allergy mediators and, therefore, depend on the set and number of allergy mediators.

The increased sensitivity of the body in such cases is specific: it manifests itself in relation to the allergen that previously caused the state of sensitization.

Nonspecific allergic reactions occur upon first contact with an allergen without prior sensitization. Their development goes through only two stages – pathochemical and pathophysiological. An allergen that enters the body itself causes the formation of substances that damage cells, tissues and organs.

Classification of specific allergic reactions

There are different classifications of specific allergic reactions. Among the existing classifications, the most widespread was proposed in 1968 by Gell and Coombs (P. Gell and R. Coombs), according to which 4 types of allergic reactions are distinguished. Currently, a modified classification is used, with 5 types of reactions. Each of these types has a special immune mechanism and its own set of mediators, which determines the clinic of the disease.

I, II, III, V types of allergic reactions belong to the category of humoral type reactions, since the efferent link of their development are B-lymphocytes and allergic Ab belonging to different classes of Ig. Allergic reactions of type IV are ensured by the involvement in the immune process of T-system lymphocytes, macrophages, target cells that are destroyed.

1. The first type of allergic reactions is an allergic reaction of the immediate type (reaginal, IgE-mediated, anaphylactic or atopic type)

The development of an allergic reaction of the immediate type is associated with the formation of antibodies, which were called "reagins". They belong mainly to the IgE class. Reagins are formed upon initial contact with Ag and are fixed on tissue basophils (i.e., their sensitization to the causative Ag occurs. Upon repeated exposure of Ag from the outside, its interaction with Ab occurs and an Ag-Ab complex is formed on the surface of sensitized cells with their subsequent degranulation of sensitized basophils with the release of BAS – histamine, leukotrienes, chemotactic factors, heparin, platelet-activating factor, which affect various organs and tissues and determine the clinical manifestations of the disease. They usually occur 15–20 minutes after the contact of a sensitized organism with a specific allergen (hence the name "immediate type reaction").

The consequences of an allergic reaction of the immediate type are diverse:

- inflammation of the mucous tissue of nose (rhinitis) and eyes (conjunctivitis);
- local edema (Quinke's edema);
- pollinosis;
- bronchial asthma (BA);
- urticaria;

- atopic dermatitis (AD),
- anaphylactic shock.

Atopic BA, AD, allergic rhinitis, pollinosis belong to the group of so-called atopic diseases. Hereditary predisposition plays a big role in their development – the increased ability to respond to the formation of IgE and an allergic reaction to the action of allergens.

2. The second type of allergic reactions is cytotoxic

In cytotoxic reactions, tissue cells become allergens (Ag). This usually occurs as a result of the harmful effects of drugs, enzymes of bacteria and viruses during infectious processes, as well as lysosomal enzymes of phagocytes.

In response to the appearance of changed cells, antibodies are formed, represented mainly by IgG and IgM classes. At interact with Ag, fixing on the surface of the cell, which leads to the inclusion of one of two cytotoxic mechanisms – complementary or the mechanism of antibody-dependent cellular cytotoxicity. The type of mechanism depends on the number and nature of Ab (class, subclass), which interact with Ag fixed on the cell surface. In the first case, the complement is activated, its active fragments are formed, which causes cell damage and even their destruction. In the second case, T-killers are attached to Ab fixed on the surface of the target cell, forming superoxide anion radical (reactive form of oxygen), which damages the target cell. Damaged cells are phagocytosed by macrophages.

The cytotoxic type of reactions include:

- development of leukopenia, thrombocytopenia, hemolytic anemia in case of drug allergy,
- allergic hemotransfusion reactions during blood transfusion,
- development of hemolytic anemia in hemolytic disease of newborns, myasthenia,
- postinfarction and postcommissurotomy myocarditis,
- effect of antireticular Bogomolets's cytotoxic serum.

3. The third type of allergic reactions - tissue damage by immune complexes (Artus type reaction, immune complex type)

Unlike the first and second types of reactions, Ag and Ab are not components of cells, and the formation of the Ag-Ab complex occurs in the blood and intercellular fluid in allergic reactions of the immune complex type, the allergen is present in a soluble form (bacterial, viral, fungal Ag, drugs, food substances). Formed antibodies mainly belong to classes IgG1, IgG2, IgG3 and IgM. These Ab are called precipitating because of their ability to form a precipitate when combined with the corresponding Ag. Such an immune complex can be deposited in tissues, which is facilitated by an increase in the permeability of the vascular wall, the formation of a complex in a small excess of Ag, a decrease in the activity of phagocytic cells, which leads to the suppression of the process of cleansing the body of immune complexes and to an increase in their circulation time in the body.

Complexes deposited in tissues interact with complement. When its active fragments are formed, which have chemotaxic activity, stimulate the activity of neutrophils, increase the permeability of blood vessels and contribute to the development of inflammation. Neutrophils phagocytose immune complexes and at the same time secrete lysosomal enzymes. Proteolysis in places where immune complexes are deposited increases. The kallikrein-kinin system is activated. As a result, tissue damage occurs and, as a response to this damage, inflammation occurs.

The third type of allergic reactions is leading in development:

- serum sickness,
- exogenous allergic alveolitis,
- some cases of drug allergy,
- food allergy,
- food allergy,
- a number of autoallergic diseases (rheumatoid arthritis, SLE, etc.),
- glomerulonephritis,
- local reactions according to the type of experimental phenomenon of Artyus.

4. The fourth type of allergic reactions is a delayed-type allergic reaction (delayed-type hypersensitivity, cellular hypersensitivity)

In this type of reaction, the role of Ab is performed by sensitized lymphocytes that have structures similar to Ab on their membranes. A delayed-type reaction in a sensitized organism manifests itself 24–48 hours after contact with the allergen.

The basis of delayed-type reactions is the formation of so-called sensitized T-lymphocytes (T-killers). In chronic infections, such as tuberculosis, toxoplasmosis, viral hepatitis, the pathogen multiplies intracellularly and there is a need to destroy infected cells, which is carried out by T-killers capable of recognizing infected cells. In the process of this reaction, interleukins and other mediators are released, which initially attract neutrophils to the site of events. Then neutrophilic infiltration changes to mononuclear, epithelioid cells appear and a granuloma is formed.

Contact dermatitis is also caused by reactions of the delayed type: simple chemical compounds, for example, chromium salts, join the proteins of skin cells, and these proteins become foreign to the body (auto-Ag). Sensitization develops, and with repeated contact with the allergen, the disease occurs.

Reactions of the delayed type include:

- bacterial allergy, i.e. accompanying infectious diseases (in connection with the special expressiveness of the allergic component of these diseases, they are called infectious-allergic): tuberculosis, leprosy, brucellosis, syphilis, fungal diseases of the skin and lungs, protozoan infections, infectious-allergic bronchial asthma, rhinitis, conjunctivitis,
- allergic contact dermatitis,
- viral hepatitis,
- reaction of rejection transplantant.

Often type IV allergy is the leading factor in the pathogenesis of autoimmune diseases.

5. The fifth type of allergic reactions is a receptor-mediated allergic reaction of the immediate type

Neurotransmitters or hormones (acetylcholine, insulin, TSH) that induce the synthesis of Ab, mainly of the IgG class, interact with the structures located in the receptor complex, causing a stimulating or inhibitory effect on the target cell, play the role of Ag in these reactions.

During the implementation of reactions of this type, cell damage does not occur, but, on the contrary, cell function is activated or inhibited. The peculiarity of these reactions is that they involve Ab, which do not have complement-binding activity. If such Ab are directed against cell surface components involved in physiological activation of clinins (for example, against receptors of physiological mediators), then they will cause stimulation of this type of cells.

Thus, the interaction of Ab with Ag-determinants included in the structure of the TSH receptor leads to a reaction similar to the action of the hormone itself, that is, stimulation of thyroid cells and the production of thyroid hormones. In fact, such Abs belong to autoimmune Abs. This immune mechanism underlies the development of diffuse toxic goiter. The possibility of inhibitory effect of Ab on cells and inhibition of insulin effects is described.

The activation of one or another immune mechanism is determined by the properties of antigens and the reactivity of the body.

Conditions can be external (amount of allergen, duration and nature of its action) and internal. Internal conditions are represented in a generalized form by the body's reactivity, which largely determines whether there will be a disease or not. Therefore, it is possible to change the body's reactivity in a direction that makes it difficult to implement the action of potential allergens.

Idiosyncrasy (Greek. Idios – own, own, synkrasis – displacement) – special sensitivity of some people to certain food substances or medicines.

Desensitization

Desensitization is the withdrawal of the organism from the state of sensitization.

Ways of desensitization:

1. Suppression of Ab production:

• allergen elimination;

• reproduction of specific tolerance (prenatal or neonatal administration of this Ag; in adults – large doses of soluble Ag);

• immunosuppressive conditions (irradiation, immunosuppressants, antilymphocyte serum).

2. Specific desensitization according to Bezredko (introduction of allergen in small doses, since BAS released during this process are quickly inactivated by the body itself and do not cause pathogenic effects).

3. Desensitization can be caused by substances acting on the nervous system (non-specific desensitization) – chloral hydrate, adrenaline, atropine, etc.

4. BAS inactivation.

5. Protection of cells from the action of BAS.

6. Correction of pathophysiological disorders.

Setting up the experiment.
Discussion of results and formulation of conclusions

Experiment No. 1: study of mast cell degranulation during anaphylactic shock in rats.

1. The rats that were sensitized before lesson by three subcutaneous injections of normal horse serum with complete Freund's adjuvant (a mixture of killed tuberculosis mycobacteria, petroleum jelly and lanolin) (1:1). 0.5 ml of the mixture was injected under the skin. Injections were performed every other day. Freund's adjuvant serves to increase the sensitivity of rats to horse serum, since rats have a natural refractoriness to foreign protein.
2. At the height of sensitization (12–17 days after the last injection of allergen with adjuvant), animals were intravenously injected with 1 ml of horse serum to reproduce anaphylactic shock.
3. Control animals at the height of sensitization were injected with an isotonic solution of sodium chloride.
4. After the death of the control animals, mesentery preparations were prepared: the pieces were fixed in 10 % formalin with the addition of 0.1 % acetic acid and stained with a 1 % solution of toluidine blue. Adipose tissue was removed, mesenteric tissue was passed through alcohols of increasing concentration, clarified with xylene and placed in polystyrene.
5. During the lesson, perform microscopy of preparations at a magnification of ×400 (ocular ×10, objective ×40).
6. Draw prepatrations.
7. Explanation of preparations:

Preparation No. 1 **(***CONTROL***)**. Mast cells are round or oval in shape, compact, well stained with toluidine blue in an intense blue color. Degranulated cells occur very rarely and make up no more than 2–4 %.

Preparation No. 2 **(***experiment***)**. Mast cells are enlarged, their edges are indistinct. Most cells show signs of degranulation to varying degrees. Degranulated cells often do not form a single whole and resemble a "bunch of grapes" because they consist of a collection of separate clearly visible granules. Individual cells, due to the dissolution of granules in the intercellular fluid, represent a blurred spot.

Experiment No. 2: familiarization with the method of reproduction and local manifestations of the Artus phenomenon in rabbits.

1. In the experiment, take two rabbits, which were given 4 injections (5 ml every 5 days) of normal horse serum under the skin of the previously depilated middle third of the thigh for the purpose of sensitization. The fifth, separate, injection was given to one rabbit under the skin, to another – into a joint.
2. During the lesson, pay attention to the local external manifestations of the Artyus phenomenon (skin and joint): hyperemia, local temperature increase, swelling, dysfunction, etc.

Experiment No.3: Study of morphological manifestations of the Artyus phenomenon by histological method.

In class, during microscopic examination, pay attention to the phenomena of hemorrhagic vasculitis: leukocyte thrombi in microvessels, tissue infiltration by leukocytes, edema and hemorrhage.

Discussion of the results of experiments

The first injections of horse serum, carried out at certain times, increased the animal's sensitivity to the injected substance (sensitization). Later injections of the same serum caused the development of a violent inflammatory reaction at the site of its introduction (separate injection). A necessary condition for the development of the Artus phenomenon is a high titer of precipitating antibodies in the blood. After a separate injection, a large amount of precipitate (antigen-antibody complex) is formed locally in the vessel walls, which leads to the development of hemorrhagic vasculitis with hemorrhagic-necrotic tissue damage. In the genesis of local allergic reactions, it is necessary to take into account the role of leukocytes and platelets, a significant role in the Artus phenomenon belongs to the blockage of blood vessels by leukocyte thrombi. Disturbances of exchange processes play a significant role in the mechanism of the Artyus phenomenon. research,

Leukocyte thrombi, tissue infiltration with leukocytes, and fibrinous necrosis of vessels can be seen in the micropreparation of the focus of the Artus phenomenon.

Degranulation of mast cells during an anaphylactic reaction is associated with the interaction of the antigen with antibodies of the Ig E class, which were fixed on the surface of mast cells. Rapid release of biologically active substances from mast cells is one of the most important mechanisms of anaphylaxis.

Formulation of conclusions based on the experiment

1. Rats sensitized with Freund's adjuvant developed anaphylactic shock, as evidenced by the degranulation of dangerous cells. The rapid release of biologically active substances (histamine, etc.) from dangerous cells led to generalized vasodilatation of peripheral vessels, a drop in blood pressure, which was clinically manifested by the development of anaphylaxis.
2. A sensitized rabbit with repeated administration of horse serum developed the Artus phenomenon in the form of local external manifestations (skin and joint): hyperemia, local increase in temperature, swelling, impaired function, etc. Artyus' phenomenon is a local manifestation of an immune complex allergic reaction (type III) and is caused by the formation of CIC A/g – A/b (Ig M, IgG).
3. The basis of the development of an immune complex allergic reaction (type III) is the formation of CIC with the development of hemorrhagic vasculitis – leukocyte thrombi in microvessels, tissue infiltration by leukocytes, edema and hemorrhage.

Tasks for independent work

It is necessary to substantiate the relationship between immunity and allergy, the relationship of allergy to reactivity. Be able to explain the mechanism of occurrence. Analyze the errors with an explanation of the correct answers

List of questions and works to be studied:

1. Concept of allergy.
2. Definition of allergens
3. Mechanisms of the immunological stage of allergic reactions:

a) the essence of the mechanisms of sensitization and manifestation in the case of allergies of the delayed and immediate type;

b) allergy as overstrain or dysfunction of the immune system.

4. Mechanisms of the biochemical stage of allergic reactions:

a) production and deactivation systems of biologically active substances (BAS);

b) features of the implementation of the biochemical stage.

5. Mechanisms of the pathophysiological stage of allergic reactions.
6. Classification of mechanisms of development of allergic reactions
7. Mechanisms of the main allergic reactions of the immediate type (anaphylactic shock, bronchial asthma, urticaria, apnoea phenomenon, hay fever, etc.) and delayed (tuberculin reaction, reactions to infectious antigens, contact dermatitis, immunological reactions against the transplant).
8. Mechanisms of autoallergic reactions, hetero- and paraallergy.
9. Mechanisms of desensitization and allergy prevention.
10. The relationship between allergy, immunity, immunological reactivity and inflammation.

List of practical skills that must be mastered:

Be able to simulate anaphylactic shock in an experiment, to explain the mechanisms of the main clinical manifestations of anaphylaxis.

Situational tasks KROK-1 to determine the final level of knowledge

1. In August, after working at the farm, the patient developed a condition characterized by a doctor as a state of increased and qualitatively altered reaction to the introduction of compounds of an antigenic or haptenic nature into the body. Which of the conditions best fits the characteristics described by the doctor?

A. Anaphylaxis. *C. Allergy.* *E. Immunological tolerance.*
B. Paraallergy. *D. Tachyphylaxis.*

2. Prior to tooth extraction, the patient underwent conductive anesthesia with novocaine, after the administration of which swelling and hyperemia appeared around the injection site, skin itching, general weakness, hypotension, motor excitement. What is the name of this complication?

A. Allergy. *C. Tachyphylaxis.* *E. Inflammation.*
B. Idiosyncrasy. *D. Drug dependence.*

3. To simulate anaphylactic shock, guinea pigs were subjected to passive sensitization. What should be introduced for the purpose of passive sensitization?

A. Specific immunoglobulins. *D. Tissue basophils.*
B. Horse serum. *E. B-lymphocytes .*
C. Sensitized T-lymphocytes.

4. The dentist administered a solution of novocaine to the patient for pain relief during the removal of a carious tooth. A few minutes later, the patient developed symptoms: a drop in blood pressure, an increase in BP, and convulsions. What type of allergic reactions can this condition be attributed to?

A. Anaphylactic. *C. Immunocomplex.* *E. Stimulating.*
B. Cytotoxic. *D. Delayed hypersensitivity.*

5. A 27-year-old woman complained of itching and burning in the eyes, lacrimation, sneezing, running from the nose. The symptoms appeared after a trip out of town in the summer. Diagnosed pollinosis. What type of allergic reaction developed?

A. Cytotoxic. *D. Anaphylactic.*
B. The reaction of the formation of immune complexes. *E. Stimulating.*
C. Delayed sensitivity.

6. Immediately after repeated administration of the antibiotic, the patient developed shortness of breath, a feeling of fear, a decrease in blood pressure. What type of allergic reactions underlie this condition?

A. Humoral cytotoxicity. *C. Cellular cytotoxicity.* *E. Stimulants.*
B. Immunocomplex. *D. Anaphylactic.*

7. At the end of spring, a man shows signs of rhinitis, redness of the conjunctiva of the eyes. An increased content of eosinophils was found in the blood. What type of allergic reaction?

A. Anaphylactic. *C. Immunocomplex.* *E. Stimulating.*
B. Cytotoxic. *D. Delayed-type hypersensitivity.*

8. During haymaking, one of the workers had a fever, chills, lacrimation, and a runny nose. The worker said that he sees this every year at this time. What is the type of allergic reaction according to Coombs and Gell?

A. Type II. *B. Type I.* *C. Type III.* *D. Type IV.* *E. Type V.*

9. A 37-year-old man was treated with a solution of novocaine during the treatment of acute pulpitis. A few minutes later, the patient developed anaphylactic shock. What Ig mainly interacts with in the body of Ag during this allergic reaction?

A. IgM. *B. IgA.* *C. IgE.* *D. IgD.* *E. IgG.*

10. A 44-year-old man with acute pneumonia was prescribed intramuscular penicillin. After the injection, the patient's condition deteriorated sharply: shortness of breath appeared, the patient was covered in cold sweat. Pulse 140/min., weak filling. Blood pressure 90/40 mm Hg. What complication is most likely to occur?

A. Anaphylactic shock. *D. Infectious-toxic shock.*
B. Thromboembolism of the pulmonary artery. *E. –.*
C. Cardiogenic shock.

11. A 40-year-old man was treated with a lidocaine solution for pulpitis. A few minutes later, the patient developed tachycardia, a sharp drop in blood pressure. What condition has the patient developed?

A. Anaphylactic shock. *C. Bronchial spasm.* *E. Burn shock.*
B. Crash syndrome. *D. Stress-adaptation syndrome.*

12. The patient developed anaphylactic shock after administration of anti-tetanus serum. What cells secrete mediators in the classical version of anaphylaxis?

A. Tissue basophils. *C. T-lymphocytes.* *E. B-lymphocytes.*
B. Eosinophils. *D. Neutrophils.*

13. In the patient, after 30 min. after treatment at the dentist, red itchy spots appeared on the skin of the face and the mucous membrane of the mouth. Urticaria was diagnosed. Which of the BAS that causes vasodilation and itching is released in this type of allergic reaction?

A. Prostaglandin E2. *C. Interleukin-1.* *E. Histamine.*
B. Leukotriene B4. *D. Bradykinin.*

14. A 54-year-old woman turned to a doctor with complaints about intolerance to chicken eggs, which appeared recently. The antihistamine drugs prescribed by the doctor led to some improvement in the patient's condition. What At could contribute to the development of this reaction?

A. Ig A. *B. Ig D.* *C. Ig G.* *D. Ig M.* *E. Ig E.*

15. With the development of anaphylactic reactions, marked hyperemia is observed, pain. What mediator of anaphylaxis determines the development of the above-mentioned disorders?

A. Platelet activation factor. *C. Heparin.* *E. Complement proteins.*
B. Chemotaxis factors. *D. Histamine.*

16. A few minutes after the administration of the drug, the patient's blood pressure dropped to 70/30 mm Hg. Art. Which of the chemical mediators of anaphylaxis causes vasodilation and shock?

A. Heparin. *D. Chemotaxis factor of eosinophils.*
B. Interleukins. *E. Neutrophil chemotaxis factor.*
C. Histamine.

Standards of correct answers to the task KROK-1

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
C	*A*	*A*	*A*	*D*	*D*	*A*	*C*	*D*	*A*	*A*	*A*	*E*	*E*	*D*	*C*

Recommendations for registration of work results

1. Written answers to test tasks (initial level of knowledge).
2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.
3. Protocol for solving situational tasks with an explanation of the correct answers.

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Topic 6. Typical disorders of peripheral blood circulation and microcirculation

Justification of the topic: Peripheral or local (organ) blood circulation is blood circulation within individual organs, that is, in vessels from small arteries to small veins. Its violations are widespread in the pathology of many organs and systems. Microcirculatory blood vessels include vessels whose diameter does not exceed 100 μm (arterioles, metaarterioles, capillary vessels, venules, and arteriovenular anastamoses). Under the action of various pathogenic agents, and especially in the case of disorders of the neuro-humoral regulation of blood circulation, local blood circulation disorders develop in the vessels. This leads to the fact that the tissues are not sufficiently supplied with oxygen and nutrients, in addition, carbon dioxide and metabolites are poorly removed from them. All this can lead to severe functional changes in organs and tissues.

Disorders of peripheral blood circulation and microcirculation include: arterial and venous hyperemia, ischemia, stasis. Thrombosis and embolism are most often identified as the causes of local blood circulation disorders.

Knowledge of the pathogenesis of typical disorders of peripheral blood circulation and microcirculation will allow the doctor to effectively treat them and develop preventive measures.

Purpose of the lesson:

General – study of changes in local blood circulation, which are characteristic of arterial and venous hyperemia, ischemia, embolism, their types, causes and mechanisms of development, as well as manifestations.

Specifically:

Know:

1. Definition of the term peripheral blood circulation and microcirculation.
2. Arterial hyperemia, its causes, types, pathogenesis. Manifestations, their mechanisms. Consequences.
3. Venous hyperemia, its causes, pathogenesis. Manifestations, their mechanisms. Consequences.
4. Ischemia. Causes, types, pathogenesis. Manifestations, their pathogenesis. Consequences.
5. Stasis. Its types, pathogenesis.
6. Thrombosis. Reasons. The process of thrombus formation, its mechanisms. Types of blood clots. Consequences of thrombosis.
7. Embolism. Reasons, types. Experimental models. Consequences.
8. Parenchymal bleeding. Causes, types, pathogenesis. Consequences.

Be able:

1. Experimentally simulate arterial hyperemia and microcirculatory phenomena in arterial hyperemia, venous hyperemia, ischemia and embolism.
2. Explain the mechanisms of arterial and venous hyperemia, ischemia, thrombosis and embolism, microcirculation and lymph circulation disorders.
3. Determine the main clinical manifestations of arterial hyperemia, venous hyperemia, ischemia, thrombosis, and embolism.

Practical experience:

1. Determination of signs of peripheral blood circulation and microcirculation disorders using case tasks:

• arterial hyperemia
• venous hyperemia
• ischemia
• thrombosis
• embolism (fat, air, gas, thromboembolism of the pulmonary artery).

The graphological structure of the topic "Typical disorders of peripheral blood circulation and microcirculation" is attached.

Material and methodological support of the topic "Typical disorders of peripheral blood circulation and microcirculation":

1. Lectures;
2. Methodical instructions for teachers;
3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational tasks to determine the final level of knowledge;
6. Set of tasks KROK-1;
7. A set of schemes and tables (presentation);
8. A set of illustrative cards with disorders of peripheral blood circulation and microcirculation;
9. Video films;
10. For the experiment (experimental animals – rabbits, frogs; cork with a side groove, cork board for fixing the animal, rubber tourniquet, pins, tweezers, syringes, scissors, microscope, 0.1 % hydrochloric acid solution, petroleum jelly emulsion).

Oriented map of students' work on the topic "Typical disorders of peripheral blood circulation and microcirculation"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of knowledge	10	Written answer to test tasks	Test tasks	Study room
2	Analysis of theoretical material	35	Analysis of theoretical material based on control questions of the topic, situational tasks, tasks KROK-1	Topic control questions, KROK-1 tasks, situational tasks	
3	Practical part (conduct experiment)	30	Introduction and preparation for setting up the experiment. Setting up the experiment. Discussion of the results of the experiment and formulation of conclusions	Rabbit. Frog. Microscope, cork board, tweezers, syringes, isotonic solution NaCl	
4	Determination of the final level of knowledge and skills. Summary.	15	Determination of the initial level of formation of knowledge and skills	KROK-1 tasks, situational tasks	

LOCAL CIRCULATORY DISORDERS

The following circulatory disorders are distinguished: arterial Hyperemia, venous Hyperemia, ishemia, stasis, hemorrhages, thrombosis and embolism.

ARTERIAL HYPEREMIA

Arterial hyperemia is an increased content of blood in a part with more blood following through its dilated vessels. It hyperemia may be physiologic or pathologic. Physiologic arterial hyperemia arises normally during hyperfunction of organs eases delivery of nutritive substances to these organs by the blood.

Pathologic arterial hyperemia arises under the influence of pathogenic agents and is usually characterized by a lack of correspondence between the circulation and the function of organs; the blood circulation may be increased even when the or in state of relative rest.

Arterial hyperemia may be caused by:

1) greater – then-normal effect usual physiologic stimuli for example, prolonged exposure of the skin to sunlight or effect of too much blood on the gastrointestinal tract;

2) effect of unusual stimuli – poisons, toxins, loved atmospheric pressure, elevated temperature, etc.;

3) increased sensivity of the vessels to physiologic stimuli as an allergic sensitization of the organism;

4) primary legions in the nervous system leading to pareses and paralyses.

The mechanism of arterial hyperemia's is essentially neurogenic. Arterial hyperemia may be a result of reflex action of stimuli on the central nervous system or on the peripheral nervous apparatus or may be due to direct action on the central vasomotor structures.

Arterial hyperemia due to increased tone of the vasodilatators or it's center's (neurotonic hyperemia) may develop by the conditioned reflex mechanism in cases of blushing caused by strong emotin (rege, shame), or redness of the face in pneumonia or toothach.

Arterial hyperemia due to damaged vasoconstrictor nerves (neuroparalytic hyperemia) may be the result of injury to the vasoconstrictor centres, as in trauma of the cervical or thoracic divisions of the spinal cord or as transection of vasoconstrictor nerves. Of the chemical substances which produce a paralytic effect on the vasoconstrictor centres and sometimes cause symmetric hyperemia of the skin and mucous membranes mention mast be made of the toxins of certain infectious agents.

Postanemic hyperemia develops in various vascular cavities of the body (pleural, abdominal) when fluid of a congestive is rapidly aspirated from them. This hyperemia is called postanemic becouse it is preceded by is ischemia due to constriction of vessels. On aspiration of the fluid subsequent lowerig of external pressure the vessels, which have lost a good deal of their tone, immediately dilate under the pressure of the blood rushing through them. A certain role in the pathogenesis of postanemic hyperemia also play stimulation of the reseptor apparatus of the anemic part by the products of disturbed metabolism (histamine, acetylcholine, etc.).

Maine appearences of arterial hyperemia

Arterial hyperemia is marked by: 1) redness of the tissue, which particularly noticeable on the mucous membranes and the skin; 2) pulsation of small vessels due to dilatation of the supplying arteries, acceleration of the blood flow; 3) elevated blood pressure in the vessels of the hyperemic part due to increased flow and greater mass of circulating blood; 4) swelling of the tissues and enlargement of the hyperemic part due to increased lymph formation and greater filtration of fluid through the capillary walls; 5) elevated temperature of the skin and mucous membranes due to increased inflow of arterial and greater heat loss.

The effects of arterial hyperemia are due to circulatory changes in the tissues and elevated blood pressure. The increased blood pressure. The increase blood supply favourable affects tissue nutrition, expecially during simultaneous hyperfunction of the given organs. In pathology arterial hyperemia sometimes leads to hemorrage. Arterial hyperemia is the most dangerous in the central nerves system. Hemorrages from cerebral vessels, as in cases of pathologic changes in their elasticity and permeability, are particularly dangerous.

VENOUS HYPEREMIA

Venous hyperemia is an increased content of blood and diminished blood circulation in a part due to impeded outflow of the blood.

Venous hyperemia may be caused by:

1) constriction of veins without injury to the arteries as a result of a ligature, pressure by a tumor, gravid uterus or constriction of the lumen of vessel by cicatrising tissue;

2) action exerted on tissues by physical and chemical agents which disturb nutrition and cause relaxation of vascular walls for a example, the action of adhering and irritating apparatus (cups) heat and cold; in these cases arterial hyperemia changes to venous hyperemia with all its characteristic consequences;

3) thrombosis of veins, occlusion of vessels, which hinders the outflow of blood from a corresponding part;

4) cardiac weakness is cases of heat discase, expecially in right ventricular insufficiency in these cases the blood flow towards the heart slows down and venous congestion is observed in the underling parts, mainly in the large and medium sized veins;

5) dysfunction of the pulmonary apparatus accompanied by diminished elasticity of pulmonary tissue with resultant changes in intrathoracic pressure, decreased aspiration action of the thorax and consequent venous hyperemia in the lower part of the body;

6) long confinment to bed, which may cause development of congestive hyperemia in the lower parts of the body. This form of hyperemia is also observed as a result of pendulous limbs, longcontined life (for example, hemostasis in hemorrhoidal veins) or long standing: in all these cases the outflow of blood through the veins is impeded.

The mechanism of venous hyperemia

1. In the pathogenesis of venous hyperemia a very impotant role plas the obstruction of venous vessels by embolism or construction of venous vessels by exudate, tumors, ligature and other.

2. A very important role, in addition to the obstruction to the blood flow, is played by impairment of nervous mechanisms of its regulation.

Maine appearances of venous hyperemia

Venous hyperemia is marked by: 1) redness of the part with a cyanosis (from the Greek word Kyanos – dark blue), due to hemostasis and the excess of reduced hemoglobin; 2) lowered temperature of the affected part; at fist the temperature of the part somewhat rises, but subsequent diminished outflow of blood and continued heat loss lead to drop in its temperature; 3) elevated blood pressure in the veins peripherally from the obstruction of blood in the veins below the site of obstruction; 4) enlargement, swelling of the hyperemic part due to increased filling with blood and intensified transudation of fluid into the tissue, as well as possible development of edema; this phenomen is a result of elevated intravascular pressure, change the permeability of the vessels due to insufficient delivery of oxygen disturbed tissue metabolism; 5) decelerated blood flow due to an obstruction on the way to the heart; 6) consequentment of venous hyperemia disturbed tissue nutritation of the hyperemic part; this also depends on the site and duration of venous occlusion and extent of development of collateral circulation, which is of compensatory importance; nutritation disorders due to insufficient delivery of oxygen in chronic stasis increase the permeability of vessels and affect the endothelium, thereby often causing hemorrhages; 7) induration, atrophy of specific elements and reaction growth of connective tissue due to venous congestion, nutritional disturbances in and disfunction of the hyperemic organs, general circulatory disorders due to venous hyperemia are particularly strongly pronounced when rapid ocdusion of large vessels occurs.

In some cases, however, venous hyperemia is beneficial. For example chronic venous congestion may hasten the healing of wounds by stimulation the growth of connective tissue (or during since) venous congestion alters metabolism and fosters accumulation in the tissues of biologically active products which create negative unfavourable conditions for the development of microorganisms in the focus of affection.

ISHEMIA (LOCAL ANEMIA)

Ishemia is a local diminution in the blood supply due to dimination or cessation or inflow of arterial blood.

Several forms of ischemia are distinguished according to the causes of their development.

1. Compresson ischemia due to compresson of the supplying artery, may be produced by ligature of the artery, application of a tourniquet or compresson of vessel by a growing tumour, cicatrix or foreign body.

2. Ischemia due to obstruction of the supplying artery (thrombus, embolus) or obliteration, occlusion of the vascular lumen as a results of pathologic changes in the wall.

3. Neurotic or spastic due to a reflex spasm of vessels (angiospasm) caused by stimulation of the vasoconstrictor apparatus. Angiospasm may be evoked by the following stimuli: cold applied to the body surface, severe trauma, I may develop is cases of an increased blood flow to some other part of the organism (collateral). Cerebral due to sharp dilatation of the vessels in the abdominal cavity and a increased flow of blood to the abdominal organs may serve as an example.

Ishemia is characterized by: 1) pallor of the tissue and loss of the normal color; 2) coolling of the tissue; 3) contraction of the ishemia part due to diminished blood supply; 4) metabolic disturbances which cause dystrophy to the extent necroses; 5) dysfunction of the organ; ishemia produce particularly important changes in central nervous system (pareses and paralyses); 6) pain, numbness, priching and a number of other phenomen.

Ishemia often termninates in restoration of the functions of the affected tissue. Favorable results depend on the extent of development of compensatory collateral circulation. The sooner collateral circulation develops, the less danger there is for the tissue.

Collateral circulation is established because the blood pressure drops below the obstruction in the vessels and the blood rushes through capillaries from the higher parts of the vascular bed to the lower part.

Wormally only very small amount of blood flows through arterial anastomoses because the difference in pressure between a and b is negligible. But the obstruction of the vessels at cause a drop in blood pressure below b and a rise in a. The difference in blood pressure between a and b appreciably increasis and the blood current is directly through the anastomosis.

Complications. Consequenmetns of ishemia

The part of tissue supplied by an arterial branch usually has a form of a cone. In cases of occlusion of an artery and limited collateral circulation due to circulatory disturbances the corresponding part of tissue undergoes certain changes. A focus of tissue necrosis, called an infarct develops. An infarct usually has the form a cone with its base toward the surface of organ.

Infarcts may occur as a result of vascular spasm; some myocardial infarcts are causes by spasm of the coronary arteries. Infarcts of myocard, cerebral brain and kidney are a dangerous complication.

STASIS

In Greek the word stasis means standing. Stasis is complete cessation of the blood flow with vessels dilated and filled with a mass of closely adhering erytrocytes. Venous, ischemias and capillary, or true, stasis is obstingueshed.

Venous stasis is a result of empeded outflow of blood through a draining vein.

Ischemias stasis a result of empeded inflow of blood through a arteria.

Capillary stasis appeor irrespective of any obstacles to the outflow and inflow blood. In occurs as a result of various excessive strong influence for example, effects of heat or cold, acids, alkalis.

The result of stasis

In cases where no major disturbances in the vascular walls and the blood of the given part have occurred the blood flow may be restored after elimination of the cause of stasis. But in cases of damage the vascular wall and adhesion of erytrocytes in the blood stasis is irreversible and necrosis of the corresponding part develop.

EMBOLISM

Embolism is occlusion of blood and lymphatic vessels with bits of the matter carried by the blood or limp and usually foreign to the blood stream. The bits of matter are called emboli. The emboli may be endogenous or exogenous origin. Several types of endogenous emboli are distinguished according to the material of which the emboli consist.

1. Embolism originating from thrombi.
2. Tissue embolism.
3. Fat embolism.

Exogenous embolism is distinguished according to their origin.

1. Air embolism.
2. Gas embolism.
3. Bacterial and parasitic embolism.
4. Foreign body embolism.

The results of embolism depend on the site of their occurrence. Coronary and cerebral embolism are especially dangerous. When collateral circulation is in adequate embolisms are usually accompanied by necrosis of tissue or formation of infarcts.

THROMBOSIS

Thrombosis is the formation of blood clots in blood vessels with the result that they impede the circulation. These blood clots are called thrombi. From the Greek word thrombos – lump, clot.

HEMORRHAGE

Hemorrhage is an escape of blood from the vessels into environment.

Setting up the experiment. Discussion of results and formation of conclusions

Modeling of arterial hyperemia: Viewing rabbit ear vessels in transmitted light. Subject the ear to mechanical irritation (rubbing with hands) and observe changes in the color of the ear, the number of visible blood vessels, their diameter, and the temperature of the ear. As a result of the mechanical impact on the ear, a change in the color of the ear (redness), an increase in the number of functioning blood vessels and a local increase in temperature were visually observed (increased arterial blood flow and increased

heat transfer, the subsequent increase in temperature causes an increase in oxidative processes and contributes to an even greater increase in temperature).

Modeling of microcirculatory phenomena in arterial hyperemia: A decerebrated frog is fixed on a cork board with its back to the top so that the front edge of the lower jaw is at the edge of the board opening. Fix the lower jaw with two pins at the corners of the mouth. Stretch the tongue over the hole of the board. In order not to interfere with microscopy, the pins fixing the tongue should be inserted at an angle to the center. Under low magnification, familiarize yourself with the blood circulation in the vessels of the tongue and sketch what you see. Then apply a drop of 0.1 % hydrochloric acid solution to the surface of the tongue. Observe changes in the blood flow rate, the size of the vessel lumen, the number of functioning capillaries and sketch what you see. Microscopy observed dilation of blood vessels, pulsation of small arteries and capillaries (dilation of afferent arteries, acceleration of blood flow and pulse wave transmission along the expanded blood vessel), an increase in the number of functioning vessels.

Modeling venous hyperemia: Look at the vascular network of a rabbit ear. Place a plug with a side groove on the auricle so that the central artery of the ear is under the groove. Put a rubber tourniquet on the outer surface of the ear. After 15–20 minutes, compare both ears of the rabbit (vascular condition, color, thickness, transparency, temperature).

Visually, one ear of the rabbit is of a cyanotic color, a decrease in the temperature of the auricle, swelling of the tissue is felt to the touch. In the final stages of hyperemia, the development of a pendulum-like movement of blood and stasis.

Modeling of ischemia: Look at the vessels of the rabbit ear. Use tweezers to apply painful irritation. Observe changes in the color of the ear, blood vessel filling, and the number of visible vessels. Explain the mechanism and determine the type of ischemia. In the animal, the paleness of the ear, a decrease in the number of functioning capillaries, a decrease in the temperature of the rabbit's ear, and a decrease in tissue turgor were observed. In this case, an angiospastic type of ischemia was reproduced, caused by reflex spasm of blood vessels from painful irritation of their vasoconstrictor apparatus.

Modeling of embolism: fix the decerebrated frog on a cork board in the "lying" position. Take out the tongue, straighten it and fasten it over the hole. Open the chest and open access to the heart. Remove the pericardium. Look at the blood circulation in the vessels of the tongue under a microscope. Slowly inject 0.5–1.0 ml of emulsion into the ventricle of the heart using a syringe. Shake the emulsion well beforehand. Observe the movement of emboli in the lumen of vessels and changes in blood circulation. Draw the observed phenomena and explain their mechanisms. Vascular spasm developed in the animals, and sometimes instantaneous insufficiency of coronary blood circulation, also of a reflex nature.

Discussion of the results of the experiment

- As a result of mechanical and chemical influence, arterial hyperemia develops, as a result of which the arterio-venous pressure difference increases, the speed of blood flow in the capillaries increases, the intra-capillary pressure increases and the number of functioning capillaries increases. The volume of the microcirculatory channel with arterial hyperemia increases due to an increase in the number of functioning capillaries and veins. As a result of the increase in the number of functioning capillaries, the plane for transcapillary metabolism increases, the cross-section of the microcirculatory channel increases, which leads to a significant increase in the volumetric velocity of blood flow. An increase in the volume of the capillary bed leads to an increased blood supply to the organ. An increase in the pressure in the capillaries leads to an increase in the filtration of liquid into tissue gaps, as a result of which the amount of tissue fluid increases.
- Since the pressure in the veins before the obstruction exceeds the diastolic pressure in the afferent arteries, normal blood flow is observed only during heart systole, and (reverse) blood flow (pendulum-like current) occurs during diastole. Increased intravascular pressure stretches the vessels and causes them to expand. All functioning veins become wider, non-functioning venous vessels open. Capillaries also dilate, usually in venous compartments. The blood supply to the organ increases. Although the cross-sectional plane of the vascular bed of the organ increases, the linear velocity of blood flow falls much more and therefore the volumetric velocity of blood flow remains reduced. That is why microcirculation in the body and blood supply to tissues weakens.
- An increase in resistance in the afferent arteries causes a decrease in intravascular pressure and creates conditions for their narrowing. The pressure falls primarily in small arteries and arterioles to the periphery from the site of occlusion or blockage, and therefore the arterio-venous pressure difference during the microcirculatory channel decreases and causes a decrease in the linear and volumetric blood flow velocities in the capillaries. Weakening of microcirculation causes disruption of tissue nutrition: the delivery of oxygen (circulatory hypoxia) and energy materials decreases, metabolic products accumulate. As a result of the decrease in pressure in the capillaries, the filtration of liquid from the vessels into the tissue decreases and conditions are created for its increased resorption from the tissue into the capillaries. Therefore, the amount of tissue fluid in the intercellular spaces is significantly reduced and the outflow of lymph from the area of ischemia is weakened to the point of complete stoppage.
- Reflex vasospasm during embolism is due to increased pressure in the pulmonary arterioles, mechanical irritation of the vessels by emboli, a decrease in blood flow in the vessel below the embolus, the release of substances (serotonin, histamine) at the site of the blockage, which have the properties of causing contraction of non-striated muscle fibers of the vessels.

Forming conclusions based on the experiment

• Arterial hyperemia. As a result of mechanical impact or chemical irritation (0.1 % hydrochloric acid solution), arterial hyperemia develops. Mechanism: Caused by cholinergic mechanism (effect of acetylcholine). It is observed in organs and tissues that are innervated by parasympathetic nerve fibers.

• Venous hyperemia is caused by applying a tourniquet. Mechanism: the effect of an obstacle that arose on the path of blood flow, as well as a violation of the nervous mechanisms of its regulation.

• Ischemia during painful irritation. Mechanism: reflex spasm of blood vessels from irritation of their vasoconstrictor apparatus. An important role in the occurrence of ischemia is played by an increase in the sensitivity of the muscle elements of the vessel wall to norepinephrine and vasoactive peptides, due to the accumulation of Na+ ions in them.

• Embolism caused by emulsion injection. Mechanism: the general reactivity of the organism is of great importance. The direction of emboli is often determined by the activity of the nervous system. In this case, vascular receptors play a major role. Irritation of angioreceptors can affect the speed of blood flow and the process of blood circulation as a whole and thereby the transfer of an embolus.

Tasks for independent work on the topic
"Typical disorders of peripheral blood circulation and microcirculation"

The student is offered 2-3 cases with various variants of peripheral blood circulation and microcirculation disorders. It is necessary to determine the main signs and type of peripheral blood circulation and microcirculation disorders. Be able to explain the mechanisms of occurrence. Analysis of errors with an explanation of the correct answers.

List of questions and works to be studied:

1. Definition of peripheral blood circulation and microcirculation.
2. Arterial hyperemia, its causes, pathogenesis. Manifestations, their mechanisms. Consequences.
3. Venous hyperemia, its causes, pathogenesis. Manifestations, their mechanisms. Consequences.
4. Ischemia. Causes, types, pathogenesis. Show their mechanisms. Consequences.
5. Stasis. Its types, pathogenesis.
6. Thrombosis. Reasons. The process of thrombus formation, its mechanisms. Types of blood clots. Consequences of thrombosis.
7. Embolism. Reasons. Kinds Experimental models. Consequences.
8. Parenchymal bleeding. Causes, types, pathogenesis. Consequences.

A list of practical skills that must be mastered.

Determination of signs of peripheral blood circulation and microcirculation disorders using case studies:

- Arterial hyperemia
- Venous hyperemia

- Ischemia
- Thrombosis
- Embolism

Situational tasks KROK-1 to determine the final level of knowledge

1. During the game of volleyball, the athlete landed on the outer edge of the foot after a jump. There was acute pain in the ankle joint. Then swelling appeared, the skin reddened, became warmer to the touch. What type of peripheral circulatory disorder developed in this case?

A. Ischemia. *C. Stasis.* *E. Thrombosis.*
B. Arterial hyperemia. *D. Venous hyperemia.*

2. Edema began to form in a patient with a hand injury. At what stage of local blood circulation disorder does this occur?

A. Arterial hyperemia. *C. Venous hyperemia.* *E. Prestasis.*
B. Stasis. *D. Spasm of arterioles.*

3. In an experiment, K. Bernard, irritating the chorda tympani (branches of the n. facialis), observed increased secretion of the submandibular salivary gland and the development of arterial hyperemia. What is the mechanism of development of this hyperemia?

A. Neurotonic. *C. Metabolic.* *E. Working.*
B. Neuroparalytic. *D. Reactive.*

4. When simulating inflammation on the mesentery of frogs, expansion of arterial vessels, acceleration of blood flow, and axial blood flow were observed under a microscope. What type of arterial hyperemia occurred in this case?

A. Postischemic. *C. Vacant.* *E. Working.*
B. Metabolic. *D. Reactive.*

5. In a patient with a fracture of the ankle joint, after removing the plaster cast, there is swelling of the foot, cyanosis, a local decrease in temperature, and an increase in the volume of the organ. What type of blood circulation disorder is observed in this case?

A. Working hyperemia. *C. Venous hyperemia.* *E. Ischemia.*
B. Metabolic arterial hyperemia. *D. Reactive hyperemia.*

6. A plaster cast was applied to a patient with a closed fracture of the humerus. The next day, swelling, bluishness and cooling of the hand of the injured hand appeared. What disorder of peripheral blood circulation do these signs indicate?

A. Arterial hyperemia. *C. Venous hyperemia.* *E. Embolism.*
B. Ischemia. *D. Thrombosis.*

7. A patient with periodontitis has swelling of the gums. They have a dark red color. What local blood circulation disorder prevails in the patient's gums?

A. Arterial hyperemia. *C. Thrombosis.* *E. Embolism.*
B. Ischemia. *D. Venous hyperemia.*

8. After caries treatment, the patient developed hyperemia, swelling, and pain in the gum area around the diseased tooth. What violation of local blood circulation occurred in this case?

A. Thrombosis. *C. Stasis.* *E. Venous hyperemia.*
B. Ischemia. *D. Prestasis.*

9. In a patient with varicose veins, when examining the lower extremities, the following is noted: cyanosis, pastiness, a decrease in skin temperature, isolated petechiae. What hemodynamic disorder does the patient have?

A. Venous hyperemia. *D. Thromboembolism.*
B. Compression ischemia. *E. Arterial hyperemia.*
C. Obstructive ischemia.

10. A 25-year-old patient complains of the appearance and intensification of pain in the leg muscles while walking, due to which he was forced to stop often. Objectively: the skin on the legs is pale, the hair cover is absent, the nails on the toes have trophic changes. There is no pulsation of the arteries of the feet. The likely reason for these changes will be:

A. Ischemia. *C. Arterial hyperemia.* *E. Embolism.*
B. Venous hyperemia. *D. –.*

11. In a 48-year-old man, a violation of peripheral blood circulation with a limitation of arterial blood flow was detected, while there is pallor of this area, a decrease in local temperature. This violation is called:

A. Venous hyperemia. *C. Reperfusion syndrome.* *E. Sludge.*
B. Stasis. *D. Ischemia.*

12. After a mechanical injury, a tourniquet was put on the patient's arm to stop the bleeding. Below the harness, the hand turned pale, a feeling of numbness appeared. This condition is a consequence of:

A. Venous stasis. *C. Angiospastic ischemia.* *E. Thrombosis.*
B. Obstructive ischemia. *D. Compression ischemia.*

13. The pilot had an emergency depressurization of the cabin at an altitude of 14,000 m. What type of embolism did he develop?

A. Gaseous. *C. Thromboembolism.* *E. Fatty.*
B. Embolism by a foreign body. *D. Aer.*

14. After the forced rapid ascent of the diver from the depths to the surface, he developed signs of caisson disease – pain in the joints, itching of the skin, flickering in the eyes, clouding of consciousness. What type of embolism were they caused by?

A. By air. *B. Fatty.* *C. Fabric.* *D. Thromboembolism.* *E. Gas.*

15. A 54-year-old woman was taken to the trauma department after a car accident. The traumatologist diagnosed multiple fractures of the lower limbs. What type of embolism is most likely to develop in this case?

A. Textile. *B. Thromboembolism.* *C. Air.* *D. Fatty.* *E. Gaseous.*

Standards of correct answers to the KROK-1 task

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
B	*A*	*A*	*B*	*C*	*C*	*D*	*E*	*A*	*A*	*D*	*D*	*A*	*E*	*D*

Recommendations for registration of work results

1. Written answer to test tasks (initial level of knowledge).

2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.

3. Independent work of students. Protocol for solving a case with typical disorders of peripheral blood circulation.

4. Protocol for solving situational tasks with an explanation of the correct answers.

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Topic 7. Inflammation

Justification of the topic: Inflammation is the most widespread typical pathological process. It arises in response to any damage to body tissues, is the basis of many diseases of infectious and non-infectious nature in humans and animals. There is no field of medicine that is not related to the prevention, diagnosis and treatment of the inflammatory process.

In this regard, knowledge of the general mechanisms of the occurrence, development and outcome of inflammation is necessary for a doctor to timely and correctly diagnose diseases of an inflammatory nature, to carry out rational pathogenetic therapy at any stage of the development of the inflammatory process.

Purpose of the lesson:

General – to be able to characterize inflammation as a typical pathological process, to study changes in the body, the main causes and mechanisms of inflammation, principles of therapy.

Specifically:

Know:

1. Definition of the term "inflammation". The main signs of inflammation.
2. Etiology of inflammation. General pathogenesis of inflammation.
3. Mediators of inflammation.
4. The sequence of vascular phenomena of the focus of inflammation.
5. Classification of inflammation.
6. Definition of the terms exudation and exudate.
7. The concept of emigration of leukocytes. Mechanisms of emigration.
8. General manifestations of inflammation.
9. Relationship between local and general changes during inflammation.

Be able:

1. Simulate Kongheim's experiment to determine vascular reactions during inflammation.
2. To determine microscopically the cellular composition of the exudate in the temporal dynamics of the inflammatory process.

Practical experience:

1. Determination of signs and mechanisms of metabolic disorders during inflammation using case studies.
2. Determination of general (fever, leukocytosis, increased ESR, dysproteinemia, abnormal enzyme activity, changes in the content or activity of components of the coagulation, anticoagulation, and fibrinolytic systems, allergy of the body) and local (rubor, calor, dolor, tumor, functio leasa) tasks using case studies) signs of inflammation.
3. Determination of the type of inflammation depending on the cellular composition of the exudate (serous, hemorrhagic, fibrinous, diphtheritic, purulent and mixed).

The graphological structure of the theme " Inflammation" is attached.

Material and methodological support of the theme " Inflammation":

1. Lectures.
2. Methodical instructions for teachers.

3. Methodical instructions for students.
4. A set of test tasks to determine the basic level of knowledge.
5. A set of situational tasks to determine the final level of knowledge.
6. A set of krok-1 tasks.
7. A set of schemes and tables (presentation).
8. A set of cases for determining manifestations of inflammation.
9. Video films.
10. For the experiment (experimental animals – a frog, a mouse; syringes, glass and ground glasses, petri dishes, a microscope, ether, thiopental anesthesia, suspension of staphylococcal cultures, romanovsky dye).

Oriented map of students' work on the topic "Inflammation"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of knowledge	10	Written answer to test tasks	Test tasks	Study room
2	Analysis of theoretical material	35	Analysis of theoretical material based on control questions of the topic, situational tasks, tasks KROK-1	Topic control questions, KROK-1 tasks, situational tasks	
3	Practical part (conduct experiment)	30	Introduction and preparation for setting up the experiment. Setting up the experiment. Discussion of the results of the experiment and formulation of conclusions	Frog. Syringes, slide and ground glasses, Petri dishes, microscopes, ether	
4	Determination of the final level of knowledge and skills. Summary	15	Determination of the initial level of formation of knowledge and skills	KROK-1 tasks, situational tasks	

Inflammation (from the Latin word inflammatio – ignition) is the reaction of organism to its local injury characterized by phenomena of alteration, disturbances of the local circulation and microcirculation (with exudation and leukocyte emigration) and proliferation.

The cardinal signs of an inflammatory process

The internal and external local cardinal signs of an inflammatory process are distinguished. Alteration, disturbances of the local circulation and microcirculation (with exudation and emigration of leukocytes) and proliferation are the internal signs, or main components, or phenomena, of inflammation. Redness (rubor), swelling (tumor), heat (calor), pain (dolor) and dysfunction (functio laesa) are the external, or clinical, signs of inflammation.

Etiology of inflammation

Any factor capable to cause the tissue injury can be the cause of inflammation. The factor caused an inflammation is named an inflammatory agent, or phlogogene (from the Greek word phlogogen – caused an inflammation). The exogenic and endogenic phlogogenes are distinguished. The exogenic

phlogogenes on their origin can be: 1) biological (the infectious agents, nematods, toxins, venoms, etc); 2) physical – the mechanical, electrical, thermal, radiation energy; 3) chemical – acids, alcalis, etc.

The endogenous causes of inflammation are tissue necrosis, thrombosis, infarction, massive hemorrhage, local allergy, formation of stones, deposition of salts, etc.

After its etiology inflammation is divided into infectious (septic) and non-infectious (aseptic).

General pathogenesis of inflammation

Inflammation is the reaction of an organism as a whole to its injury, however, its effector systems are blood, the local circulation and microcirculation and connective tissue. Blood plays the decisive role in realization of inflammation as far as leukocytes are the main cell effectors of the process and the blood system as a whole provides the occurrence and maintenance of leukocytic infiltration as the main component of inflammation; the connective tissue is the trigger (starting) system of inflammation, and the local circulation and microcirculation provide the interrelation between blood and connective tissue.

Initial effectors of inflammation are: neurons of the autonomic nervous system, neuropeptide containing fibres of the sensory neurons, cell of connective tissue (resident macrophages, mast cells, fibroblasts), factors of tissue fluid (kininogen, complement). Roughly, phlogogene causes activation and damage of the above mentioned cells and biochemical factors of tissue fluid (the primary alteration) that is followed by release or formation the appropriate mediators of inflammation (the primary mediators of inflammation). Mediators execute killing and lysis of microbes, and simultaneous injury of the own tissue (the secondary alteration with the release and formation of the secondary mediators of inflammation). The secondary alteration is directed to increased struggle with phlogogene and localisation of phlogogene and injured own tissue. Thus by increase of vascular permeability, by causing of leukocyte chemotaxis and fibroblast activation, etc. mediators start the standard mechanism of reinforcement from plasma and blood cells, and from environmental connective tissue (phenomena of exudation, leukocyte emigration and proliferation). With exudate and leukocytes mediators of plasma and blood cells arrive to the inflammatory focus. Due to this the struggle with phlogogene and injury of the own tissue are amplified (expansion of the secondary alteration), that increases and prolongs exudation and infiltration. At first leukocytic infiltration is executed by involving of the circulating leukocytes, and then is supported by the strengthened haematopoiesis. The destruction of phlogogen and injured own tissue is also executed by phagocytosis. According to cleansing of the inflammatory focus from phlogogene and damaged tissue exudation and infiltration become calm and proliferation intensifies, and the restoration of tissue or reparation of tissue defect is happened. Thus, inflammation is the automatic reaction wich ensure its own development, maintenance and calming.

Alteration

Alteration (from the Latin word alteratio – change), or dystrophy, is an injury of tissue, disturbance of its nutrition (trophy) and metabolism, its structure and functions. The primary and secondary alterations are distinguished. The primary alteration is a consequence of damaging action of an inflammatory agent. Its expression depends on the properties of phlogogene in the other equal conditions (reactivity of the organism, localisation).

The primary alteration is not a component of inflammation as the latter is the reaction to damage caused by phlogogene, that is, to the primary alteration. However, it is practically difficult to separate the primary and secondary alterations from each other. At the same time the primary alteration is rather short-term and insignificant in comparison with general its volume.

The secondary alteration does not depend on phlogogene directly; its development does not need a further presence of phlogogen. It is the reaction of organism to the already caused damage by phlogogene, that is, it is the integral part of inflammatory reaction. Moreover, the secondary alteration is the necessary component of inflammation as a defensive adaptive reaction. By the secondary alteration the all other inflammatory phenomena are reached. It initiates exudation, leukocyte infiltration and proliferation, through them provides self-regulation, that means the automatism of inflammatory reaction. The secondary alteration is a result of action lysosomal enzymes, reactive oxygen species, nitrogen oxide released extracellularly and of lytic complex of complement C5b-C9 on connective tissue, microvessels and blood.

Alteration includes tissue destruction and intensified metabolism ("the fire of metabolism") resulted in series of physical and chemical changes of tissue, such as accumulation of acid products (local acidosis, or H^+-hyperionia), increased osmotic pressure (osmotic hypertension, or hyperosmia) and increased colloid osmotic, or oncotic, pressure (hyperoncia).

The changes of osmotic and oncotic pressure are important factors of exudation and, accordingly, of inflammatory edema.

The strengthened metabolism in an inflammatory focus underlies increased thermoproduction, which is, in its turn, the main cause of such external local phenomenon of inflammation as heat is.

Mediators of inflammation

During the primary and the secondary alteration a large quantities of various biologically active substances are released or formed which become mediators of inflammation, that is, they cause or support various inflammatory phenomena. The release and formation of mediators is a cascade reaction, which is one of the features and mechanisms of the automatism of inflammation. The mediatoric cascade is the main link of inflammatory reaction. Mediators provide the arising and interconnection all of the inflammatory phenomena, the change of cellular phases of an inflammatory focus, the transition from development of the reaction to its being calm down.

All of the known mediators on their origin can be separated into two groups: 1) humoral, i.e. occurring from tissue fluid and plasma, and 2) cellular (from cells of tissues and blood), as well as into: 1) preexisting, or being present in fluids and cells before their activation (with reference to cellular mediators they are granulo-associated), and 2) new-formed, or membrano-derivative, which are produced during activation of cells.

Leukocytes are the main source of the majority of mediators, and their products are the main mediators (lysosomal enzymes, reactive oxygen species, nitrogen oxide, eicosanoids, cationic proteins, monokines). The other cellular mediators are: vasoactive amines (histamine and serotonin), neuropeptides (substance P, calcitonin gene-related peptide, neurokinin A), acethylcholine, platelet-activating factor, lymphokines. From the humoral mediators (the active components of complement, kinins, the blood clotting factors) the active components of complement are the most important as far as they, alongside with leukocytic factors, are essential in lysis of microbes and in expansion of the secondary alteration.

Despite a large number of mediators and their effects after the main effects it is possible to separate them into potentially responsible for: 1) vascular reaction (including increased vascular permeability) – vasoactive amines, kinins, lysosomal enzymes, cationic proteins, reactive oxygen species, nitrogen oxide, neuropeptides, acethylcholine, platelet-activating factor, and 2) chemotaxis of leukocytes – active components of complement, blood clotting factors, eicosanoids, monokines, lymphokines.

Being the real mediators one of the above mentioned inflammatory phenomena the same substances can be modulators of the other one.

Circulatory disturbances

The vascular reactions are developed after the action of the inflammatory agent as far as the initial from them are reflex. They are well observed under the microscope in the classical Cohnheim's experiment (1867) in a preparation of the frog's inflammed mesentery and are characterized by the following sequence:

1. Short-term ischemia stipulated by spasm of arterioles. It is the result of the reflex excitation of the vasoconstrictor nerves following the direct action of the inflammatory agent. It lasts from several tens of seconds up to several minutes, so it is not always possible to observe it.

2. Arterial hyperemia stipulated by dilation of arterioles. Its mechanism, on the one hand, is connected with the axon-reflex excitation of vasodilator nerves, and, on the other hand, with the direct vasodilating effects of the inflammatory mediators: neuropeptides, acethylcholine, histamine, brady-kinin, prostaglandins, etc.

Arterial hyperemia underlies two main external local signs of inflammation – redness and heat.

3. Venous hyperemia. It can be developed for some minutes after the action of the inflammatory agent, however is characterized by the long-term duration – accompanies the further course of inflammatory process as a whole.

Accordingly, with its participation all of the main inflammatory phenomena are executed. It is considered as the veritable inflammatory hyperemia.

Among the mechanisms of venous hyperemia three groups of factors are distinguished:

1) disturbances of reologic properties of blood and properly its circulation. They are: a) increase of viscosity of blood owing to its concentration, loss of albumin stipulated by exudation, increase of globulin content, change of colloid state of proteins; b) increase of resistance to blood flow as a result of leukocyte margination, swelling and aggregation of erythrocytes; c) formation of thrombi owing to activation of coagulation and thrombocyte-vascular components of haemostasis; d) disturbance of the character of blood flow – slowing down of blood flow in axial zone and reduction of marginal plasmatic zone;

2) changes of vascular wall including: a) loss of vascular tone owing to paralysis of the neuromuscular apparatus of the vessels; b) reduction of elasticity of the vascular wall; c) swelling of the endothelial cells and increase of their adhesity resulted in narrowing of the vessels, the condition are created for adhesing of leukocytes to endothelium;

3) tissue changes consisting in: a) compression of venules and lymphatic vessels by swollen infiltrated tissue; б) reduction in elasticity of connective tissue.

The inflammatory hyperemia differs from the other kinds of hyperemia by the considerable weakening or even perversion of the vascular reaction of the inflammed tissue to vasoconstrictor agents (adrenalin, caffeine) and to stimulation of vasoconstrictor nerves. This phenomenon can be connected with tachyphylaxy of the vessels to vasoconstrictor stimuli.

4. Stasis which can be developed in some branches of the vessels of the inflammed tissue. Widespread stasis is characteristic of the acute fast developing inflammation, for example, hyperergic one. The mechanism of stasis consists in disturbance of the reologic properties of blood, which, in its turn, is connected with the changed structure of blood flow, increased intravascular aggregation of erythrocytes owing to changes of physical and chemical properties of their membranes, blood protein composition, and blood flow slowing down. The prestatic state precedes to stasis which is characterized by pendulum-like movement of blood, when during systole blood moves from arteries to veins and during diastole in the opposite direction. It is the result of the increasing stagnation of blood, loss of vascular tone and strong dilation of capillaries and venules. As a rule the disturbance of blood flow in the inflammatory stasis is transient, however at occurrence of damages of the vascular wall and thrombi in many vessels the stasis becomes irreversible and results in necrosis of the environmental tissues.

Exudation

Exudation (from the Latin word exsudatio – perspiration) is passage of protein-containing blood fluid though the walls of vessels into the inflammed tissue with formation of the inflammatory edema. The passing fluid is called

exudate. The terms "exudation" and "exudate" are applied only in relation to inflammation.

The mechanism of exudation consists in: 1) increased vascular permeability (of venules and capillaries) owing to the action of the inflammatory mediators and in some cases of the inflammatory agent; 2) elevated blood pressure in the vessels of the inflammatory focus owing to hyperemia; 3) heightened osmotic and oncotic pressure in the inflammed tissue as a result of alteration and started exudation and sometimes – in decreased this pressure in blood because of loss of electrolytes and proteins in strong exudation.

The degree of the increased vascular permeability determines the protein composition of exudate. Albumins exude first, as the most dispersed blood proteins; as permeability increases, the albumins are followed by globulins and, lastly, by fibrinogen.

Dependently on their qualitative composition the following kinds of exudate are distinguished: serous, fibrinous, purulent, putrefactive, hemorrhagic and mixed.

Serous exudate is characterized by moderate amount of protein (3–5 %), mainly albumin, and by small number of polymorphonuclear leukocytes. On its structure it is the most similar to transsudate. It is most frequently observed in inflammation of serous membranes (serous pleurisy, peritonitis, pericarditis).

Fibrinous exudate is characterized by large amount of fibrin. It is observed in diphthery, dysentery, tuberculosis, etc.

Purulent exudate is characterized by enormous number of leukocytes, mainly neutrophils, mostly destroyed. It appears mainly in inflammation caused by cocci, pathogenic fungi, and chemical phlogogenes such as turpentine, croton oil, war gases, etc.

Putrefactive exudate is characterized by presence of the products of putrefactive tissue decomposition. It is formed by putrefactive microorganisms. The result is gangrenous inflammation, for example, putrid bronchitis, pleurisy, etc.

Hemorrhagic exudate – one containing a large number of erythrocytes and having a pink or pinkish-red colour. It is observed in tuberculosis (tuberculous pleurisy), anthrax, plague, etc.

Mixed exudates are observed in inflammation in the loosed organism with affiliation of the secondary infection. Serofibrinous, seropurulent, serohemorrhagic and pyofibrinous exudates are distinguished.

Exudate together with infiltrate stipulates such external local sign of inflammation as swelling. Besides alongside with the action of bradykinin, histamine, prostaglandins, neuropeptides pressure of exudate on endings of the sensory nerves has some significance in occurrence of the inflammatory pain.

Emigration

Emigration (from the Latin word emigratio – emigration) is passage of leukocytes from the vessels into the inflammed tissue. It is executed by diapedesis through the venule walls.

Emigration with the leukocyte infiltration of the tissue is the main component of inflammation. Leukocytes are the main cell – effectors of inflammation.

They play the decisive role in localization and elimination of phlogogene and in realization of inflammation as a whole. The intensity and dynamics of the leukocytic infiltration and the changes in blood system interconnected with them are the main criteria of inflammation, efficiency of anti-inflammatory drugs and appropriate therapy.

There are exogenic and endogenic chemotaxins (chemoattractants). The first ones include the products of the vital activity and decomposition of bacteria, the second ones are mainly the chemotactic mediators of inflammation, as well as the products of granulocyte decomposition.

As a result of the binding of chemoattractants with the specific receptors on leucocytes the functional activity of cells increase. The result is the increased secretion of mediators, adhesity of leukocytes, the change in colloid state of cytoplasm, activation of actin and myosin microfilaments.

Leukocytes leave from axial blood flow to marginal plasmatic zone. The disrurbance of reologic properties of blood promote it.

Simultaneously the adhesive properties of endothelial cells increase.

The adhesion of leukocytes to endothelial cells is happened – marginal position of leukocytes.

The leukocytes form pseudopodia wich penetrate endothelial channels and the cells pass through the endothelial layer. Emigration is promoted by the increased vascular permeability and fluid flow from the vessels into the tissue.

The emigrated leukocytes detach themselves from the wall of the vessel and proceed with ameboid movements to the inflammatory focus.

In the beginning of inflammation most of the emigrant leukocytes are neutrophils, and then monocytes-macrophages. While microphages phagocytise mainly bacteria, macrophages take part mainly in phagocytosis of the destroyed tissue elements and granulocytes.

The cellular composition of exudate largely depends on the phlogogene, reactivity of the organism and course of the process. Exudate is especially rich by neutrophils, if the inflammation is caused by cocci. In the allergic inflammation there are a lot of eosinophils in the inflammatory focus. In chronic inflammation there are a small number of neutrophils, and monocytes and lymphocytes prevail.

The emigrated leukocytes together with the proliferating tissue cells form the inflammatory infiltrate. Infiltrate alongside with exudate stipulates swellind and takes part in the onset of pain.

Proliferation

Proliferation (from the Latin word proliferatio – reproduction) is reproduction of the local cellular elements in an inflammatory focus. Proliferation is developed from the beginning of inflammation alongside with phenomena of alteration, exudation and emigration but becomes prevailing later with calming down of exudative-infiltrative phenomena. It begins from periphery of the focus.

The progress of proliferation directly depends on the efficiency of cleaning of inflammatory focus from microbes or other phlogogene, products of

alteration, dead leukocytes (wound cleaning). Macrophages play the leading role in wound cleaning.

Wound cleaning is executed mainly by extracellular degradation as well as by phagocytosis owing to such enzymes as proteoglycanase, collagenase, gelatinase. Their activity is regulated by monokines.

The process of proliferation is under the complex humoral control. Macrophages have the decisive significance. They are the main source of fibroblast growth factor. Fibronectine and interleukin-1 play the important role too. Macrophages also stimulate the proliferation of endothelial and smooth muscular cells, the growth of basal membrane and thus the formation of microvessels.

The other cells of inflammatory focus modulate proliferation influencing the functions of fibroblasts, macrophages and lymphocytes, for example, mast cells stimulate macrophages and fibroblasts, and supervise lymphocytes. It is supposed that the excessive influence of biogenic amines induces tissue sclerosis.

Proliferation is followed by regeneration. The latter is not a component of inflammation, however without fail follows it and is difficultly separated from it. It is the late reparative phase on the site of inflammation and consists mainly in growth of connective tissue and blood vessels and least of all in proliferation of the specific tissue elements. In insignificant damage the relatively total its regeneration happens. In marked tissue defect it is filled firstly by granulation tissue, which then is replaced by mature connective tissue with formation of scar.

General manifestations of inflammation

Except for the local signs inflammation can be also manifested by the general signs which depend on the intensity and expansion of process. The general manifestations of inflammation include fiver, the bone marrow reactions with the development of leukocytosis, faster erythrocyte sedimentation rate, accelerated metabolism, change of immunologic reactivity, intoxication. The general manifestations of inflammation are stipulated by influences from the inflammatory focus, mainly by mediators of inflammation.

Thus, fiver is a result of the action of endogenic pyrogenes, for example, of interleukin-1, prostaglandin E2 released by activated leukocytes. The accelerated metabolism is the consequence of the strengthened secretion of catabolic hormones under the influence of monokines. The increased contents of glucose, globulins, residual nitrogen in blood are observed. The increased erythrocyte sedimentation rate reflects the absolute or relative prevalence of globulin in plasma that happens as a result of strengthened production "acute phase proteins" by hepatocytes under influence of monokines or as a result of albumine loss during exudation. The prevalence of globulins in plasma reduces the negative charge of erythrocytes and their mutual pushing off. The agglutination and thus the sedimentation of erythrocytes increase.

Inflammation is one of the ways of formation of immunologic reactivity ("the immunity through disease").

The especially large changes are observed in blood system that reflects its role of the main effector system of inflammation. Except for emigration blood system reactions include the series of changes in hematopoietic tissue and blood: 1) initial transient decrease of number of circulating leukocytes in blood (leukopenia) stipulated by their margination and emigration; 2) increased efflux of leukocytes from bone marrow into blood with development of leukocytosis; 3) activation of hematopoiesis; 4) development of bone marrow hyperplasia. All of this changes provide the development and long-term maintenance of infiltration.

The acute inflammation is characterised by neutrophilic leukocytosis with the shift to the left (increased number of young, band, neutrophils) as well as monocytosis, the chronic inflammation is characterised by monocytosis.

Except for humoral mechanisms the reflex ones are important in occurrence of the general manifestations of inflammation. For example, reflex of Goltz, i.e., cardiac arrest following mechanical irritation of the abdomen in the frog, is increased in cases of inflammatory changes in the abdominal organs.

Forms of inflammation

Depending on the character of the reaction (on the predominance of one of the inflammatory phenomena) alterative, exudative-infiltrative and proliferative (productive) inflammatory processes are distinguished.

Alterative inflammation occurs in cases of infections and intoxications in parenchymatous organs, therefore it is called parenchymatous one. In cases of expressed necrotic changes alterative inflammation is named necrotic one.

Exudative-infiltrative inflammation is divided into serous, fibrinous, purulent, putrefactive, hemorrhagic and mixed.

Proliferative, or productive, inflammation is observed in chronic infections: tuberculosis, syphilis, leprae, rheumatism, in granulomatous acute infections (typhus), as well as in prolonged irritation of skin with various chemical substances, etc.

Course of inflammation

According to its course, inflammation may be acute, subacute and chronic.

Acute inflammation is characterized by enough expressed intensity and by short duration. It is accepted to think, that clinically it is finished during two weeks. After its form it usually is exudative-infiltrative one. Polymorphonuclear leukocytes are the main its effectors.

Chronic inflammation differs by weak intensity and large duration – from several months up to many years and decades. After its form it is proliferative one. Monocytes and lymphocytes play the leading role. Chronic inflammation can be primary and secondary chronic one (owing to transition of acute inflammation into chronic one).

Subacute inflammation takes the intermediate position. Its clinical duration roughly is 3–6 weeks.

Outcomes of inflammation

The following outcomes of inflammation are possible:

1. Practically total restoration of structure and functions (return to normal state). It is observed in insignificant damage, when the restoration of specific elements of tissue happens.

2. Formation of scar (return to normal state with partial restoration). It is observed in the significant tissue defect on the site of inflammation and its replacement by connective tissue. Scar can not affect functions or can lead to disturbances of functions as a result of a) deformations of organs and tissues (for example, scar changes of heart valves) or b) displacement of organs (for example, lungs as a result of formation of scar tissue in the thoracic cavity in cases of pleurisy or pericarditis).

3. Destruction of tissue and sometimes of the organism as a whole in necrotic inflammation.

4. Death of the organism in definite localization of inflammation, for example, in asphyxia owing to diphteritic exudate in larynx. The localization of inflammation in vital organs is menacing.

5. Development of complications of inflammatory process:

a) efflux of exudate into cavity, for example, with development of peritonitis in inflammatory processes of the abdominal organs;

b) formation of pus with development of abscess, phlegmon, empyema, pyemia;

c) sclerosis or cirrhosis of organ as a result of the excessive growth of connective tissue in proliferative inflammation.

6. Transition of acute inflammation into chronic one.

In the clinical outcome of inflammation the main disease has the large significance, if occurrence of the inflammatory focus (focuses) is connected with it.

Setting up the experiment. Discussion of results and formation of conclusions.

Simulation of the "Kongheim experiment": Fix the frog on the cortical plate in a prone position so that the lower third of its abdomen is at the edge of the side opening of the plate. Cut the skin on the lateral surface of the abdomen. Open the abdominal cavity (the length of the incision is 0.5–0.7 cm). With tweezers, carefully remove the loop of the small intestine, straighten the mesentery above the opening of the plate and fix the loop of the small intestine to the plate with pins. Observe under a microscope (at low and medium magnification) the development of the main vascular phenomena during inflammation. Draw the vascular changes observed under the microscope and record their sequence. In animals with inflammation, the following vascular phenomena were observed under a microscope: short-term ischemia, arterial hyperemia, venous hyperemia, prestasis and stasis.

Modeling the cellular composition of exudate in the dynamics of inflammation:

Smears-imprints with the cellular composition of the exudate are prepared in advance: 1 ml of staphylococcal culture suspension (2 billion microbial bodies) is injected into the peritoneum of ants. Animals are removed from

the experiment after 40 minutes (after 3 and 24 hours) with the help of thiopental anesthesia. The abdominal cavity is opened and smears-prints are prepared, touching the wall of the intestine with a glass slide. Smears are air-dried, fixed for 5 minutes and stained with Romanovsky dye for 15 minutes. To examine under a microscope with immersion the pre-prepared preparations of 40-minute, 3- and 24-hour exudates. To determine changes in the cellular composition of the exudate in the dynamics of inflammation. Pay attention to the phenomena of phagocytosis by leukocytes. Draw drugs. Initially, granulocytes predominate among exudate leukocytes in the focus, mainly neutrophils, and monocytes-macrophages predominate later.

Discussion of the results of the experiment

- It is known that vascular reactions develop simultaneously with the influence of an inflammatory agent, since the initial ones are reflex. First of all, short-term ischemia develops, which is caused by spasm of arterioles. It is a consequence of reflex excitation of vasoconstrictors from direct exposure to an inflammatory agent. Short-lived, from a few seconds to a few minutes.
- Arterial hyperemia, which in turn is caused by the expansion of arterioles, the mechanism of which is associated with axon-reflex excitation of vasodilators or with direct vasodilator effects of inflammatory mediators (neuropeptides, AX, etc.). Observed for about half an hour.
- Venous hyperemia, which is based on several groups of factors: 1) violation of the rheological properties of blood; 2) changes in the vascular wall; 3) tissue changes.
- Pre-static state, characterized by a pendulum-like movement of blood, when due to increasing stagnation of blood, loss of vascular tone and sharp expansion of capillaries and venules, it moves from arteries to veins during systole, and in the opposite direction during diastole.
- Then stasis develops, the mechanisms of which are associated with a violation of the rheological properties of blood, which in turn is associated with changes in the structure of blood flow in microvessels, enhanced intravascular aggregation of erythrocytes due to changes in the physicochemical properties of their membranes, the protein composition of blood, and slowing of blood flow.
- Since the slowing down of blood flow in certain branches of the microcirculatory channel and the marginal state of leukocytes can develop quite quickly, and it takes 2–12 minutes for an emigrating neutrophil to pass through the vascular wall, the appearance of a significant number of granulocytes in the focus of inflammation can be observed up to 10 minutes after its onset . The rate of accumulation of neutrophils in the focus of inflammation is highest in the first two hours, then decreases. Granulocytes predominate in the focus of inflammation up to 24 hours, and in the period from 24 to 48 hours they are replaced by monocytes, the number of which reaches a maximum on the 2nd–3rd day. Emigration of monocytes begins simultaneously with the release of neutrophils, but at first its speed and mass are much lower. In addition, neutrophils, which are short-lived, undergo apoptosis and disappear en

masse between 24 and 48 hours, while monocytes survive longer, especially when transformed into macrophages.

Forming conclusions based on the experiment

Vascular reactions observed in Kongheim's experiment occur at the same time as exposure to the phlogogenic agent and have a staged course: short-term ischemia, arterial hyperemia, venous hyperemia, and prestasis and stasis.

When studying the cellular composition of the exudate in the dynamics of the course of the inflammatory process, an increase in the number of leukocytes, in particular neutrophils in the focus of inflammation, and subsequently an increase in monocytes-macrophages was primarily revealed.

Tasks for independent work on the topic "Inflammation"

The student is offered 2-3 case studies with metabolic disorders during inflammation. It is necessary to determine the signs and type of inflammation depending on the predominant component. Be able to explain the mechanisms of occurrence. Analysis of errors with an explanation of the correct answers.

List of questions and works to be studied:

1. Definition of the term "inflammation". The main signs of inflammation.
2. Etiology of inflammation. General pathogenesis of inflammation.
3. Mediators of inflammation.
4. The sequence of vascular phenomena of the focus of inflammation.
5. Classification of inflammation.
6. Concept of exudation, exudate.
7. The concept of emigration of leukocytes. Mechanisms of emigration.
8. General manifestations of inflammation.
9. Relationship between local and general changes during inflammation.

List of practical skills that must be mastered:

Determination of signs of the inflammatory process using case tasks:

- Redness;
- Swelling;
- Pain;
- Increase in local temperature;
- Violation of function.

Determination of the type of exudate by cellular composition: fibrinous; serous; hemorrhagic; purulent; putrid and mixed exudate.

Situational tasks KROK-1 to determine the final level of knowledge

1. After tearing the meniscus, the athlete developed inflammation of the knee joint. Which of the pathogenetic factors is the main link in the pathogenesis of inflammation?

A. Arterial hyperemia. *C. Damage.* *E. Venous hyperemia.*
B. Pain. *D. Edema.*

2. Microscopy of the frog mesentery preparation revealed that in some capillaries a pendulum-like movement of blood is noted, while formed elements (in particular, leukocytes) move from the axial layer to the parietal layer, and some even release pseudopodia into the capillary wall. What stage of the vascular reaction during inflammation corresponds to the described phenomenon?

A. Stasis. *D. Arterial hyperemia.*
B. Short-term vasospasm. *E. Venous hyperemia.*
C. Prestasis.

3. When simulating inflammation of the lower limb in animals, the body temperature increased, the content of antibodies and leukocytes in the blood increased. What substances caused the development of these general reactions of the body during inflammation?

A. Interleukins. *C. Mineralocorticoids.* *E. Somatomedins.*
B. Glucocorticoids. *D. Leukotrienes.*

4. A patient with an acute inflammatory process complains of headache, pain in muscles and joints, drowsiness, fever. Leukocytosis, an increase in the content of proteins, including immunoglobulins, was found in the blood. Which of the mediators of inflammation causes these changes to the greatest extent?

A. Interleukin-1. *C. Bradykinin.* *E. hromboxane A2.*
B. Histamine. *D. Complement.*

5. During the examination of the skin, the doctor found a purulent process in the patient in the form of rounded reddish elevations, surrounded by a zone of hyperemia. What mediators of inflammation caused the phenomenon of vascular hyperemia?

A. Interleukin-1. *D. Thromboxane.*
B. Histamine. *E. Lysosomal enzymes.*
C. Platelet activation factor.

6. The woman was bitten by a dog in the area of the right calf muscle. During examination: edema, swelling of tissues, hyperemia of the skin is observed in the area of the bite. Which of the listed mechanisms is involved in the development of arterial hyperemia during inflammation?

A. Compression of venules by swollen tissue. *D. Swelling of the endothelium.*
B. Release of histamine. *E. Increase in blood viscosity.*
C. Decreased elasticity of the vascular wall.

7. According to Schade's physicochemical theory, the following occurs in the inflammation zone: hyperosmia, hyperonkyia, acidosis. The development of hyperosmia, to some extent, is associated with an increase in the concentration of K+ in the area of inflammation. State the causes of hyperkalemia in inflammatory exudate.

A. *Intensive destruction of damaged cells.*
B. Increased permeability of the vascular wall.
C. Activation of proliferative processes.
D. Suppression of glycogenolysis in the area of inflammation.
E. An excess of Ca++ ions.

8. A 60-year-old man fell ill with croupous pneumonia as a result of prolonged stay in wet clothes at a low ambient temperature. What is the cause of this form of lung inflammation?

A. Effect of low humidity on the body. *D. Pneumococcus.*
B. Decreased reactivity of the body. *E. Age.*
C. Effect of low temperature on the body.

9. The patient's caries was complicated by pulpitis, which was accompanied by unbearable pain. What phenomenon in inflammation of the pulp is the main cause of pain?

A. Primary alteration. *C. Exudation.* *E. Proliferation.*
B. Ischemia. *D. Emigration of leukocytes.*

10. A 30-year-old man complains of shortness of breath, heaviness in the right half of the chest, general weakness. Body temperature is 38.9 °C. Objectively: the right half of the chest lags behind the left. Exudate was obtained during pleural puncture. What is the leading factor of exudation in the patient?

A. Increased permeability of the vessel wall. *D. Hypoproteinemia.*
B. Reduction of resorption of pleural fluid. *E. Aggregation of erythrocytes.*
C. Increase in blood pressure.

11. When modeling inflammation on the mesentery of a frog, the marginal standing of leukocytes and their emigration through the vascular wall is observed. Which of the listed factors determines this process?

A. Influence of chemotactic substances.
B. An increase in oncotic pressure in the focus of inflammation.
C. Reduction of oncotic pressure in blood vessels.
D. Increase in hydrostatic pressure in blood vessels.
E. Reduction of hydrostatic pressure in blood vessels.

12. A microscopic examination of a punctate from a focus of inflammation in a patient with a skin abscess revealed a large number of different blood cells. Which of the cells listed below are the first to arrive from blood vessels in tissues during inflammation?

A. Monocytes. B. Basophils. C. Neutrophils. D. Eosinophils. E. Lymphocytes.

13. A 34-year-old woman developed sharp pain, redness, and swelling on her right index finger after careless handling of an iron. After a few minutes, a bubble filled with a clear straw-yellow liquid appeared. The changes will be described as a manifestation of which pathological process?

A. Traumatic edema. *D. Proliferative inflammation.*
B. Exudative inflammation. *E. Vacuolar dystrophy.*
C. Alterative inflammation.

14. A 38-year-old man was admitted to the therapeutic department with a diagnosis of "right-sided exudative pleurisy." The fluid obtained from the pleural cavity of the chest is transparent, has a relative density of 1.020, contains 55 g/l of protein, an albumin-globulin ratio of 1.6, the total number of cells in 1 μl is 2.8, and the pH is 6.5. What type of exudate does the patient have?

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

15. A 17-year-old boy became acutely ill, his body temperature rose to 38.5 °C, he developed a cough, runny nose, lacrimation, and discharge from the nose. What inflammation developed in the young man?

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

16. A 5-year-old child developed an acute respiratory disease, which was accompanied by coughing and discharge of a significant amount of mucus from the nose. What is the type of inflammation in a sick child?

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

17. The patient's knee joint swelled a day after the injury. During its puncture, 30 ml of pink liquid with a specific density of 1.020 was obtained. Its total protein content is 3%, albumins – 0.3 %, globulins – 2 %, fibrinogen – 0.7 %. Leukocytes – 1–3, erythrocytes – 15–20, sometimes up to 50 in the field of vision. What is the nature of the exudate obtained during the puncture of the patient's knee joint?

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

18. A foul-smelling liquid containing biogenic amines and gases was found in the pleural cavity of a patient with pleurisy. What kind of inflammation in this case?

A. Alterative. B. Catarrhal. C. Purulent. D. Fibrinous. E. Rotten.

19. With gout, the patient often observes an increase and deformation of the joints due to the development of the inflammatory process. What type of inflammation underlies these changes?

A. Alterative. B. Exudative. C. Fibrinous. D. Mixed. E. Proliferative.

20. The patient has a purulent wound in the maxillofacial area. Which of the listed cells play the main role in the regeneration phase of the wound process?

A. Neutrophils. B. Monocytes. C. Eosinophils. D. Fibroblasts. E. Lymphocytes.

21. When studying inflammation, animals were injected with a lethal dose of tetanus toxin into the cavity of an abscess induced by turpentine. But the animal did not die. Indicate the most likely reason for this research result.

A. Formation of a barrier around inflammation.

B. Activation of antibody synthesis during inflammation.

C. Stimulation of leukopoiesis during inflammation.

D. Increased vascularization of the site of inflammation.

E. Activation of the detoxification function of phagocytes.

22. With various inflammatory processes in a person, the number of leukocytes in the blood increases. This regularity is a manifestation of:

A. Adaptations. *C. Reparations.* *E. Degenerations.*

B. Regeneration. *D. Transplants.*

Standards of correct answers to the KROK-1 task

1	2	3	4	5		6	7	8	9	10	11
C	*C*	*A*	*A*	*B*		*B*	*A*	*D*	*C*	*A*	*A*
12	13	14	15	16	17	18	19	20	21	22	12
C	*B*	*B*	*A*	*A*	*D*	*E*	*E*	*D*	*A*	*A*	*C*

Recommendations for registration of work results

1. Written answer to test tasks (initial level of knowledge).

2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.

3. Independent work of students. Protocol for solving cases of tasks with the identification of signs of inflammation.

4. Protocol for solving situational tasks with an explanation of the correct answers.

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Topic 8. Fever

Justification of the topic: Being a typical pathological process that arose evolutionarily and is manifested by an increase in body temperature due to the action of pathogenic stimuli, fever accompanies many diseases. In other words, fever is a nonspecific reaction of the body, which is associated with a temporary adjustment of thermoregulation to a new, higher level, regardless of the effects of the external environment. It should be emphasized that fever is not an independent disease, it exists as a specific or non-specific symptom of a large group of diseases. That is, it has similar features and a single mechanism of development in various infectious and non-infectious diseases. Since, together with a number of pathological phenomena in the body, fever activates a number of protective and adaptive reactions in the body, and this, in turn, allows it to be used in practical medicine in a complex of medicinal measures. That is why the study of the main causes, mechanisms of development and course of fever is important for doctors.

Purpose of the lesson:

General – to be able to characterize fever as a typical pathological process, to study functional changes in the body, the main mechanisms of their development, and the principles of fever therapy.

Specifically:

Know:

1. Interpretation of the concepts "fever", "hyperthermia", "pyrogenic substances".
2. Classify fever, pyrogenic substances.
3. Identify the main manifestations of a febrile reaction, explain the mechanism of their occurrence in the dynamics of the development of the process.
4. Explain the difference in the pathogenesis of fever and hyperthermia.
5. To determine which phenomena in the body during fever are actually pathological, and which are protective and adaptive in nature, in order to justify the symptomatic and pathogenetic therapy of fever.

Be able:

1. Simulate fever in animals by injecting pyrogenal and justify your conclusions.
2. Explain the general mechanisms of fever, metabolic disorders during fever.
3. Identify and differentiate the main signs of different variants of fever according to the nature of temperature curves (fever of constant, weakening, intermittent, reversed, hectic, perverse, atypical, wave-like, short-term type).

Practical experience:

Determination of the nature of fever on the temperature curve:

- Permanent type;
- Weakening;
- Intermediate;
- Reverse;
- Hectic;
- Perverted;
- Atypical;

- Wave-like;
- Short-term type.

The graphological structure of the topic "Fever" is attached.

Material and methodological support of the theme "Fever":

1. Lectures;
2. Methodical instructions for teachers;
3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational tasks to determine the final level of knowledge;
6. A set of step-1 tasks;
7. A set of schemes and tables (presentation);
8. A set of cards (temperature sheets) with different variants of temperature curves;
9. Video films;
10. For the experiment (experimental animals – rabbit; electric thermometers or medical thermometers, syringes, pyrogenal solution containing 2 units in 1 ml (1 unit is the minimum pyrogen dose), petroleum jelly).

Oriented map of students' work on the topic "Fever"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of knowledge	10	Written answer to test tasks	Test tasks	Study room
2	Analysis of theoretical material	35	Analysis of theoretical material based on control questions of the topic, situational tasks, tasks KROK-1	Topic control questions, KROK-1 tasks, situational tasks	
3	Practical part (conduct experiment)	30	Introduction and preparation for setting up the experiment. Setting up the experiment. Discussion of the results of the experiment and formulation of conclusions	Rabbit; electric thermometers or medical thermometers, syringes, pyrogenal solution containing 2 units. in 1 ml (1 unit is the minimum pyrogenic dose), petroleum jelly	
4	Determination of the final level of knowledge and skills. Summary.	15	Determination of the initial level of formation of knowledge and skills	KROK-1 tasks, situational tasks	

FEVER

Fever (febris in Latin) is a general reaction of warm-blooded animals and man to the action of a harmful, mainly infectious, agent, which is characterised by a disturbance of heat regulation with elevation of body temperature regardless of the temperature of the external environment.

Etiology of fever

There are infectious and noninfectious fevers.

1) Infectious fevers are mainly observed. They result from the action of bacteria, viruses, protozoa, their toxins and products of vital activity, as well as specific pyrogenic substances, received from microorganisms or which are contained in products of bacterial origins and tissue destruction, for example, in pus, tissue extracts from an inflammatory focus and putrescent tissues (lipopolysacharides, nucleoproteides).

2) Noninfectious fevers: induced by proteins, salts, drugs and neurogenic one.

A) Protein-induced fever is caused by parenteral injection of heterogenic protein or various highmolecular endogenic products of protein destruction which are formed in haemorrhages, necroses of tissues, bone fractures, erythrocyte hemolysis, malignant tumors, burns. This kind of fever is also caused by action of toxic products of protein nature, which are absorbed through changed mucous membrane of intestine, or by decreased function of excretory organs which excrete these products.

B) Salt fever is caused by injection of hyperosmotic solutions of sodium chloride. It probably results from osmotic disturbances and tissue destruction.

C) Drug fever – fever induced by pharmacologic substances arises after injection of adre-naline, thyroxine, cocaine, caffeine, alpha-dinitrophenole, etc. Ones of them are sympatheticotropic and stimulate the centre of thermoregulation, the others act directly to tissue metabolism causing the increased oxidative processes and excessive thermoproduction.

D) Neurogenic fevers arise from injuries and contusions of brain, in thermal prick, tumors of the intermediate brain, epilepsy, psychic traumas, haemorrhages to the 3rd ventricle of brain and reflex irritations of centre of thermoregulation (hepatic or renal colic).

The pyrogenic substances are the direct cause of development of fever (from the Greek words pyros – fire and pyretos – heat). They are endogenic and exogenic.

Exogenic (primary) pyrogenes are obtained from microorganisms, they are components of endotoxins. After their chemical structure they are lipopolysacharides which contain lipoid A, or free of proteins polysacharides. Some bacterial exotoxins have pyrogenic properties (diphteritic toxin, toxin of haemolytic streptococcus). Protein substances of series of infectious agents (dysentery, paratyphus, tuberculosis) also have pyrogenic properties. Exogenic pyrogenes cause fever indirectly through production of endogenic pyrogenes.

Endogenic (secondary, leukocytic) pyrogenes are thermolabile polypeptides or proteins with m.m. from 1,5 to 40 KD, which do not have species specificity. Interleukin-1 also has the properties of endogenic pyrogenes. Endogenic pyrogenes are produced by all of the phagocytising cells, mainly by neutrophils, monocytes, mobile and fixed macrophages.

Thus, production of endogenic pyrogenes is the main pathogenetic factor of fever.

Pathogenesis of fever

In fever thermoregulation "is switched" to new, higher, temperature level (P.N. Vesyolkin). Under the action of endogenic pyrogene "the fixing point" in the preoptic region of hypothalamus is set up to higher temperature level, than in norm, and recognizes the normal temperature of body as a very low one. As a result "the fixing point" directs the impulses to centres of the autonomic nervous system, which regulate processes of thermoproduction and thermoexcretion. The stimulation of the sympathetic nervous system and inhibition of the parasympathetic one is happened. Thermoproduction is increased and thermoexcretion is decreased. Further the new balance between thermoproduction and thermoexcretion on higher level is formed.

Stages of fever

I) The Stage elevation of the body temperature (stadium incrementi). It usually is short-term. The thermoproduction is increased and thermoexcretion is decreased owing to spasm of skin vessels and reduced perspiration. In the fast rise of temperature it is accompanied by rigor. Rigor is developed owing to difference between the temperature of internal environment and temperature of skin and is reflex.

II) The Stage in which the temperature is at its acme (stadium fastigii) is characterized by new balance between thermoproduction and thermoexcretion on higher level. These processes counterbalance one another and the increase of body temperature is ceased. The increased thermoexcretion is due to dilation of skin vessels and increase of frequency of respiration. Paleness is followed by hyperemia, skin temperature is increased, rigor is ceased and followed by heat.

III) The Stage of decreasing temperature (stadium decrementi) is characterized by strengthened thermoexcretion and its prevalence to thermoproduction, which remains the increased. The strengthened thermoexcretion is due to increased perspiration and dilation of skin vessels.

The decrease of temperature can happen by degrees during several days (lysis) or very fast during several hours (crisis). The critical decrease of temperature, especially in insufficiency of cardiovascular system, is dangerous because of fall of blood pressure and development of collapse owing to dilation of skin vessels.

Types of temperature curves

There are following fevers after degree of increased temperature:

1) subfebrile (increase of temperature to 38 degrees);

2) moderate (increase of temperature to 39 degrees);

3) high (increase of temperature from 39 to 41 degrees);

4) excessively high, or hyperpyretic (above 41 degrees).

After the character of temperature curves there are following main fevers.

1. **Continuous fever (febris continua).** The increased temperature for some time is on high level. The difference between the morning and evening temperature does not exceed 1 degree. The ending of fever can be sudden (crisis) or gradual (lysis). It is observed in abdominal typhus in the first half of disease, in croupous pneumonia, in typhus and others infectious diseases.

2. **Remittent fever (febris remittens).** The difference between the morning and evening temperature is more than 1 degree, but it does not decrease to norm. It is occurred in the majority of viral and many bacterial infections, in the second half of abdominal typhus, catarrhal pneumonia, tuberculosis, exudative pleurisy, sepsis.

3. **Intermittent fever (febris intermittens)** is characterized by correct alternation of the short-term attacks of fever (paroxysms) and nonfever periods (apyrexia). The high temperature is observed for some hours, then it decreases to norm and below it, then it is increased again. The duration of nonfever periods can be various one. This temperature curve is characteristic to malaria. The separate paroxysms of fever can be observed each 3-rd day (febris quartana) or 2-nd day (febris tertiana), or be repeated daily (febris quotidiana). Besides it is characteristic to purulent infections, tuberculosis, uvenile rheumatoid arthritis, lymphomas, etc.

4. **Recurrent fever (febris recurrens).** In comparison with intermittent fever it is characterized by longer periods of increased temperature (5–8 days), between the periods of normal temperature. The duration of this apyrexia corresponds to the duration of fever paroxysms. Such curve is characteristic to returnable typhus.

5. **Exhausting fever (febris hectica).** It lasts for a long time with significant daily fluctuations (3-5 degrees). It is characteristic to sepsis and severe tuberculosis.

6. **Perverted fever (febris inversus)** is characterized by increase of temperature in the mornings and fall in the evenings. It is occurred in some forms of sepsis and tuberculosis.

7. **Atypical fever (febris athypica)** is characterized by several amplitudes of temperature during a day with total disturbance of circad rythmus. It is observed in sepsis.

Besides **ephemeric fever (febris ephemera)** can be occur – the easy short-term increase of temperature not more than 37,5–38 degrees with nonregulary fluctuations. It is observed in various neuro-endocrine disturbances and chronic infections.

Involvement of the nervous, endocrine and immune systems in the development of fever

The development of febrile reaction is closely related to the functional state of the cortex and subcortical centers of thermoregulation. In a classic experiment with thermal injection into the region of the gray hill proved participation in the central nervous system temperature rises. The body temperature may increase a person under the influence of hypnosis, and mental illness, hysteria (psychogenic fever).There are cases of short-term increase in temperature from the speakers, artists, students examinees (emotional fever).

In animals deprived cortex, thalamus and striatum, and retained the ability to thermotaxis fever. For example, in dogs with bilateral decortication fever occurs even with a large rise in temperature than in intact animals. Apparently, when decortication eliminates the inhibitory effect on the cortex lowers the center of thermoregulation.

With deep ether anesthesia, when braking extends from the cortex to the subcortex, fever dramatically suppressed.

Region of the hypothalamus considered the main automated thermoregulation center. All three groups of nuclei of the hypothalamus (anterior, middle and rear) complex involved in the occurrence of febrile reactions.

The rear and middle part of the hypothalamus part mainly regulate heat production and heat retention in the body through the sympathetic nervous system (increased metabolic oxidative processes, peripheral vasoconstriction) and somatic innervation of skeletal muscle (increase in muscle tone and muscular tremor). The front part of the hypothalamus regulates heat mainly through the parasympathetic innervation (vasodilation), cholinergic sympathetic fibers (sweating) and somatic innervation of respiratory muscles (rapid breathing).

During stimulation the anterior nuclei (supraoptic, paraventikulyarnoe) body temperature falls. With the destruction of their excessive temperature rise. Complete destruction of the hypothalamus or transection of the brain stem below the hypothalamus turns homoiothermal poikilothermal animals: they lose their thermoregulation and fever are not capable. Of hypothalamic thermoregulation center impulses are sent to the spinal cord. After transection of the spinal cord in the thoracic chemical thermotaxis is not broken, and the physical is lost. The febrile reaction is preserved, but animals can quickly overheat in conditions of high ambient temperature. At high transection of the spinal cord in the cervical spine is broken and the chemical, physical and thermotaxis, the animal is approaching poikilothermic and can not be a fever.

Experimental studies of P.N. Veselkin confirmed their participation nervous reflex mechanisms as triggers febrile reactions. Under the influence of pyrogens activates the pituitary-adrenocortical system. Primary dysfunction of the endocrine glands may be affected by the nature of the febrile reaction due to the fact that endocrine disorders vary metabolism and reparative processes, the reactivity of the central nervous system, autonomic centers and the Office of thermoregulation.

If hyperthyroidism is observed constant low-grade fever. The hormone thyroxine increases the oxidative processes in tissues, and thermogenesis in the body increases. In patients with thyrotoxicosis fever develops rapidly and with a higher rise in temperature due to increased excitability of the centers of thermoregulation in relation to pyrogens. The deficit in the formation of prostaglandins thermostatic hypothalamic nuclei may be due to excessive concentration of glucocorticoids in the blood, neurological damage hypothalamic nerve centers with hemorrhages. Inhibition of prostaglandin production inhibits the development of febrile reactions when exposed to the body of pathogenic factors expressed even in the face of neutrophilic leukocytosis.

Change the excitability of the sympathetic-adrenal system in different ways affects the development of febrile reactions. Lack of activity of the sympathetic-adrenal system (toxic diphtheria, myxedema, cretinism) is combined with the weakening of fever due to lack of production of catecholamines in the hypothalamic thermostatic centers, weak stimulation of

uncontractile and contractile thermogenesis. Inhibition of development of fever does not allow the body to create effective mechanisms of nonspecific and specific defense. Increased activity of the sympathetic-adrenal system facilitates the development of fever, as noted in the overproduction of thyroxine (hyperthyroidism), hyperkateholaminemia (chromaffin tissue secreting tumors, pheochromocytoma), taking sympathomimetic drugs. The rapid development of fever is due to stimulation of phagocytosis and the formation of pyrogens by leukocytes, enhancing education of neurotransmitters in the hypothalamic thermostatic centers, increasing mainly uncontractile thermogenesis and heat transfer limitations. In these cases, the participation of fever in the formation of specific and nonspecific defenses is limited by the degree of metabolic disorders, and other immunogenesis processes induced by prolonged increase in adrenergic influences.

Metabolic changes during fever

Metabolic diseases with fever **caused by:**

1) The characteristics of the etiological factor, most infectious;

2) increase in body temperature;

3) fasting, which is usually accompanied by fever, as febrile body due to loss of appetite and digestive disorders, and consumes less assimilates food than usual.

In most cases there is increased metabolism, underlies the increased heat generation.

When fevers moderate **basal metabolic** rate may increase by 5–10 %. Oxidative processes increased somewhat mainly due to increase respiration and heart activity.

Basal metabolism is enhanced by activation of the sympathetic-adrenal and hypothalamic-pituitary-adrenal systems, release of iodine in the blood of thyroid hormones and temperature stimulation of metabolism. These processes lead to a generalized intensification and acceleration of the individual to the predominant limiting parts of metabolism. On the one hand, it provides energy and substrates for increased metabolic function of several organs and physiological systems, and on the other – improves the body temperature. In stage I, fever increase metabolic rate increases body temperature by 10–20 %. Basal metabolic rate decreases in III stage fever.

Protein metabolism. If fever with high fever spending a disproportionate expenditure of protein fat and carbohydrates. The strong decay of the protein leads to an increase in nitrogen excretion in the urine (negative nitrogen balance). People with mild fever part of the protein in the overall energy balance often remains within the normal range (15–20 %). In fevers with high temperature part of the protein can be 30 % or higher. In the urine increases the urea content. Especially increased breakdown of protein in infectious fevers (toxigenic collapse), such as pneumonia. The urine is increased ammonia and urea. In the strong decay of the protein are important degree of intoxication, degenerative and inflammatory changes in tissues, starvation due to reduced appetite and digestion of food deterioration.

Carbohydrate metabolism increased and changed, is characterized by a significant activation of glycogenolysis and glycolysis. Products of high carbohydrate decomposition are used in the activated oxidative processes. This is evidenced by regular increase of respiratory rate. However, activation of glucose oxidation combined with low energy efficiency of its. This greatly stimulates the breakdown of lipids.

There is a depletion of liver glycogen and hyperglycemia due to activation of the sympathetic nervous system and increased release of adrenaline, as well as more frequent than normal, the occurrence of alimentary glycosuria. The respiratory rate in stage I is a fever.

Fat metabolism in fever is characterized by a predominance of catabolic processes, particularly in the prolonged phase II. This is evidenced by reduction in respiratory rate to 0.5–0.7. Given the increased consumption of carbohydrates and advanced to the growing deficit in the body lipid oxidation is blocked at the stage of intermediate products, mainly – ketones, addition of metabolic disorders, it leads to increased acidosis. In this regard, during prolonged fevers, patients must consume a large amount of carbohydrates.

Markedly increased fat metabolism, especially with prolonged fever of infectious origin. With the depletion of carbohydrates increases fat oxidation, which often does not reach the end-products accumulate in the blood and ketone bodies (ketonemia) and acetone in the urine released (acetonuria).

Water and electrolyte metabolism. Water exchange is subject to considerable change. Under increased loss of fluids due to sweating and urine output.

As a result, increase metabolism and accumulation of incompletely oxidized products of metabolism in tissues is water retention, is of great importance, and renal dysfunction due to intoxication and the filter of the increase in temperature. In stage II of fever there is a delay in tissue water and chlorides, due to increased secretion of aldosterone decreased urine output. In stage III, along with a sharp increase in heat transfer and sweating is an increase of allocation of water by the kidneys, increase urine output, which is accompanied by loss of NaCI. In most cases of fever due to the collapse of the tissue increases the allocation of phosphates and potassium salts.

Exchange of electrolytes changed dynamically in the development of fever. In stages I and II in many tissues accumulate Na+, Ca2+,Cl-and other irons. In stage III irons are excreted in large quantities due to increased diuresis and diaphoresis.

Changes in the functions of internal organs during fever

The nervous system effects are observed excitation followed by inhibition of the higher nervous activity: a headache, fatigue, apathy, fatigue, drowsiness, inhibition of conditioned reflexes. Infectious fever often accompanied by confusion, delirium, hallucinations. Children react to the rise in temperature more strongly excited than the adults. In malnourished patients with fever usually occurs with symptoms of depression of the nervous system. The autonomic nervous system function is dominated its sympathetic division.

The cardiovascular system. Heart rhythm quickens due to excitation of the sympathetic nervous system and direct the heated blood to the sinus node. Typically, increased body temperature by 1 °C is accompanied by an acceleration rate of 8–10 beats. However, there may be inverse phenomenon, related, apparently, with irritation of the vagus nerve center in the medulla oblongata. For example, inflammation of the meninges, particularly tuberculous meningitis, accompanied by a lag in pulse rate from the heat. In addition to heart rate, important for the assessment of cardiovascular activity has the character of the pulse wave (pulse hard, full or thready, bisferious, etc.). Changes in the state of vessels associated with the disorder of physical heat regulation, such as a fever accompanied by a spasm of peripheral vessels and the rush of blood to internal organs. In II and especially in stage III fever vessels are dilated. Blood pressure in stage I may be somewhat increased by increasing the activity of the heart and stimulation of vasomotor centers in II – is normal or somewhat reduced, III, especially at the critical temperature drops – can dramatically decrease due to the fall of vascular tone (collapse may develop).

Breathing quickens. Shortness of breath goes in parallel increased heart rate and raise body temperature. The function of the respiratory center also strengthened due to increased blood temperature and acidosis associated with the accumulation of incompletely oxidized products of metabolism.

Function of the digestive system changed: reduced secretion of digestive glands and the secretion of bile, there is dryness of the mucous membranes of the mouth and tongue, which is usually lined with white coating, developed spasms of the pylorus, inhibited gastric motility and emptying it inhibited, which causes vomiting. Reduced intestinal peristalsis, which leads to constipation with amplification processes of decay, flatulence and bloating development. For intestinal infections (dysentery, typhoid fever) is characterized by diarrhea. Formed in the intestine toxins acting on different parts of the central nervous system and peripheral tissues, help reduce blood pressure, weakening of the heart, headache, etc. The lack of digestion and absorption lead to a lack of appetite, decrease food absorption.

Renal function also changed, especially in infectious fevers (such as scarlet fever, septic conditions). The amount of urine at the height of fever significantly reduced. Water retained by tissues. The urine content increases nitrogenous substances, sometimes there is the appearance of protein (proteinuria) and an increase in products of protein metabolism.

The endocrine system. There is activation of the pituitary-adrenal cortex, with an infectious fever increases the release of thyroid hormone, which increases the basal metabolic rate. Excitation of the sympathetic nervous system in stages I and II is accompanied by fever, increased formation of adrenaline.

In fevers with high temperature sometimes observed degenerative changes predominantly in parenchymatous organs. Changes are in the nature of

cloudy swelling, sometimes waxy degeneration, fatty infiltration. The phenomena of degeneration in the internal organs causing a violation of their functions, in turn affecting the course of the hectic process.

In general, at a fever function of organs and systems are changed due to effects on the primary pyrogenic agent of an infectious or noninfectious origin, fluctuations in body temperature, influence the regulatory systems of the body; involvement in the implementation of a variety of thermoregulatory responses. Consequently, this or that deviation functions of the organs in the feverish reaction is an integrative response to the above factors. Biology is the meaning of these changes – to ensure optimum life of the organism under these conditions. However, fever is often damaged and the bodies themselves.

Protective value and pathological manifestations of fever

Fever is seen primarily as formed in the evolution of protective and adaptive reaction to the action of different pathogenic factors. However, like inflammation, it can provide, along with positive and negative effects on the body.

Fever – general thermoregulatory reaction to the impact of pyrogenic agents. This is typical, stereotyped reaction. In each patient is accompanied by both adaptive (mostly) and, under certain conditions, pathogenic (less) effects. The leading criterion for evaluating the significance of fever is a useful criterion for achieving the body of adaptive outcome. It lies in the development of such a reaction, which provides the inactivation and / or destruction of the media and pyrogenic properties usually increase the body's resistance to this as well as to other similar effects.

By the adaptive effects include fever, direct and indirect bacteriostatic and bactericidal effects, potentiation of specific and nonspecific factors of immunobiological surveillance of non-specific activation of the stress response.

Protective and adaptive value of fever is confirmed by the following observations:

1) fever is enhanced immune response due to the activation of T and B lymphocytes, the acceleration transformation of B lymphocytes into plasma cells that stimulate antibody production, increases the formation of interferon;

2) a moderate degree of increase in body temperature can activate phagocytic cells and IR-lymphocytes;

3) activated by enzymes that suppress the reproduction of viruses;

4) slow proliferation of many bacteria and decreases the stability of microorganisms to medicines;

5) increases the barrier and antitoxic liver function;

6) hepatocytes strongly produce acute phase proteins, some of these proteins divalent cations bind necessary for the reproduction of microorganisms.

The negative impact of fever on the body is detected mainly in a pronounced and prolonged increase in body temperature. It is associated with stimulation of the heart's functions, which can lead to overload a form of heart failure. Poses a risk of collapse, the possibility of a critical reduction in body temperature in the final stages of fever. With a high degree of fever may occur suppression of immune responses. In children with high fever

may develop seizures, cerebral edema, or acute circulatory failure due to the lability of the water-salt metabolism.

A large part of the observed in fever of metabolic and functional changes is a manifestation of the acute phase response, one component of which is itself a fever. Manifestation of this reaction is the development of stress, leukocytosis, synthesis in the liver of acute phase proteins, increased activity of the immune system. The major pathogenic role in the development of the acute phase response are secondary pyrogens – IL-2, IL-6, TNF, interferon. Secondary pyrogens are responsible for the development of stress and other hormonal changes, for stimulating the synthesis of acute phase proteins, the development of negative nitrogen balance, leukocytosis and activation of phagocytes function and immunological changes. With their action related to anorexia, muscle weakness and apathy.

Pathophysiological principles of antipyretic therapy

The main pathogenetic principle of antipyretic therapy is to reduce the "setpoint" center of thermoregulation, which is achieved by inhibition of prostaglandin E formation by cyclooxygenase inhibitors (acetylsalicylic acid, indomethacin, acetaminophen), and inhibitors of phospholipase A2.

Treatment of fever is built to meet the requirements etiotrop, pathogenetic and symptomatic principles. However, it must be remembered that the increase in body temperature during fever has adaptive value, consisting in the activation of protective and compensatory adaptive reactions aimed at the destruction or weakening of the pathogenic agent. These reactions include the reaction of cellular and humoral immunity, metabolic, plastic.

Etiotropic treatment aims to eliminate and / or termination of the pyrogenic agent.

Regardless of the origin of the primary pyrogen may conduct activities to inhibition of synthesis and the effects of leukocyte pyrogen (IL-1, IL-6, tumor necrosis factor. Y-IFN).

Symptomatic treatment aims to eliminate the problem of painful and unpleasant feelings and events, contributing to the status of a patient with fever These symptoms include severe headache, nausea and vomiting, pain in joints and muscles, cardiac arrhythmia. With these and other similar signs are used appropriate medication and non-medical drugs (painkillers, tranquilizers, cardiotropic).

The use of fever

Detected at a fever processes, the importance of which can be evaluated as a protective-adaptive. Thus, fever stimulates the production of antibodies, interferon, the processes of phagocytosis, hematopoiesis, and the antitoxic barrier function of the liver. It inhibits the development of certain allergic reactions. When the body temperature to 38–39 °C disrupted replication of certain viruses, bacteria and tumor cells, the influence of IL-1 on cellular and humoral immunity. Fever can lower the survival of microbes. At a fever-induced damage in the striatum of animals, observed more favorable course

of pneumonia and chicken cholera. Artificial fever contributed to the survival or extends the life of animals infected with anthrax, erysipelas streptococcus or staphylococcus. Fever was used for the treatment of hypertension of renal origin (vasodilation, increased blood flow to the kidneys, leading to lower blood pressure).

As adaptation of the body, formed in the process of evolution, fever in cases of moderate temperature increases may be useful in the fight which caused her body to an infectious agent. At the same time it must be assumed that the positive effects of fever on the body manifests itself only when it is moderate and is briefly flow. Pyrotherapy carried out by playing with fever pyrogens.

Currently used for therapeutic purposes Highly drugs pyrogen – pirogenal, etc. pireksal pyrotherapy used to treat late-stage syphilis, osteoarticular tuberculosis and other infectious diseases.

The use of pyrogen in the treatment of syphilis effectively because in the later stages of the disease agent in the brain, there is difficult access of drugs and antibodies because of the blood-brain barrier. The permeability of this barrier increases with increasing body temperature.

The main differences between fever and hyperthermia

Fever should be distinguished from excessive heat, or hyperthermia. The mechanism of these states are not only different but opposite. First, when overheating is no effect of pyrogenic substances, the temperature increase is the result of external influence, limiting the heat transfer. Hyperthermia as a result of delays in the body heat is observed in the production of high ambient temperature, in hot climates, with an insulating clothing, etc. In these cases, it contributes to increased heat production due to muscular work. Compensation for overheating is to overcome the difficulties with regard to heat and maintain thermal homeostasis. Since the ambient temperature around 33 °C heat loss by radiation and convection practically ceases, then this process can only be performed by evaporation of sweat and moisture from the respiratory tract. However, at high ambient humidity it also becomes impossible, all the compensatory mechanisms are ineffective, and body temperature rises, but this is not a state of fever.

If fever does not occur violation, and alteration of thermoregulation. The body itself maintains a high temperature, since the "mounting point" thermoregulatory center is set to a higher level. If febrile animal to cool, then its temperature is reduced, remains high.

When hyperthermia is disturbed thermoregulation. The body temperature rises in spite of the desire to maintain body temperature homeostasis. "Setpoints" thermoregulatory center does not change. If the animal is cooled with hyperthermia, the result is a sharp increase in heat transfer body temperature begins to decrease. So, the alteration of the function at a fever heat regulation center is aimed at active retention of heat in the body regardless of ambient temperature. When hyperthermia tends rid of excess heat by means of the maximum stress of heat transfer, which prevents the high temperature environment.

Setting up the experiment. Discussion of results and formulation of conclusions

Simulation of fever in animals by the introduction of a pyrogenic substance - pyrogenal. (Pyrogenal is a high-molecular lipopolysaccharide obtained from the culture of gram-negative microorganisms): Measure the body temperature, determine the rate of respiration and heart rate in a rabbit. Body temperature should be measured in the rectum (if an electrothermometer is available – on the skin). Lubricate the tip of the thermometer with petroleum jelly in advance. After measuring the initial indicators, inject 1 ml of pyrogenal solution subcutaneously into the rear third of the thigh of the rabbit. Measure the body temperature, determine the frequency of breathing and heart rate every 20 minutes.

Discussion of the results of the experiment

• In this case, the increase in temperature is due to the fact that under the influence of pyrogen, the "set point" in the preoptic area of the hypothalamus adjusts to a higher temperature level than normal and perceives the normal body temperature as very low. As a result of such a change in perception, the "set point" directs impulses to the centers of the vegetative system, which regulate the processes of heat generation and heat transfer. Under the influence of these pulses, heat generation increases, and heat transfer decreases. Subsequently, a new balance between heat production and heat output is achieved at a higher level.

• The heart rhythm increases as a result of the stimulation of the sympathetic nervous system and the direct effect of heated blood on the sinus node. An increase in temperature by 1 °C was observed in the animal, which was accompanied by an acceleration of the rhythm by 8 beats. In parallel with increased heart rate and increased body temperature, increased breathing rate was observed, which is associated with increased functioning of the respiratory center, as well as increased blood temperature and acidosis, which in turn is caused by the accumulation of underoxidized metabolic products.

• Formulation of conclusions based on the experiment

• In an experimental animal, when pyrogenal was administered, an increase in temperature and an increase in pulse and breathing were observed, which is due to changes in the "set point" of the hypothalamus, and the resulting changes in thermoregulation (increased heat production and decreased heat output).

Tasks for independent work on the topic "Fever"

The student is offered 2–3 cards (temperature sheets) with different variants of temperature curves. It is necessary to determine the main features and type of temperature curve. Be able to explain the mechanism of occurrence. Analysis of errors with an explanation of the correct answers.

List of questions and works to be studied:

1. Definition of the term "fever".
2. Etiology of fever. Exogenous and endogenous pyrogens.

3. Mechanisms of disturbance of thermoregulation and increase in body temperature during fever.

4. Stages of fever. The relationship between heat production and heat output at different stages of fever.

5. Types of temperature curves.

6. Changes in metabolism and body functions during fever.

7. Harmful and protective and adaptive value of fever.

List of practical skills that must be mastered:

Definition on temperature sheets of the type of temperature curve:

- Permanent type;
- Weakening;
- Intermediate;
- Reverse;
- Hectic;
- Perverted;
- Atypical;
- Wave-like;
- Short-term type.

Situational tasks KROK-1 to determine the final level of knowledge

1. In an experiment on a rabbit, the introduction of pyrogenal led to an increase in the animal's body temperature. Which of the listed substances plays the role of a secondary pyrogen, which takes part in the mechanism of febrile reaction?

A. Interleukin-1. *C. Histamine.* *E. Immunoglobulin.*
B. Pyromen. *D. Bradykinin.*

2. A patient with pneumonia has a fever. What directly causes a change in the temperature set point in the neurons of the hypothalamus of this patient?

A. Prostaglandins E1, E2. *D. Interleukin-2.*
B. Endotoxin. *E. Platelet growth factor.*
C. Exotoxin.

3. A 25-year-old man complains of general weakness, chills, sore throat. Objectively: redness in the area of the tonsils. Body temperature is 38.6 °C. Which of the listed cells are the main source of endogenous pyrogens that cause fever in the patient?

A. Neutrophils. *C. B-lymphocytes.* *E. Mast cells.*
B. Eosinophils. *D. Basophils.*

4. A patient with fever has pale skin, "goosebumps", chills, tachycardia. What stage of fever does this condition correspond to?

A. Stages of temperature rise. *D. –.*
B. Stages of standing temperature. *E. –.*
C. Stages of falling temperature.

5. After the introduction of a pyrogen, a person experiences pallor of the skin, chills, "goosebumps", when gas exchange is determined – an increase in oxygen consumption. For which stage of fever are these changes most characteristic.

A. Standing temperature at an elevated level.
B. Reduction of temperature by crisis.
C. Lowering the temperature by lysis.
D. –.
E. Increase in temperature.

6. During the examination of a patient with a temperature, the following objective data were found: the skin is hyperemic, moist to the touch, polyuria, polydipsia are observed, the body temperature is 37,2 °C. What stage of fever does this condition correspond to?

A. Temperature rise. *D. –.*
B. Standing temperature. *E. Decrease in temperature.*

7. In a patient with acute bronchitis, which lasted for a week, an increase in body temperature to 38.5 °C is determined by a decrease in temperature to 37 °C. Which of the listed mechanisms is leading in the 3rd stage of fever?

A. Strengthening of heat production.
B. Development of chills.
C. Increased diuresis.
D. Expansion of peripheral vessels.
E. Increased breathing rate.

8. A patient with a long-term fever had a temperature in the range of 36.4–36.9 °C in the morning, and it rose to 37.0–38.0 °C in the evening. What type of fever is observed in the patient according to the degree of temperature rise?

A. Moderate. B. Hyperpyretic. C. High. D. Subfebrile. E. –.

9. The flu epidemic this year was characterized by the fact that the body temperature of most patients fluctuated between 36.9–37.9 °C. This type of fever is called:

A. High. B. Hyperpyretic. C. Subfebrile. D. Apyretic. E. Moderate.

10. In a patient with a long-term fever, the morning body temperature was in the range of 36.4–36.9 °C. In the evening, it rose to 37.0–38.0 °C, on some days to 38.8 °C. The patient has a fever for more than 2 months. What type of fever does the patient have?

A. Attenuating. B. Exhausting. C. Permanent. D. Wavy. E. Hectic.

11. In the afternoon, the patient's temperature suddenly rose to 39.5 °C and returned to normal in 6 hours. On the second day, the attack was repeated and the temperature reached 41.5 ˚C, the period of apyrexia came after 8 hours. What type of temperature curve?

A. Intermittent. *C. Septic.* *E. Permanent.*
B. Attenuating. *D. Exhausting.*

12. In the afternoon, the patient's temperature instantly rose to 39 °C and after 6 hours it returned to normal. On the second day, the attack was repeated: during the paroxysm, T˚ reached 41 °C, the period of apyrexia came after 8 hours. What is this type of temperature curve called?

A. Intermittent. *C. Hectic.* *E. Permanent.*
B. Reverse. *D. Septic.*

13. Patient N. has fever attacks every other day. During an attack, the temperature rises sharply and remains at a high level for up to 2 hours, and then decreases to the initial level. This type of fever is characteristic of:

A. Typhoid fever. *C. Sepsis.* *E. Typhus fever.*
B. Malaria. *D. Brucellosis.*

14. A patient with osteomyelitis of the upper jaw has an increase in body temperature during the day to 40 ºC, which sharply decreases to 35.6 ºC. What type of temperature curve is this typical for?

A. Constant [sontinua]. *D. Revolving [recurrens].*
B. Hectic [hectica]. *E. Atypical [atypica].*
C. Intermittent [intermittens].

15. The patient developed a fever, which is accompanied by a shift of the set point of the thermoregulatory center to a higher level, with successive alternation of the following stages: incrementi, fastigii, decrementi. In what disease can similar changes be observed?

A. Acromegaly. *C. Renal diabetes.* *E. Acute pneumonia.*
B. Diabetes. *D. Myocardial hypertrophy.*

16. A patient with hypertrophy of the thyroid gland has an elevated body temperature. What disturbances in energy exchange are the main causes of temperature rise in this case?

A. Increased breakdown of glycogen.
B. Enhancement of lipolysis.
C. Activation of enzymes in the Krebs cycle.
D. Activation of respiratory chain enzymes.
E. Separation of oxidation and oxidative phosphorylation.

Standards of correct answers to the KROK-1 task

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A	*A*	*A*	*A*	*E*	*E*	*D*	*D*	*C*	*C*	*A*	*A*	*B*	*B*	*E*	*E*

Recommendations for registration of work results

1. Written answer to test tasks (initial level of knowledge).
2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.
3. Independent work of students. Protocol for the analysis of temperature sheets with different variants of temperature curves.
4. Protocol for solving situational tasks with an explanation of the correct answers.

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Topic 9. Tumor

Justification of the topic: Human tumors have been known since ancient times. A description of individual forms of tumors can be found in the works of Hippocrates. Neoplasms of bones were found in some mummies of ancient Egypt. The study of this topic introduces students to the problem of malignant growth, which is extremely relevant. This is due to the fact that many people die from tumors. In addition, this problem is relevant not only for clinical but also for experimental medicine. But despite the age of this pathology, there are many unknowns in modern ideas about the etiology and pathogenesis of tumors.

Purpose of the lesson:

General – to get acquainted with the methods of experimental reproduction of tumors, with the peculiarities of tumor growth by demonstrating various strains of experimental tumors that grow, as well as tumors that are induced by exposure to chemical carcinogens.

Specifically:

Know:

1. Definition of the term "tumorous growth".
2. Characteristics of the conditions necessary for successful tumor resection.
3. Types of transplantation.
4. Performing a reexamination of the experimental tumor.
5. Carcinogenic environmental factors.
6. Etiology and pathogenesis of tumor growth.
7. Relationship between the tumor and the body.

Be able:

1. Experimentally model tumors and justify their conclusions.

2. Explain the general mechanisms of the occurrence and development of tumors, the relationship between the body and the tumor.

3. To determine the main signs of various variants of atypism (morphological, functional, biochemical, physicochemical anaplasia). Explain the mechanisms of their occurrence. To determine the main mechanisms and ways of metastasis of tumors.

Practical experience:

Determination of the signs of the tumor process using case studies:

- Mechanisms of disruption of cell division;
- Origin of mutations;
- Processes of tissue growth regulation;
- Types of tissue growth;
- Biochemical processes, the violation of which occurs during tumor growth;
- Factors that are important in the etiology of tumor growth.

The graphological structure of the topic "Tumor" is attached.

Material and methodological support of the topic "Tumor":

1. Lectures;
2. Methodical instructions for teachers;

3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational tasks to determine the final level of knowledge;
6. A set of KROK-1 tasks;
7. A set of schemes and tables (presentation);
8. Set of ECG with heart rhythm disturbance;
9. Video films;
10. For experiment (museum tumor preparations: 1) rat sarcoma M-1, 2) Brown-pierce carcinoma, 3) Ehrlich adenocarcinoma, 4) tumor induced by 20-methylcholarnthrene in mice and rats, 5) tumors of viral origin – milk factor; smears prepared from ascitic fluid of mice, microscopes, immersion oil).

Oriented map of students' work on the topic "Tumor"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of nowledge	10	Written answer to test tasks	Test tasks	Study room
2	Analysis of theoretical material	35	Analysis of theoretical material based on control questions of the topic, situational tasks, tasks KROK-1	Topic control questions, KROK-1 tasks, situational tasks	
3	Practical part (conduct experiment)	30	Introduction and preparation for setting up the experiment. Setting up the experiment. Discussion of the results of the experiment and formulation of conclusions	Museum preparations of tumors, smears prepared from ascitic fluid of mice, microscopes, immersion oil	
4	Determination of the final level of knowledge and skills. Summary	15	Determination of the initial level of formation of knowledge and skills	KROK-1 tasks, situational tasks	

Tumor (blastomatous, neoplastic) growth – is a special kind of abnormal tissue growth that arises from the transformation of normal tissue in the tumor and is characterized by atypical structure and function, by the relative autonomy (lack of proper regulation of the growth), the infinite growth and progressive development.

Distinguish benign and malignant tumors.

Atypicality of tumors

Atypicality of the tumor tissue – is the change of the structure and function of tumor cells comparing with the tissue from which a tumor began. At the bottom of the Atypicality is anaplasia (cataplasia) – lowering of the tissue differentiation, as its reverse development and return to an embryonic state (dedifferentiation).

The following types of anaplasia are distinguished:

1. Structural – is reflected in the fact that the parenchyma of the tumor can be of different sizes (giant and dwarf cells) and forms of the cellular elements,

increase in the number of chromosomes, appearances of hyperchromatism, an increase of centrosomes and Golgi apparatus, the discrepancy between weight and mass of protoplasm and mass of an increased nucleus rich in chromatin, large nucleolus, a decrease in the number of mitochondria and changes in their structure, atypical mitoses. Cytoskeleton of tumor cells and its microtubules undergo significant changes. In cancer cells the number of intercellular contacts is greatly reduced, which facilitates metastasis. Contact inhibition of cell growth disappears.

Tumor bottles do not contain the contractile elements, the size of their lumen is not regulated by the body. Proliferation of endothelial cells is far behind the proliferation of cancer cells, so during the growth of tumor the capillary network is reduced, especially in the center, which becomes necrotic. Tissue of tumors in most cases is not innervated. The nerve endings are located in the stroma, but even here the innervation is insufficient.

In addition, morphological changes combine with the functional ones (functional anaplasia) (eg, synthesis of bile pigments stops in hepatoma).

2. Biochemical anaplasia. Tumors are able to synthesize and secrete embryonic proteins along with the usual adult proteins (alpha-fetoprotein in hepatomas, cancer embryonic antigen, etc.) that serve as markers of malignancy. In tumors there are also found fetal isoforms of some enzymes (pyruvate kinase, aldolase, thymidine kinase), there is an active gamma-glutamyl, the amount of DNA-polymerase 3 decreases and the number of DNA-polymerase 2 increases. As a rule, production of enzymes and proteins that allow cells to perform specialized functions, and activate enzymes that provide cellular division is repressed, there is an increased ability to absorb amino acids from the environment. Some tumors synthesize and secrete ectopic hormones that are not characteristic of normal tissues (squamous cell lung cancer – parathyroid hormone, and small cell cancer – corticotrophin, kidney cancer - erythropoietin, or thyroxin).

3. Physico-chemical anaplasia. Tumor tissue is characterized by an increase in water content, lactic acid, acidity, content of potassium and sodium ions, the swelling of colloids, reducing the amount of calcium and magnesium, changes in colloidal properties of the cytoplasm (increase dispersion of colloids, decreasing their surface tension). The osmotic concentration of the internal environment, the electrical conductivity are Increased, negative charge of tumor cells is increased (increasment of the number of negative radicals in neuraminic acid in the cell membrane), which is close to the charge of lymphocytes.

4. Antigenic anaplasia. Changes in the tumor antigens are parallel to the disruption of differentiation of tumor cells. Antigenic differences in tumor and normal cells are expressed in the increasing content of ones (antigenic "complication") and a sharp decrease in others (antigenic "simplification") antigens. In tumors the synthesis of embriospecific antigens is resumed and the synthesis geteroantigens is increased. In the process of neoplastic transformation of cells the synthesis of some normal antigens that are

characteristic of the initial normal tissues is reduced – species-and organ-antigens as well as izoantigens. The reduction in organ-antigens is emphasized, as they attributed a crucial role in vital processes of cells of differentiated tissues, especially because it goes hand in hand with reduction of morphological differentiation and is accompanied by a complete or almost complete loss of the tumor cells of specialized functions.

Taken together, all kinds of anaplasia characterized the atypicality, which distinguishes tumor tissue from other tissues. The degree of atypicality is expressed by more than a malignant tumor.

Tumor growth is only possible as a result of its cells escaping from immunological surveillance, due to:

- antigenic simplification (loss of antigens characteristic of normal tissue);
- appearance of fetal antigens, to which there is immunological tolerance;
- masking of antigens (cells of chorionepithelioma have a neutral polysaccharide capsule);
- presence of antigenic determinants, stimulating T-suppressors, which leads to inhibition of immune responses;
- suppression of the immune system (immunosuppression).

Autonomy of the tumor

Compared with other types of tissue growth, tumors are characterized by autonomous growth. Intractability of tumor cells is greater and, consequently, tumor grows faster than its less differentiated cellular elements. However, the autonomy of the tumor is, of course, relative.

Infinity tumor growth

Tumors characterize by the infinite relative growth, i.e. potential ability to grow without apparent limit. In malignant tumors the body disappears before the tumor reaches a large size.

Infinite growth is based on the fact that out-of-normal control of neurohumoral and genetic regulation, tumor cells do not respect the principle of contact inhibition and limit of cell division of Hayflick.

Tumor progression

Tumor development occurs continuously through qualitatively different irreversible stages, that manifest in the genetic changes in one or more features (growth rate, invasiveness, anaplasia, and metastasis) in the direction of increasing its aggressiveness. One of the first phases of progression considered benign. However, the facts of malignancy of normal cells at once are known (in the colon).

Formulated an idea of progression, L. Foulds (1969), who established an important law – signs of malignancy arise and are amplified independently of one another, giving rise to a variety of combinations and infinite variability of phenotypes of tumors. This is the fundamental difference between tumor and normal progression of differentiation of tissue.

The doctrine of tumor progression, supplemented by domestic scientists (V. S. Shapot) representation of the disparity of its attributes. Distinguish

primary radical sign inherent in any tumors – uncontrolled growth. Properties that characterize the malignant tissue should be considered secondary, arising in the course of progression. Among these properties distinguish mandatory, without which there is no cancer: invasive and destructive growth, systemic effects on the body. With regard to metastasis, it is not a mandatory feature of malignancy, although very frequent.

It is now recognized monoclonal origin of the vast majority of tumors, focus consists of the descendants of a single transformed cell (tumor growth "of itself", i.e. without the involvement of tumor growth in normal neighboring cells). This cell produces a clone of cells like themselves with the same phenotype. However, due to increased genetic variability of the transformed cells at a certain point of one clone, there are several clones that differ in their phenotype (population of heterogeneity of the tumor). This polyclone population becomes the object of the current in the internal environment of the organism of directed natural selection that favors the most rapidly proliferating, resistant to the immune defenses of the body, aggressive clones, i.e. the transition to malignancy.

Benign and malignant tumors. Biological characteristics of tumor growth.

Benign characteristics

1. Slower growth
2. Expansive growth (exception: some fibroids and angiomas)
3. No or minimal degradation of the tumor tissue and surrounding normal tissues
4. Does not form metastases (exception: some thyroid adenomas, chondromas)
5. Relapses are extremely rare
6. Does not cause cachexia (exception: the tumor violating patency of GIT)
7. Biological atypia (anaplasia) is weakly expressed

Malignant characteristics

1. Rapid growth
2. Infiltrative growth
3. Severe destruction of tumor tissue and surrounding normal tissues
4. Metastasizes
5. Often forms relapses
6. Causes cachexia
7. Biological atypia is pronounced

Metastasis, its mechanisms

Metastasis – one of the manifestations of fatal irregularities of tumor growth – moving cells at a distance from the main (parent) node and the development of tumors of the same biological structure to other tissue or organ.

Ways of metastasis:

1. Lymphogen (with a current of lymph through the lymph vessels). This is the most common way of metastatic tumors, especially carcinomas. Even with a small amount of tumor it is possible to transfer some of its cells in the lymphatic vessels and fixing them in regional and remote lymph nodes.

2. Gematogenic (with the blood flow through blood vessels). The cells of sarcomas metastasize mostly through this way.

3. Tissue or implantation. Metastasis in this way is carried out in contact of tumor cells with the surface of normal tissue or organ (eg, in contact of gastric cancer with the surface of the peritoneum or with pleura); implantation of blastomic cells in body fluids such as peritoneal, pleural cavity, the cerebrospinal fluid on the surface of, respectively, abdominal and chest cavities, spinal cord and brain.

Often, tumors metastasize to multiple paths simultaneously or sequentially.

Stages of lymph and Hematogenous metastasis are the following:

1. Department of malignant cells from the tumor and its invasion into the wall of lymphatic or blood vessel (intravasation).

2. Embolism-circulation in the lymph and blood vessels of the tumor cells with its subsequent implantation on the inner surface of the endothelium of the vessel wall. This step is carried out by the action of metastasis of several factors:

3. Reduce the effectiveness of anticancer anticellular mechanisms protecting the organism;

4. Screening of tumor cell antigens fibrin film formed on their surfaces.

5. Invasion of tumor cells in the vessel wall and beyond – in the surrounding tissue (exavasation). Subsequently, the cells proferate to form another tumor node metastasis.

Stages of Tissue metastasis are the following:

1. These cells are attached to the basement membrane through receptors that have affinity for clocoproteid and collagen of fourth matrix;

2. producing hydrolytic enzymes (protease, collagen, glycosidase), melting the basement membrane and lining the capillaries with endothelial cells, tumor cells can form in these passages and

3. Penetrate into the blood or lymph vessels.

With the help of hydrolytic enzymes ensuring invasion, the tumor cells penetrate into the tissue of the container body, proliferate to form metastases.

Metaphases are characterized by organ selectivity of metastasis (tropism). Because cancer cells often metastasize to the bones, liver, brain; stomach cancer – in the ovaries, tissues, bottom of the pelvis; breast cancer – in the bones, lungs, liver. Such factors determine the affinity of metastasis: the specifics of metabolism in the body, especially of lymph and blood supply, low efficiency of the mechanisms of antiblastomic resistance, positive chemotaxis.

The assumption of the role of the nervous system in tumor metastasis says the need for its implementation of a secretive period, which is a characteristic feature of all neuro-degenerative processes. During the latent period, by those neuro-degenerative changes of their chemical properties that contribute to tumor proliferation in them these particles are apparently committed.

The value of the nervous system in tumor metastasis is confirmed by the fact that the traumatic impact on it with bandages of the nerves or their irritation with chemicals can change the direction of metastases.

The etiology of tumor

Causes of tumors are the factors that cause the transformation of a normal cell into a tumor. They are called carcinogens (blastomogenic). Carcinogens are capable of: a) directly or indirectly affect the cell's genome, leading to mutations (mutagenicity) and b) to penetrate through the outer and inner barriers, and c) cause little damage of cells, which allows it to survive; d) create conditions for the manifestation of some carcinogenic factors and unfavorable for others (organotropnost) e) inhibit tissue respiration and the immune response, f) enhance tumor formation by the action of some carcinogens (sincancerogenesis); sometimes factors that are not carcinogens, can exacerbate the effects of carcinogens – cocancerogenesis.

The nature of carcinogens are divided into 3 groups:

1) the matter of local action, exert their effects at the site of application (polycyclic aromatic hydrocarbons cause sarcomas at the site of subcutaneous or intramuscular injection or skin cancer in its flushing);

2) the substance of the remote organotropic action that induce tumors in certain organs and tissues, rather than in place of the primary administration (beta-naphthylamine, etc.) (organotropity of cancerogens explain the formation of active substances from less active precursors in the affected body);

3) multiple actions substances, causing a variety of tumors in organs and tissues from the same animal.

Distinguish carcinogenic chemical, physical and biological (mainly viruses).

The classification of chemical carcinogens.

Chemical carcinogens – are chemical substances which may cause the development of malignant tumors.

I. By origin may be distinguished natural and man-made carcinogens.

II. By chemical structure the carcinogens may be distinguished as:

a) polycyclic aromatic hydrocarbons (PAHs);
b) aromatic amines;
c) nitro compounds;
d) mycotoxins;
e) aminoazo compounds;
f) simple compounds.

III. In relation to the body chemical carcinogens may be exogenous and endogenous.

IV. On the mechanism of the carcinogenic effect distinguish carcinogens of direct and indirect action.

All chemical carcinogens can be divided into two main groups: pro-carcinogens and direct carcinogens. The vast majority of chemical carcinogens belong to the first group. To become a true, end-carcinogens, pro-carcinogens must undergo metabolic conversions of pre-catalyzed fabric enzymes (nonspecific oxidases), mainly localized in the endoplasmic reticulum and partly in the cell nucleus. PAHs are usually become the end carcinogens, turning to the corresponding epoxides. Some pro-carcinogens become end

as a result of spontaneous reactions. Direct carcinogens (nitrosamines, beta-propionlakton, dimetilkarbamilhlorid) act as such, without being modified.

Direct carcinogens – are highly active chemical compounds, including lactones, hloretilamines, epoxides. They are able to directly interact with the structures of cells and cause tumor development. These compounds do not require any transformations in the body to manifest their carcinogenic effects. With its high reactivity, direct carcinogens cannot accumulate in the environment as well as they are destroyed within the interaction with environmental carcinogens, and do not represent a great danger to human as carcinogenesis factors.

Indirect carcinogens – are controversial in their chemical properties of the compound. These include PAHs, aromatic amines, nitroso compounds, aflatoxins. With its low reactivity, these carcinogens may accumulate in the environment and therefore pose a greater danger to humans. These compounds are carcinogens in the body only after a series of chemical enzymatic reactions, resulting in the formation of their active forms – the actual carcinogens. Similarly, epoxides are resulting of of PAHs, hydroxylamines of aromatic amines, alkyl radical of nitrosamines. These forms of carcinogens affect the genetic apparatus of the cell and cause its transformation into a tumor.

The role of hormones in carcinogenesis

During the violation of the regulation of the secretion of tropic hormones of the adenohypophysis (in violation of the feedback mechanisms), their number in the blood may increase substantially. Affecting the organs – the targets, they can stimulate the proliferation and tumor development.

This possibility is demonstrated in the following experiment. The animal was removed one ovary and the other one transplanted into the spleen. Blood from the spleen enters the liver, where estrogens formed in the ovary, are destroyed. The pituitary gland receives blood, in which there is little estrogen. This causes stimulation of gonadotropin-releasing hormone, but they are still not enough in blood flowing to the pituitary, since it involves the destruction of the liver estrogen. Rushing stimulating effect of gonadotropin hormone on the ovary causes the proliferation of the cells and in many cases the development of malignant tumors.

Physical carcinogens

Ionizing radiation – is a universal cancer-causing agent. Described the radiation-induced malignant tumors of all organs. most often Occur a tumors of the skin and bone, leukemia, endocrine dependent tumors (breast cancer and ovarian cancer). Skin and bone tumors occur predominantly in local irradiation, and the rest – in general. Radiation carcinogenesis, is probably put into practice through the conversion of proto-oncogenes of cell in oncogenes as a result of a sharp increase in genomic instability induced by ionizing radiation. At the heart of the radiation blastomatosis is the damage of nuclear apparatus of heredity of somatic cells after irradiation. All that matters is the local damaging effect of radiation and proliferative processes in the tissue damaged by irradiation. They create a higher probability of occurrence of new mutations in somatic cells. The violations of physiological regulatory systems of the body irradiation also play a role.

In the mechanism of radiation carcinogenesis a key role plays formation of free radicals, the amount of which is directly dependent on the dose of radiation. Active radicals have a damaging effect on DNA, stimulate chromosomal aberrations and mutational processes. The human body is usually able to resist the pathogenic effect only of a weak (subthreshold) doses of ionizing radiation. This ability can be significantly enhanced by artificial activation of antioxidant protection in cells with the increased intake in the body of tocopherol, selenium, ascorbic acid and with the increased activity of enzyme systems - glutathione, superoxide dismutase and catalase. In case of insufficient activity of antioxidant systems in the cell there is a growing carcinogenic effect of ionizing radiation.

The ultraviolet spectrum (320–280 nm) of sunlight after prolonged exposure is a major inducer of most malignant neoplasms of human skin. Most sensitive to solar radiation are ethnic groups with light skin and hair.

Biological carcinogens

It's found that some biological factors are also able to induce carcinogenesis, in particular, the products of fungi. For example, aflatoxin – a fungus synthesized by Aspergillum flavum (parasitic on peanuts, corn, rice, etc.) and sterigmatotsistin (synthesized by the fungus Aspergillus nidulans) cause the development of liver tumors. However, the basic biological carcinogens are oncogenic viruses. Experimental evidence of viral origin of tumors is their appearance after the introduction of cell-free filtrates of tumor tissue in an animal. These filtrates are prepared from a suspension of tumor cells by passing it through a porcelain filter that inhibit bacteria and tissue cells (see above).

Classification of oncogenic viruses

By the type of viral nucleic acid oncogenic viruses are divided into DNA-containing and RNA-containing.

DNA genes of oncoviruses are capable to directly introduce into the genome of a target cell. Plot of DNA oncoviruses (actually oncogene), integrated with cellular genotype may carry out a tumor cell transformation. Do not rule out also that one of the genes of an oncoviruse may play a role of a cellular proto-oncogene promoter.

DNA-containing oncoviruses include some adenoviruses, papovirusy and gerpevirusy. For example, Epstein-Barr virus causes the development of lymphoma, hepatitis B and C that can cause liver cancer.

RNA-containing viruses – are retroviruses. This means that the integration of the viral RNA genes in the cell genome is not direct, but after the formation of DNA copies. This DNA copy is integrated into the genome of the cell, being expressed and cause its transformation into a tumor one.

Oncogenic viruses include (by AI Ageenko):

I) RNA-containing viruses of spiral (multiply in the cytoplasm), or polyhedral shapes – more than 100 species (oncoviruses – oncogenic, RNA-containing, or retroviruses – convey information in the opposite direction – from RNA to DNA). These include leukemia viruses in mice and chickens, the Rous sarcoma, Bittner milk virus, etc.

II) DNA-containing viruses (more than 55 types):

1. Popes-virus (propagated in cell nuclei) – rabbit papilloma viruses, polyoma, human papilloma, vacuolating virus of monkeys – SV40).

2. Adenoviruses.

3. Viruses of smallpox (multiply in the cytoplasm, forming characteristic cellular inclusions) - Yaba virus that causes reversible human tumors.

4. Viruses of the herpes [Epschteyna-Barr virus, the causative agent of lymphoma Berkita, herpes simplex virus type 2 (SH-2) – agent of cervical cancer].

Depending on the carcinogenicity retroviruses are divided into two groups:

1) Acute transforating retroviruses. Cause the development of tumors after a short latency period. These viruses have in their genome an oncogene, and therefore at the heart of cells transformation in the tumor there is the epigenomic mechanism. To this group, in particular, are related the acute leukemia virus of birds, mice, Rous sarcoma.

2) Slowly transforming retroviruses. Cause the development of tumors after a long latent period. These viruses do not have a part of an oncogene, and therefore the main mechanism of action of the transformation – is the mutation. This group of viruses includes lymphocytic leukemia viruses.

Oncogenic human virus is a virus of a T-cell lymphoma – leukemia. It is transmitted from a person to person through prolonged intimate contact, blood transfusions. This lymphotropic virus has many similarities with the human immunodeficiency virus (HIV) that causes AIDS.

Viral carcinogenesis is associated with exposure of specific viruses on proliferating cells. Oncogenic viruses, as well as infectious diseases, have different values. Most viruses have a specific shape. Many known oncogenic viruses are widespread in nature in a latent state. Penetrating into the body of humans and animals, they, for the entire period of life, can not cause cancer and pass on the descendants. The implementation of the oncogenic action of such viruses is relatively rare, and even under laboratory conditions on the cells highly sensitive to DNA-containing viruses. In the body the action of oncogenic viruses depends on the state of immune surveillance, age, genotype, hormonal levels and on many other factors.

Mechanisms of activation of proto-oncogenes

Cellular oncogenes (transforming genes) – these are proto-oncogenes, which acquired the ability to transform cells, i.e. to transform it into a tumor. Transfer of these genes in other, healthy cells causes the transformation of the latter.

Now the existence of the mechanisms of proto-oncogenes transformation into cellular oncogenes is proved:

1) Depression of protooncogene. May occur either as a result of violations of the structure and, consequently, of the function of the corresponding anti-oncogene, or due to mutations in the genes repressors, blocking the activity (expression) of proto-oncogene;

2) Increasing the expression of proto-oncogene. Observed when the protein – a proto-oncogene product is formed and normal, but there is very little of it. Under the influence of certain genetic factors, the formation of such a product is sometimes considerably higher. This phenomenon may be happening due to the following specific arrangements:

a) gene amplification (increasing the number of copies);

b) chromosomal mutations - translocation;

c) impact of viral promoters and amplifiers (so there are retroviruses that do not have an oncogene in their structure);

d) influence of the cell migratory genes (transposons).

3) Qualitative changes in proto-oncogenes, causing the formation of a modified product. These changes are caused by point mutations in proto-oncogene. Anti-oncogenes – are cellular genes whose products cause the repression of proto-oncogenes. Anti-oncogenes loss (deletion) or mutations in them, leading to the formation of inactive products, may have the effect of depression of proto-oncogenes and cell transformation, i.e. formation of malignant tumors.

Pathogenesis of tumors

There are three stages: the transformation of healthy cells into a tumor, promotion and progression of tumors.

I. **Transformation** (initiation) – Acquisition by normal cells of the ability to proliferate indefinitely and its transfer to the daughter cells. It could probably happen in two ways – mutation and epigenomic that are mechanisms of disturbances of cell division.

Mechanism to ensure cell division is the DNA replication of the cellular genome in the S phase of the cell cycle, starting with the appearance in G1-phase of a specific initiator of cell division. Its appearance and the beginning of cell division are the result of depression of the gene encoding this initiator.

II. **Promotion** (activation). Transformed cells may be a long time in an inactive state. Additional exposure to cocancirogen can lead to cell division and formation of the tumor site. Most carcinogens are complete. Molecular mechanism of promotion is the inclusion of transmembrane signaling system, terminating the activation of protein kinase C, which may be attached to the promoter action of growth factors, oncogenes products.

III. **Progression** – are the persistent qualitative changes in the properties of the tumor in the side of its malignancy within the growth. Expression of progression is the increasing anaplasia of tumor cells, acquisition by them of greater autonomy, infiltrative growth, the ability to metastasize, etc.

Effect of tumor on the body. There are two interrelated forms of systemic tumor effect on the body: a) successful competition with the tissues for the vital factors and metabolites, and b) changes in the biological characteristics of different tissues, leading to a weakening of their features and adjustability of the body. Malignant tumors hook from the body some vitamins (B1, C) and pyrimidine precursors of nucleic acids, glutamine, other amino acids, i.e., organic nitrogen compounds.

Tumor growth causes a whole cascade of disorders of homeostasis, disrupting the normal operation of its physiological systems. The consequences of such disintegration manifest in diverse paraneoplastic syndromes. These include the state of immunosuppression (increasing the susceptibility to infectious diseases), a tendency to increased blood clotting, cardiovascular disease, muscular dystrophy, some rare dermatoses (acanthosis nigricans), etc.

In general, the development of malignant tumors can occur in three groups of common disorders in the body:

1) Cancer cachexia – is the total exhaustion. Characterized by a sharp decrease in body weight, weakness, lack of appetite, anemia. The emergence of cancer cachexia is explained by the following phenomena:

a) the tumor captures from the blood large amounts of glucose, "glucose trap", resulting in a gipogliemiya and energetic "theft" of the body;

b) the tumor captures from the blood large amounts of amino acids ("nitrogen trap "). There is a plastic " theft " of the body;

c) the toxic products of dead tumor cells enter blood - toxohormones. They determine the effects of intoxication;

d) tumor cells let out a lot of unoxidized products – develops ungased acidosis;

e) because of the release of enzymes from dying tumor cells in the blood develops enzymia;

f) when the tumor is located in the gut the functions of the digestive system are violated;

2) Common manifestations associated with local changes in tissue. This group includes ulceration, secondary infection, bleeding, pain;

3) Paraneoplastic syndromes. They often accompany the development of tumors, but their pathogenesis and relationship to malignant tumor growth remain unclear. This group includes:

a) endocrinopathies;

b) hypercalcemia;

c) neuromuscular syndrome (myasthenia, CNS and peripheral nervous system disorders);

d) dermatological disorders;

e) damage of bones and joints;

f) cardiovascular and hematological disorders (thrombosis, anemia, leukemoid reaction).

Great contribution to the study of the tumor complex mechanisms impact on the body belongs to R.E. Kavetsky, a disciple of A. Bogomolets.

Peculiarities in the behavior of tumor cells in culture

1. Lack of contact inhibition. Normal cells in culture divide until a monolayer covering the bottom of the vessel formes. And the division does not cease (contact inhibition). Tumor cells multiply all the time, forming a multilayered structure (no contact inhibition).

2. Ability to divide without attachment to any surface. Tumor cells, unlike normal, may divide, floating in a fluid and maintaining a spherical shape.

3. For the growth of tumor cells it is not necessary to have the presence of serum in the environment. The division of normal cells in a culture solution requires not only nutrients and oxygen, but also blood serum at a concentration of 10 to 30 %. It is believed that the latter contains proteins that are growth factors for normal cells.

4. Immortalization (immortality) – lack of the cell division limit. Normal cells in culture after a certain number of transfers from one vessel into the other one gradually lose their ability to divide, the culture gets older and cells eventually die. In cancer cells Hayflick limit – is a genetically programmed number of divisions, which a cell can carry out, is missing, their division during creation of the appropriate conditions has got no limits.

The mechanisms of natural antitumor defense, immune and non-immune mechanisms of resistance

Mechanisms of natural nonspecific resistance of the body to tumors do not have immunological specificity and do not require prior immunization. They are carried out by the following cells:

a) by NK-cells (natural killers) are a kind of O-lymphocytes. They recognize the tumor cells and destroy them;

b) by LAK-cells (lymphokine - activated by killer cells). They, like the NK-cells, carry out the cytolysis of tumor cells;

c) by macrophages. Destruction of tumor cells by macrophages is carried out by means of phagocytosis and extracellular mechanisms of cytotoxicity.

Mechanisms of natural nonspecific anti-tumor protection are effective if the number of tumor cells in the body is less than 10^3.

Pathophysiological basis for prevention and treatment of tumors

The aim of tumors prevention is the prevention of carcinogens cells impact on the cellular genome, a significant reduction of their blastomogenic actions and thereby preventing of the occurrence of tumor cells. To achieve this, various activities are carried out: reduction or elimination of carcinogenic agents in the human environment; personal body protection, especially in manufacturing; enhancing common and antitumor resistance of the organism; early detection and elimination of the so-called precancerous conditions. These include pockets of excessive cell proliferation (e.g., breast, uterus, prostate).

Treatment of tumors can be radical and palliative. Radical treatment is aimed at eliminating of tumors and suggests the possibility of full recovery or long-term remission. Palliative treatment can be used when radical therapy is impossible. Methods of treatment include: surgical removal; radiation therapy (the use of radiation exposure); chemotherapy; immunotherapy; increased non-specific resistance (for example, the introduction of BCG). Treatment leads to a lengthening of life and reduction of suffering. The risk of recurrence is sufficiently large, although initially the patient may feel completely healthy.

Setting up the experiment. Discussion of results andformulation of conclusions

Acquaintance with various strains of experimental tumors: Describe museum preparations of tumors (1. M-1 rat sarcoma; 2. Brown-Pierce carcinoma; 3. Ehrlich adenocarcinoma – ascites and subcutaneous forms; 4. Tumor induced by 20-methylcholanthrene in mice and rats; 5. Tumors of viral origin - milk factor), indicate the type of animal, the name of the tumor strain, localization, size, appearance, consistency.

Microscopic examination of the ascitic form of Ehrlich's adenocarcinoma: Microscopy preparations. Pay attention to the atypicality of cell division, the presence of dwarf and giant cells. Draw drugs.

Discussion of the results of the experiment

Ehrlich ascites carcinoma in mice. The source tumor is spontaneous breast cancer. The strain has existed since 1905. Life expectancy of an animal with a tumor is 7–16 days. Ascites is formed when the tumor is transplanted intraperitoneally. For this, 0.2 ml of ascites fluid, which contains many tumor cells, is injected into the abdominal cavity. When this liquid is injected subcutaneously, a tumor is formed.

Sarcoma M-1 in rats. The original tumor is a sarcoma, which was obtained from a rat using the carcinogenic substance 3,4-benzpyrene in the Shabad laboratory (1943). The histological type of the tumor is polymorphocellular sarcoma.

Brown-Pierce carcinoma in rabbits. The original tumor is a spontaneous tumor in a rabbit injected with syphilitic material into the scrotum (1916). Histological type – epithelial multicellular brain-like structureless tumor.

The tumor is characterized by intensive growth and tendency to central necrosis. It metastasizes very quickly. The primary tumor sometimes resolves, but the animal dies from metastases in the internal organs.

When studying preparations of the ascitic form of Ehrlich adenocarcinoma in rats, giant and dwarf cells were found, as well as changes in the shape of cellular elements and the presence of hyperchromatosis phenomena, an increase in centrosomes and the Golgi apparatus, a discrepancy between the mass of the cytoplasm and the mass of an enlarged and chromatin-rich nucleus, a large nucleolus, and a decrease in the number mitochondria and changes in their structure, the presence of signs of atypical mitosis.

Forming conclusions based on the experiment

Under the influence of various carcinogens, malignant tumors develop in experimental animals (rats, rabbits, and mice), which are characterized by the presence of signs inherent in this type of tumors, i.e. unlimited cell division, unlimited growth, infiltrative growth, pronounced destruction of tumor tissues and surrounding normal tissues, the formation of metastases, and expressiveness of biological atypism.

Tasks for independent work on the topic "Tumors"

The student is offered 2–3 case assignments with signs of tumor growth. It is necessary to determine the signs of tumor growth and the type of tumor.

Be able to explain the mechanism of occurrence. Analysis of errors with an explanation of the correct answers.

List of questions and works to be studied:

1. Definition of the term "tumorous growth"
2. Methods of experimental reproduction of tumors. Strains of experimental tumors.
3. Morphological, biochemical and physicochemical features of tumor tissue.
4. Etiology of tumors. Mechanism of carcinogenesis. The role of the organism in carcinogenesis.
5. The relationship between the tumor and the body.
6. Precancerous conditions.
7. The role of domestic scientists in the development of experimental oncology.

List of practical skills that must be mastered:

1. Determination of the signs of the tumor process using case studies:

- Mechanisms of disruption of cell division;
- Origin of mutations;
- Processes of tissue growth regulation;
- Types of tissue growth;
- Biochemical processes, the violation of which occurs during tumor growth;
- Factors that are important in the etiology of tumor growth.

Situational tasks KROK-1 to determine the final level of knowledge

1. A 67-year-old woman suffers from stomach cancer with metastases in the liver. What feature of tumor cells determines their ability to metastasize?

A. Biochemical atypism. *D. Antigenic anaplasia*.
B. Rapid growth. *E. Infiltrative growth*.
C. Autonomy.

2. The patient was diagnosed with a malignant neoplasm of the tongue. What are the features of this tumor that allow it to be classified as malignant?

A. Expansive nature of growth. *D. An increase in the number of mitotic cells.*
B. Anaplasia. *E. Infiltrative nature of growth*.
C. Positive Pasteur effect.

3. The absence of Hayflick's limit in tumor cells was discovered during the study of cell division in tissue culture. What experimental method of studying tumors was used?

A. Transplantation. *D. Induction by chemical carcinogens*.
B. Induction by radiation. *E. Induction by viruses*.
C. Explantation.

4. During the operation, the patient was diagnosed with a stomach tumor in the primary focus of malignancy (within the mucous membrane). Metastases in the lymph nodes and distant metastases are absent. What is the stage of tumor pathogenesis in this case?

A. Initiations. *C. Promotions.* *E. Immune suppression of the tumor.*
B. Transformations. *D. –.*

5. In a patient with leukemia, the number of blast cells in the blood increased sharply, leukemic infiltrates appeared in the liver. These changes are caused by the transition from the monoclonal stage of the disease to the polyclonal one. What stage of carcinogenesis do these changes correspond to?

A. Progressions. *C. Transformations.* *E. Latentnoi.*
B. Initiations. *D. Promotions.*

6. A patient with chronic myeloid leukemia developed signs of ulcerative-necrotic stomatitis. A mucosal biopsy revealed leukemic cells. What part of tumor pathogenesis is the lesion of the oral cavity associated with?

A. Tumor progression. *D. Promotion.*
B. Mutational mechanism of transformation. *E. Initiation.*
C. Epigenomic mechanism of transformation.

7. During the operation, the patient was diagnosed with a stomach tumor with the growth of mucous, submucous and serous membranes. Metastases were detected in the perigastric lymph nodes, there were no distant metastases. Stage 3 (T3, N1, M0) of tumor development was determined. What is the stage of tumor pathogenesis in this case?

A. Tumor progression
B. Promotions
C. Transformation of a proto-oncogene into an oncogene
D. Formation of oncoproteins
E. Transformations

8. It has been established that with the development of a hepatoma in it, the synthesis of bile acids often stops. What type of anaplasia does this indicate?

A. Functional. *C. Morphological.* *E. Physico-chemical.*
B. Energetic. *D. Biochemical.*

9. It has been established that during the development of a lung tumor, the synthesis of glucocorticoids can occur in it. What variant of tumor atypia occurs in this case?

A. Energetic. *C. Morphological.* *E. Physico-chemical.*
B. Functional. *D. Biochemical.*

10. An epidemiological study of the spread of tumors revealed a high coagulation of the development of lung tumors with tobacco smoking. The occurrence of this type of pathology is most likely associated with the action of which chemical carcinogen?

A. Orthoaminoazotoluene. *C. Methylcholanthrene.* *E. Diethylnitrosamine.*
B. Aflatoxin. *D. 3,4-benzpyrene.*

11. A 58-year-old man suffers from bladder cancer. In the course of his work, he had contact with carcinogenic substances. Which of the following carcinogens is most likely to act in this case?

A. 20-methylcholanthrene. *D. Dimethylaminoazobenzene.*
B. β-naphthylamine. *E. Orthoaminoazotoluene.*
C. Benzpyrene.

12. A medical examination of the employees of the workshop for the production of aniline dyes is conducted. The presence of a tumor of which localization can be considered as an occupational disease due to contact with beta-naphthylamine?

A. Esophagus. *B. Liver*. *C. Kidney*. *D. Urinary bladder*. *E. Legeniv*.

13. The clinical examination of the patient made it possible to establish a preliminary diagnosis: liver cancer. The presence of which protein in blood serum will confirm the diagnosis?

A. Properdin. *C. Alpha-fetoprotein*. *E. Gamma globulins*.
B. Paraproteins. *D. C-reactive protein*.

14. In a patient with a malignant tumor of the lungs, over time, a neoplasm of another location was found. What process will this phenomenon be a consequence of?

A. Expansive growth. *C. Metastasis*. *E. Metaplasia*.
B. Infiltrative growth. *D. Anaplasia*.

15. The patient complained of aching pain in the upper palate, difficulty swallowing. Recently, general weakness, weight loss appeared. During the examination, cancer of the oral mucosa with metastases in the lymph nodes was diagnosed. What is the mechanism of development of cachexia in this patient?

A. Disorders of gastric secretion.
B. Disorders of the trophic function of the nervous system.
C. Dysfunction of the endocrine system.
D. Enhancement of gluconeogenesis.
E. Reduction of plastic and energy reserves.

16. The woman was diagnosed with erosion of the cervix, which is a precancerous pathology. What protective mechanism can prevent the development of a tumor?

A. Increase in natural killers (NK cells).
B. High-dose immunological tolerance.
C. Increased activity of lysosomal enzymes.
D. Simplification of the antigenic composition of tissues.
E. Low-dose immunological tolerance.

Standards of correct answers to the KROK-1 task

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
E	*E*	*C*	*C*	*A*	*A*	*A*	*A*	*B*	*D*	*B*	*D*	*C*	*C*	*E*	*A*

Recommendations for registration of work results

1. Written answer to test tasks (initial level of knowledge).

2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.

3. Independent work of students. Protocol for the analysis of cases of tasks with signs of tumor growth.

4. Protocol for solving situational tasks with an explanation of the correct answers.

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Topic 10. Hypoxia

Justification of the topic: Oxygen starvation or hypoxia is a typical pathological process that occurs in various diseases and significantly affects their development and completion. The life of any person from birth to death is accompanied by the phenomena of hypoxia, which is why the study of hypoxic conditions attracts the attention of many researchers. Due to the fact that oxygen starvation accompanies the course of many diseases, it is necessary to use antihypoxic agents in the complex of pathogenetic therapy, and this, in turn, requires knowledge of the main external manifestations of oxygen starvation, the essence of the processes underlying hypoxia, the mechanisms of their occurrence and course.

Purpose of the lesson:

General – to be able to characterize hypoxia as a typical pathological process, to assess functional disorders in the body, to explain the main mechanisms of damage and compensation during oxygen starvation in order to develop the ability to apply symptomatic and pathogenetic treatment of this pathology at departments of a clinical profile.

Specifically:

Know:

1. Definition of the term "hypoxia", "hypoxemia", to be able to classify oxygen starvation by etiology and pathogenesis.
2. The main manifestations of hypoxia and determine which reactions are intrinsically pathological and which are protective-adaptive in nature, explain the mechanisms of their occurrence in order to justify the symptomatic and pathogenetic therapy of hypoxic conditions.

Be able:

1. Experimentally simulate oxygen starvation and justify your conclusions.
2. To explain the general mechanisms of oxygen starvation, pathogenetic and protective-adaptive reactions of the body during hypoxia.
3. Determine the main indicators of pulmonary ventilation depending on changes in the gas composition of the blood.
4. Evaluate the results of the respiratory rate study and the results of spectrometric analysis of blood for methemoglobin content.

Practical experience:

1. Determining the gas composition and pH of blood and establishing the type of hypoxia:

- hypoxic hypoxia;
- respiratory hypoxia;
- hemic hypoxia;
- circulatory hypoxia;
- tissue hypoxia;
- substrate hypoxia;
- overloading hypoxia;
- mixed hypoxia.

The graphological structure of the topic "Hypoxia" is attached.
Material and methodological support of the topic "Hypoxia":

1. Lectures;
2. Methodical instructions for teachers;
3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational tasks to determine the final level of knowledge;
6. A set of KROK-1 tasks;
7. A set of schemes and tables (presentation);
8. A set of case studies and analyzes of gas composition and blood ph;
9. Video films;
10. For the experiment (experimental animals - white mice; glass jars with a capacity of 200 ml, a crystallizer for a mixture of water and ice, a thermometer, tripods, ice, water, plasticine).

Oriented map of students' work on the topic "Hypoxia"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of knowledge	10	Written answer to test tasks	Test tasks	Study room
2	Analysis of theoretical material	35	Analysis of theoretical material based on control questions of the topic, situational tasks, tasks KROK-1	Topic control questions, KROK-1 tasks, situational tasks	
3	Practical part (conduct experiment)	30	Introduction and preparation for setting up the experiment. Setting up the experiment. Discussion of the results of the experiment and formulation of conclusions	White mice; glass jars with a capacity of 200 ml, crystallizer for mixing water with ice, thermometer, tripods, ice, water, plasticine	
4	Determination of the final level of knowledge and skills. Summary.	15	Determination of the initial level of formation of knowledge and skills	KROK-1 tasks, situational tasks	

Pathophysiology of internal respiration. Hypoxia

Hypoxia (*oxygen insufficiency or oxygen starvation*) is the state characterised by insufficient energetic maintenance of the vital processes and arises in inadequate supply of the tissues with oxygen or its utilisation by the tissues. Hypoxia is a typical pathologic process.

The following forms of hypoxia are distinguished in according with the causes of their origin.

1. *Hypoxic hypoxia* in which the arterial blood is insufficiently oxygenated and the oxygen tension in it is low with the result that the saturation of hemoglobin with oxygen is also below normal. It arises as a result of decreased oxygen in the inspired air, disturbance in respiration and in ventilation of

the alveoli (due to disoders in the apparatus of external respiration), or hindered passage of oxygen through the alveolary capillary membranes into the blood. Accordingly, the following forms of hypoxic hypoxia are distinguished:

a) due to decreased partial pressure of oxygen in the inspired air;

b) due to difficulty of oxygen passage through the respiratory ways into the blood;

c) due to disturbances in external respiration.

2. *Hematic hypoxia* in which the oxygen-carrying capacity of the blood is reduced due to a decrease in hemoglobin (in anemias) or to inactivation of hemoglobin (hereditary defects of hemoglobin, formation either of methemoglobin or carboxyhemoglobin). Accordingly, there are two forms of hematic hypoxia:

a) anemic type (a decrease in oxygen capacity of the blood);

b) hypoxia in inactivation of hemoglobin (a reduction in oxygen-binding ability of hemoglobin).

In this form of hypoxia the degree of saturation of the present or functioning hemoglobin is normal, but the total amount of oxygen in the blood is decreased.

3. *Circulatory hypoxia* in which the circulation of the blood is slow or diminished. It includes:

a) stagnant form;

b) ischemic form.

This form of hypoxia arises as a result of general circulatory disoders (in cardiac or vascular failure) or in local circulatory disturbances (in venous congestion or ischemia). In these cases oxygenation of arterial blood is normal, but the total volume of oxygen carried to the tissue per unit of time is decreased. Diminished oxygen in the venous blood and an increased arterio-venous difference are observed.

4. *Tissu*e (*histotoxi*c) *hypoxia* (disturbance in oxidative processes in the tissues) in which, as distinct from all other forms, the transport of oxygen is undisturbed and its concentration in the blood is normal, but the ability of the tissues to utilise the delivered oxygen is diminished. This is due to a primary disturbance in the oxidative processes in the tissues, as in poisoning with cyanide compounds which paralyse the cytochrome oxidase (iron-containing enzyme), or under the action of narcotics which predominantly depress the activity of diaphorases. Avitaminoses B_1, B_2 and PP, and endocrine disoders (thyroid hyperfunction) may also cause tissue hypoxia.

Mixed hypoxia most frequently occurs – in traumatic shock and intoxications, and under the action of certain poisonous substances, when there are simultaneously cardiovascular and pulmonary insufficiency and disturbances in tissue metabolism.

Disturbances in Metabolism and Functions in Hypoxia

Of the disturbances characteristic of hypoxias is not always possible to determine with sufficient certainty the symptom complex of the changes associated precisely with the oxygen deficiency in the tissues. For example, in affections of the pulmonary apparatus, the blood or tissues, the phenomena

of oxygen deficiency proper are overshadowed by phenomena of intoxication, metabolic disoders, signs of pulmonary disease, disturbances in the hemato-poietic apparatus or dystrophic phenomena in various organs.

The most characteristic indications of inadequate supply of the tissues with oxygen are dyspnea and circulatory disoders (cardiac failure, drop in blood pressure and cyanosis).

In hypoxia first of all carbohydrate and energy metabolisms are disturbed. Consumption of oxygen at first increases and then, in cases of marked oxygen deficiency, falls. The deficit of macroergous substances (increased potential of phosphorylation), increased glycolysis, the loss in glycogen and increase in pyruvate and lactate contents, and metabolic acidosis are observed. In cases of hypocapnia due to compensatory hyperventilation (see below), the relative alkalosis is developed, however, the continued development of hypoxemia and hypoxia leads to increased insufficiency of oxidative processes. Alkalosis is again replaced by acidosis which in its turn somewhat diminishes owing to the acceleration of the respiratory rhythm and diminution in the oxidative processes and partial carbon dioxide pressure. As to protein metabolism an increased protein decomposition, decreased contents of amino acids in the blood, increased quantity of ammoniac, and a negative nitrogen balance are observed; as to lipid metabolism hyperketonemia and ketonuria arise. An increase in extracellular potassium is marked that testifies to cellular damage.

A certain period of excitement is followed by fatigue, apathy, somnolence, heaviness in the head, psychic disturbances in the form of irritability and subsequent depression, partial loss of orientation, disoders of the motor function and disturbances in higher nervous activity. Internal inhibition in the cerebral cortex weakens, then diffuse inhibition develops. The condition also involves disturbances in the vegetative functions as dyspnea, accelerated heart rate, circulatory changes and digestive disoders.

Respiration firstly becomes fast and deep as a result of stimulation of the respiratory centre, the circulation of air in the alveoli appreciably improves, but the concentration and tension of carbon dioxide in the blood decrease, i.e. hypocapnia develops. When hypoxia is combined with an increased concentration of carbon dioxide in the environment hypercapnia develops. Changes in the concentration of carbon dioxide in the blood aggravate the course of hypoxia. Then respiration is inhibited, Cheyne-Stokes and lately terminal respirations develop. The respiratory disturbances lead to loss of consciousness.

The heart's action accelerates and intensificates as a result of excitation of the accelerator nerve of the heart and inhibition of the vagus nerve. Acceleration of the pulse in cases of oxygen deficiency is therefore one of the indications of the reaction of the nervous system which regulates the blood circulation.

Several other circulatory disoders arise. The arterial pressure at first rises, but subsequently begins to drop in accordance with the state of the vasomotor centres. Then heart's action noticeably weakens, the arterial pressure drops, while the venous pressure rises, cyanosis develops and arrhythmia results.

The dysfunction in the nervous system is also manifested in gastrointestinal disoders, usually as anorexia, inhibition of the function of the digestive glands, diarrhea and vomiting.

Adaptive Reactions in Hypoxia

I. The reactions providing an adaptation to short-term acute hypoxia (urgent, emergency reactions):

1. Respiratory reactions:

– increase in frequency of respiration;

– deepening of respiration;

– mobilisation of the reserve alveoli.

2. Hemodynamics reactions:

– increase in frequency of the cardiac contractions;

– increase in volume of circulating blood (mobilisation of the blood from its depots);

– increase in the venous inflow;

– increase in the systolic and minute volume of the heart;

– increase in speed of circulation;

– mobilisation of the reserve capillaries;

– redistribution of the blood (an increased inflow of blood to vitally important organs – heart, brain);

3. Hematic reactions:

– increase in oxygenic capacity of the blood (mobilisation of erythrocytes from the bone marrow and blood depots – relative erythrocytosis);

– activation of erythropoiesis (absolute erythrocytosis);

– increase in property of the blood hemoglobin to combine with oxygen;

– increase in dissociation of the oxyhemoglobin (owing to acidosis);

– occurrence of fetal hemoglobin.

4. Tissue reactions:

– increase in the ability of the tissues to absorb oxygen;

– reduction in the functional activity of the organs;

– increase in interface of oxidation and phosphorylation;

– increase in anaerobic glycolysis;

– stabilisation of the membranes of lysosomes (due to increased secretion of glucocorticoids).

II. The reactions ensuring the constant adaptation to the less expressed, but the long-term or repeated hypoxia:

1. Respiratory reactions:

– hypertrophy of the pulmonary tissue;

– hypertrophy of the respiratory muscles;

– hypertrophy of the neurons of the respiratory centre;

– increase in diffusion of oxygen (increase in permeability of the alveolary capillary membranes).

2. Hemodynamics reactions:

– hypertrophy of the myocardium;

– formation of the new capillaries, especially in the lungs.

3. Hematic reactions:

– hyperplasia of the bone marrow (a proof increase in hemoglobin and erythrocyte amounts).

4. Tissue reactions:

– increase in amount of myoglobin (which is combined with oxygen even in its low amount in the blood);

– increase in quantities of the mitochondria per unit of mass of the cell (increase in capacity of the system of oxygen utilisation).

The foregoing plastic reactions are due to increase in the potential of phosphorylation (the relation of ADP × nonorganic phosphorus to ATP). It stimulates the generic apparatus of the cells that results in increased synthesis of nucleic acids and proteins.

Setting up the experiment. Discussion of results and formulation of conclusions

Modeling the effect of hypothermia on the body's sensitivity to oxygen starvation: Take two mice and place them in separate jars (air access is free). Put jar N 1 in a mixture of water and ice (temperature 3–4 C), and jar N 2 leave at room temperature. After 15 minutes, study the initial state of both animals: behavior, reaction to sound, skin color, breathing rate. Then seal both cans at the same time. Observations lead to the death of animals. Record the results in the table every 2–3 minutes.

Discussion of the results of the experiment

• Under the influence of these factors, an increase in cardiac output due to tachycardia and an increase in systolic volume and an increase in blood pressure were observed in rats. Also increased frequency and deepening of breathing. Hyperventilation of the alveoli leads to the development of hypocapnia, which increases the affinity of hemoglobin for oxygen and accelerates the oxygenation of the blood flowing to the lungs. An increase in the mass of circulating blood due to the emptying of blood depots and accelerated washing out of erythrocytes from the bone marrow; thanks to this, the oxygen capacity of the blood increases.

• Adaptive reactions at the level of cells that experience oxygen starvation of tissues and are expressed in an increase in the affinity of oxidation and phosphorylation processes and in the activation of glycolysis, due to which the energy needs of cells can be satisfied for some time.

• When glycolysis increases, lactic acid accumulates in the tissues, acidosis develops, which accelerates the dissociation of oxyhemoglobin in the capillaries.

• In case of insufficient oxygen entering the cells, the process of anaerobic glycolysis is enhanced. Under the influence of hypoxia, the permeability of brain capillaries increases, which leads to its swelling. Already 3–4 minutes after the cessation of oxygen delivery to the myocardium, the heart loses its ability to create the arterial pressure necessary to maintain blood flow in the brain, as a result of which irreversible changes occur in it, which can cause the death of the body.

Formulation of conclusions based on the experiment

Under the influence of hypoxia, both adaptive and pathogenic reactions develop, which lead to irreversible organ damage, the basis of which is a metabolic disorder, which in turn is associated with a reduced or complete cessation of the formation of macroergic phosphorus compounds, which limits the ability of cells to perform normal functions and maintain a state of internal homeostasis.

Tasks for independent work on the topic "Hypoxia"

The student is offered 2–3 cases and analyzes with indicators of gas composition and blood pH. It is necessary to determine the type of hypoxia. Be able to explain the mechanism of occurrence. Analysis of errors with an explanation of the correct answers

List of questions and works to be studied:

1. Definition of the terms "hypoxemia", "hypoxia".
2. Classification of oxygen starvation by etiology and pathogenesis.
3. The essence and mechanisms of the development of functional disorders in the body during oxygen starvation.
4. The main pathogenetic mechanisms of the development of each form of oxygen starvation.
5. Compensatory mechanisms that prevent the development of oxygen starvation.

List of practical skills that must be mastered:

Determining the gas composition and pH of the blood and establishing the type of hypoxia:

- hypoxic hypoxia;
- respiratory hypoxia;
- hemic hypoxia;
- circulatory hypoxia;
- tissue hypoxia;
- substrate hypoxia;
- overloading hypoxia;
- mixed hypoxia.

Situational tasks KROK-1 to determine the final level of knowledge

1. When climbing to a height in a pressure chamber, the rat developed frequent breathing, tachycardia, and a decrease in pO2 tension in the blood. What form of hypoxia occurs in this case?

A. Hypoxic. B. Chemical. C. Circulatory. D. Textile. E. Respiratory.

2. A research doctor as part of a mountaineering expedition climbed to a height of 5,000 m. On the 3rd day of his stay, he developed symptoms of mountain sickness: shortness of breath, headache, loss of appetite, general weakness, cyanosis. What type of hypoxia occurs in this case?

A. Circulatory. B. Hypoxic. C. Stagnant. D. Chemical. E. Fabric.

3. Mountaineers, who were climbing to the top, developed a headache, loss of consciousness, and shortness of breath. What type of hypoxia occurred in climbers?

A. Chemical. B. Hypoxic. C. Circulatory. D. Fabric. E. Mixed.

4. To simulate a stomach ulcer, the animal was injected with atophane, which causes its sclerosing, into the gastric artery. What mechanism of damage to the mucous membrane of the stomach will be the leading one in this experiment?

A. Hypoxic. C. Mechanical. E. Neurohumoral.
B. Neurodystrophic. D. Disregulatory.

5. A 36-year-old man complains of cough with phlegm, shortness of breath, headache, and general weakness. He fell ill after severe hypothermia. During the examination: the skin is pale, the body temperature is 38 °C. Pulse – 91/min, blood pressure – 125/60 mm Hg. In the blood analysis – neutrophilic leukocytosis. The diagnosis was established: focal pneumonia. What type of hypoxia does the patient have?

A. Chemical. C. Respiratory. E. Circulatory ischemic.
B. Textile. D. Circulatory congestion.

6. In a patient during an attack of bronchial asthma, the presence of hypercapnia was detected when determining pCO2 in the blood, and hypoxemia when determining PO2. What type of hypoxia is observed in this case?

A. Chemical. B. Circulatory. C. Respiratory. D. Textile. E. Histotoxic.

7. A 40-year-old man complains of general weakness, headache, cough with phlegm, shortness of breath. After a clinical examination and examination, a diagnosis was made: focal pneumonia. What type of hypoxia does the patient have?

A. Respiratory. B. Circulatory. C. Chemical. D. Textile. E. Hypoxic.

8. A 65-year-old man suffers from chronic left-sided heart failure. Objectively: cyanosis, shortness of breath, cough with sputum, periodic attacks of suffocation. What type of hypoxia initially occurred in the patient?

A. Circulatory congestion. C. Fabric. E. Chemical.
B. Circulatory ischemic. D. Respiratory.

9. The patient is in the hospital with a diagnosis of chronic heart failure. Objectively: the skin and mucous membranes have a cyanotic shade, tachycardia, tachypnea. What type of hypoxia does the patient have?

A. Anemic. B. Toxic. C. Hypoxic. D. Fabric. E. Circulatory.

10. A man, approximately 50 years old, was carried out in an unconscious state from a closed room filled with smoke from a fire. What type of hypoxia occurred in the victim?

A. Respiratory. B. Hypoxic. C. Fabric. D. Circulatory. E. Chemical.

11. A 23-year-old patient complains of severe weakness, drowsiness, darkening of the eyes, dizziness, and a change in taste. Menorrhagia in the anamnesis. Blood analysis: Er – 2.8×10^{12}/l, Hb – 70 g/l, CP – 0.75. Which hypoxia most likely led to the development of the identified symptoms in the patient?

A. Chemical. B. Circulatory. C. Fabric. D. Respiratory. E. Mixed.

12. A man complained of feeling unwell to the district doctor. In the blood test, erythrocytes are 3×10^{12}/l, hemoglobin is 70 g/l, the color indicator is 0.7. What type of hypoxia does the patient have?

A. Krovyan. B. Respiratory. C. Cardiovascular. D. Hypoxic. E. Fabric.

13. Hypoxia was detected in a patient who is being treated for anemia. It belongs to the following type:

A. Respiratory. B. Circulatory. C. Fabric. D. Chemical. E. Mixed.

14. A utility service worker went down into the sewage well without protective equipment and after some time lost consciousness. Emergency doctors diagnosed hydrogen sulfide poisoning. What type of hypoxia has developed?

A. Overloading. C. Fabric. E. Respiratory.
B. Chemical. D. Circulatory.

15. A 55-year-old patient has been taking barbiturates for a long time, which is a favorable factor for the development of blood hypoxia. A sign of which pathological form of hemoglobin can lead to the development of blood hypoxia in this case?

A. Sulfhemoglobin. C. Methemoglobin. E. S-hemoglobin.
B. Carboxyhemoglobin. D. F-hemoglobin.

16. After an accident at a chemical plant, the environment was polluted with nitro compounds. Some of the people living in this area have experienced sudden weakness, headache, shortness of breath, and dizziness. What is the mechanism of development of this form of hypoxia?

A. Increase in methemoglobin formation.
B. Decrease in the function of flavin enzymes.
C. Formation of carboxyhemoglobin.
D. Inactivation of cytochrome oxidase.
E. Suppression of dehydrogenases.

17. The patient developed hemic hypoxia as a result of poisoning with Bertolet salt. The formation of which substance plays a role in the pathogenesis of this hypoxia?

A. Nitrous oxide. C. Carbhemoglobin. E. Methemoglobin.
B. Sulfhemoglobin. D. Carboxyhemoglobin.

19. The emergency doctor diagnosed the victim with signs of carbon monoxide poisoning. What connection caused this?

A. Carbhemoglobin. C. Deoxyhemoglobin. E. Carboxyhemoglobin.
B. Methemoglobin. D. Oxyhemoglobin.

20. After repairing the car in the garage, the driver was hospitalized with symptoms of exhaust gas poisoning. The concentration of which hemoglobin in the blood will be increased?

A. Methemoglobin. C. Oxyhemoglobin. E. Carboxyhemoglobin.
B. Carbhemoglobin. D. Glycolized hemoglobin.

21. The man lost consciousness in the garage, where he had been repairing the car for a long time with the engine running. A pathological compound of hemoglobin was found in his blood. Which one exactly?

A. Carboxyhemoglobin. *C. Oxyhemoglobin.* *E. Carbhemoglobin.*
B. Methemoglobin. *D. Deoxyhemoglobin.*

22. Patient V. 38 years old, brought to the reception department with signs of hypoxia, which developed after carbon monoxide poisoning. Moderate condition, tachycardia, shortness of breath, blood pressure 160/100. What is the mechanism of the toxic effect of carbon monoxide on the body?

A. Formation of carboxyhemoglobin.
B. Formation of methemoglobin.
C. Violation of dissociation of oxyhemoglobin.
D. Formation of carbhemoglobin.
E. Blockade of calcium channels of erythrocytes.

23. A man was brought to the hospital in an unconscious state after carbon monoxide poisoning. Hypoxia in him is due to the appearance in the blood of:

A. Methemoglobin. *C. Oxyhemoglobin.* *E. Deoxyhemoglobin.*
B. Carbhemoglobin. *D. Carboxyhemoglobin.*

24. The patient was admitted to the intensive care unit with severe hypothermia. What type of hypoxia does this patient have?

A. Hypoxic (hypobaric). *C. Chemical.* *E. Respiratory.*
B. Hypoxic (hyperbaric). *D. Fabric.*

25. Urethane poisoning was caused in an experimental animal. What type of hypoxia occurred?

A. Chemical. *B. Textile.* *C. Circulatory.* *D. Respiratory.* *E. Hypoxic.*

Standards of correct answers to the KROK-1 task

1	2	3	4	5	6	7	8	9	10	11	12	13
A	*B*	*B*	*A*	*C*	*C*	*A*	*A*	*E*	*E*	*A*	*A*	*D*
14	15	16	17	18	19	20	21	22	23	24	25	
B	*C*	*A*	*E*	*E*	*E*	*E*	*A*	*A*	*D*	*D*	*B*	

Recommendations for registration of work results

1. Written answer to test tasks (initial level of knowledge).
2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.
3. Independent work of students. Protocol of analysis of case studies and studies of gas composition and pH of blood.
4. Protocol for solving situational tasks with an explanation of the correct answers.

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Topic 11. Pathology of carbohydrate metabolism

Justification of the topic: Violations of carbohydrate metabolism (hyperglycemia and hypoglycemia) are a number of diseases. Of particular importance is the study of the etiology and pathogenesis of diabetes mellitus (DM), which occurs in 1–4 % of the population, especially among the elderly (2–30 %). Depending on the causes and degree of insulin deficiency, diabetes can be primary and secondary (symptomatic). Primary, in turn, can be insulin-dependent (type 1 diabetes) and insulin-independent (type II diabetes). Other types of DM are secondary and are associated with certain diseases, for example, acromegaly, Itsenko-Cushing's disease, diseases of the pancreas (PZ), the effect of drugs and chemicals, genetic syndromes, etc. At the same time, hypoglycemic conditions are a serious complication of a number of diseases, which is caused, first of all, by the high sensitivity of the central nervous system to the lack of glucose, which is the only source of energy for non-tear cells that do not have glycogen reserves. This, in turn, causes a violation of the functioning of vital organs and systems of the body.

Purpose of the lesson:

General – to be able to conduct a pathophysiological analysis of situations related to disorders of carbohydrate metabolism, to characterize the etiology and pathogenesis of diabetes mellitus, to know experimental models of diabetes mellitus.

Specifically:

Know:

1. The main typical forms of violation of carbohydrate metabolism. Their reasons.
2. Hypoglycemia syndrome: types, causes, mechanisms, pathogenesis of hypoglycemic coma.
3. Hyperglycemia syndrome: types, causes and mechanism of development.
4. Diabetes mellitus: definition, classification.
5. Etiology, pathogenesis of type 1 diabetes mellitus, pathogenesis of absolute insulin deficiency.
6. Etiology, pathogenesis of type 2 diabetes mellitus, variants of relative insulin deficiency in type 2 diabetes mellitus (secretory disorders of β-cells, resistance of target tissues to insulin).
7. Laboratory diagnosis of diabetes.
8. Complications of diabetes mellitus, pathogenesis. Diabetic coma: ketoacidotic, hyperosmolar, hypoglycemic. Causes, pathogenesis. Manifestations.
9. Significance in clinical practice of various forms of carbohydrate metabolism disorders.
9. Hereditary disorders of carbohydrate metabolism.

Be able:

1. To characterize the main causes of disorders of carbohydrate metabolism.
2. Characterize the syndromes of hypoglycemia and hyperglycemia, explain the causes, pathogenesis.

3. To explain the mechanism of development of clinical manifestations of the main syndromes of hypoglycemia and hyperglycemia.

4. Explain the causes and mechanisms of metabolic disorders in diabetes (hydrocarbon, lipid, protein, water-salt, acid-base).

5. Explain the mechanism of development of the main clinical signs of diabetes.

6. Explain the mechanism of development of diabetes complications (early, late).

Practical experience:

Evaluate the results of laboratory studies of impaired carbohydrate metabolism (blood plasma glucose, glycosylated hemoglobin -HbA1c, serum C-peptide, blood insulin level, glucose tolerance test, determination of glucose and acetor in urine).

The graphological structure of the topic "Pathology of carbohydrate metabolism" is attached.

Material and methodological support of the topic "Pathology of carbohydrate metabolism":

1. Lectures;
2. Methodological developments for teachers;
3. Methodical instructions for students;
4. A set of test tasks to determine the basic level of knowledge;
5. A set of situational problems to determine the final level of knowledge;
6. A set of krok-1 tasks;
7. A set of laboratory tests of blood and urine for diabetes.
8. A set of diagrams and tables (presentation);
9. Video films;
10. For the experiment (experimental animals – rabbit; centrifuge, fec, test tubes, water bath, syringe, alloxan, orthotoluidine reagent).

Oriented map of students' work on the topic "Pathology of carbohydrate metabolism"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
	Determination of the initial level of knowledge	10	Written answer to test tasks	Test tasks	Study room
	Analysis of theoret-ical material	35	Analysis of theoretical material based on control questions of the topic, situational tasks, tasks KROK-1	Topic control questions, KROK-1 tasks, situational tasks	
	Practical part (conduct experiment)	30	Introduction and preparation for setting up the experiment. Setting up the experiment. Discussion of the results of the experiment and formulation of conclusions	Experimental animals - rabbits; centrifuge, FEK, test tubes, water bath, syringe, alloxan, orthotoluide-new reagent	
	Determination of the final level of knowledge and skills. Summary.	15	Determination of the initial level of formation of knowledge and skills.	KROK-1 tasks, situational tasks	

Disturbances in carbohydrate metabolism

It is necessary to distinguish disturbances in absorption, intermediate metabolism and processes of regulation of carbohydrate metabolism.

1. Disturbances in carbohydrate absorption occur as a result of disoders of fermentative hydrolysis of polysaccharides in the intestines or of the very process of monosaccharide absorption, i.e. of the process of monosaccharide phosphorylation in the intestinal mucosa. Disturbances in phosphorylation may be caused by a diminished incretory function of the adrenal cortex (decreased secretion of glucocorticoids), inflammation of the intestinal mucosa, or poisoning with toxins which depress the process of phosphorylation. Disturbances in carbohydrate absorption lead to carbohydrate starvation and hypoglycemia.

2. Disturbances in intermediate carbohydrate metabolism consists in a) weakened glycogen synthesis (glycogenesis) in the liver and muscles, b) increased formation of glucose from glycogen (glycogenolysis) or from protein or fat decomposition products (glyconeogenesis), c) disturbances in glucose conversion in the tissues.

a) Inhibition of glycogenesis may be the result of dysfunction of the nervous system (for example, in myasthenia gravis pseudoparalytica), hepatocyte dysfunction (for example, in hepatitis, in action of phosphorus, CCl44 0etc.), and hypoxia (in which the oxygen deficiency is responsible for the lack of energy necessary for the synthesis of glycogen).

b) Intensified glycogenolysis is most frequently a result of increased energy metabolism, for example, in disoders of nervous and endocrine regulation (intense emotional excitement, pain, cooling, etc.), when the increased production of glucogenolysis stimulating hormones is happened (somatotropin, adrenalin, glucagon, thyroxin). Glyconeogenesis is observed mainly in diabetes.

c) Disturbances in glucose utilisation in the tissues are connected with its oxidation and conversion. Such disturbances usually arise in infections and intoxications, hypoxia, cancer (involving increased glycolysis accompanied by accumulation of lactic acid in the blood), avitaminosis, especially avitaminosis B410 (associated with difficulties of pyruvic acid oxidation), in liver dysfunction (when resynthesis of lactic acid into glucose and glycogen is decreased).

3. Disturbances in the regulation of carbohydrate metabolism

are the most frequent causes of carbohydrate metabolism pathology.

In 1885 Claude Bernard discovered the carbohydrate metabolism regulating centre in the floor of the fourth ventricle in the medulla oblongata. A puncture in this centre causes a temporary increase in the content of glucose in the blood and its appearance in the urine. Paths from the higher vegetative centres of carbohydrate metabolism regulation run through the spinal cord and splanchnic nerves to the adrenals. Adrenalin causes conversion of glycogen in the liver and, as a result, an increased content of glucose in the blood. There are apparently direct neural connections between the carbohydrate metabolism regulating centre in the medulla oblongata and the peripheral organs in which the processes of carbohydrate metabolism operate (mainly the liver and muscles).

Central regulation of carbohydrate metabolism is also effected in the tuber cinereum and lenticular nucleus of the corpus striatum, which are connected whith the medulla. At higher stages of phylogenesis the cerebral cortex also participate in the regulation of carbohydrate metabolism. Thus, various emotions and psychic overstrain may serve to raise the glucose level in the blood (W. B. Cannon).

An important part in the regulation of the carbohydrate metabolism is played by the endocrine glands, mainly the pancreas, hypophysis and adrenals.

The most reliable index of disturbances in carbohydrate metabolism is change in the glucose level in the blood: an increased level is called hyperglycemia, a decreased one is known as hypoglycemia.

Normal urine contains no glucose. Its appearance is called glycosuria. An increased glucose content in the blood is accopanied by the intensified glucose filtration. But hyperglycemia causes glycosuria only at a certain level of glucose concentration in the blood (8,8–11 mmol per 1l), i.e. when reabsorption of glucose in the renal tubules falls short of its filtration in the glomeruli.

This concentration of glucose in the blood is called renal threshold for glucose. At this level the fermentative processes of glucose phosphorylation in the renal tubules are insufficient.

In pathology there are glycosuria without hyperglycemia. It is called renal glycosuria. In this case changes in the functional capacity of the kidneys (lowered renal threshold for glucose) plays the principal part. Experimentally renal glycosuria is produced by administration of phlorhizin (a glycoside derived from the bark and root of apple, cherry, pear and plum trees). The development of phlorhizin glycosuria is based on a reversible disturbance in reabsorption of glucose in the kidneys (its phosphorilation).

Experimental Hyperglycemias and Glucosurias

1. **Alimentary Glycosuria.** It arises in man after ingestion of 160–180 g of glucose on an empty stomach. After ingestion of 100 g of glucose hyperglycemia usually does not exceed 8–8,5 mmol per 1l. By the end of the second hour the glucose level in the blood returns to normal. A strongly-pronounced and long-continued hyperglycemia with glycosuria denotes a reduced carbohydrate-assimilating capacity (for example, in diabetes and dysfunction of the thyroid and hypophysis).

2. **Neurogenic Hyperglycemia and Glycosuria.** They are caused by a puncture of the floor of the fourth ventricle, develop whithin 1–2 hours and last 5–6 hours in rabbits and 1–2 days in dogs. They are connected with the increased glycogenolysis. In man central hyperglycemia and glycosuria are observed in cerebral traumas, hemorrhages, inflammatory foci in the brain, emotional strain and severe psychic shock. Narcotics (ether, chlorophorm and morphine) cause hyperglycemia by inhibiting the cerebral cortex, disinhibiting the underlying centres of the hypothalamic region and intensifying secretion of adrenalin, but may also act directly on the liver and intensify glycogenolysis.

3. **Adrenalin-induced ones.** They are connected with intensification of glycogenolysis in the liver. In man they develop very rarely, for example, in pheochromocytomata – tumours of the adrenal medulla – when a large amount of adrenalin enters the blood.

4. **Pancreatic Diabetes.** It is produced by complete removal of the pancreas (Mering and Minkowski, 1899). Diabetes is developed. All of kinds of metabolism are disturbed beginning from carbohydrate one. Three or four weeks the animal dies of polyuria, considerable emaciation and intoxication. Development of diabetes is due to cessation of the internal secretion of the pancreas. Depriving the organism of the external secretion of this gland by ligation of its duct does not cause development of diabetes (L.V. Sobolev,1900). Ligation of the pancreatic duct causes atrophy of the acinar elements of the pancreas whithout affecting the islets of Langerhans. Insulin was discovered in 1922 by F. G. Banting, C. H. Best and J. J. R. Macleod. It decreases the glucose level in the blood and eliminates the changes arising in diabetes. It has been established that in the islets of Langerhans insulin is formed in and secreted by b-cells, while a-cells produce another hormone-glucagon (Burger and Murlin). Unlike insulin, glucagon causes hyperglycemia because it stimulates glycogenolysis in the liver.

5. **Alloxan Diabetes.** Administration of alloxan (mesoxalylurea) to animals causes selective degeneration of the 7b 0-cells inactivating their enzymatic complex which contains the S-S group. Compared whith pancreatic model the alloxan one has the advantage that it preserves the external secretion of the pancreas and the function of the a-cells.

6. **Dithizone-induced Diabetes.** Dithizone (diphenylthiocarbazone) affects the b-cells by forming a complex with zinc, a constituent of insulin.

7. **Streptozotocinic Diabetes.** Administration of antibiotic streptozotocin induces damage of pancreatic islets.

8. **Hypophyseal Hyperglycemia and Glycosuria (Diabetes).** Parenteral administration of the extract from the anterior lobe of the hypophysis for 2–3 weeks causes appreciable hyperglycemia with glycosuria and ketonemia in dogs. Degenerative changes are observed in the pancreatic islets. Removal of the hypophysis causes hypoglycemia. The somatotropin activates production of glucagon and insulin, which in the end leads to exhaustion of the b-cells. The corticotropin increases production of glucocorticoids in the adrenal cortex.

9. Steroid-induced Hyperglycemia and Glycosuria (Diabetes). They are produced by administration of large doses of glucocorticoids. However, under the influence of hypophyseal hormones and glucocorticoids real diabetes can develop only in cases of latent insufficiency of the beta-cells of the pancreatic islets.

Diabetes mellitus

Diabetes mellitus (from the Greek diabetes – to pass through, and the Latin mel – honey) is a disease based on absolute or relative insulin insufficiency and characterised by disturbances in all of the kind of metabolism beginning from carbohydrate one.

Etiology

Several factors are involved in the etiology of diabetes: long-continued overeating of carbohydrates, negative emotions - psychic shock or protracted neuropsychic overstrain, infections and intoxications, and congenital factors.

Pathogenesis

Insulinic insufficiency is the main pathogenetic factor of diabetes. In may be pancreatic one (absolute), connected with disorders in biosynthesis and secretion of insulin, and nonpancreatic one (relative) – in normal secretion of insulin.

Accordingly, there are insulin-dependent diabetes (the I type diabetes) – with absolute insulin insufficiency, severe metabolic disoders which are developed in juvenile age, and insulin-nondependent diabetes (the II type diabetes) - with relative insuline insufficiency and little metabolic disturbances which are developed after 40 years.

Besides, there are the primary and the secondary (symtomatic) diabetes. The secondary diabetes is observed in acromegaly, Cushing's disease, pancreatic diseases, action of drugs and chemical substances, genetic syndroms, etc.

Pancreatic insulin insufficiency becomes clear from the role of insuline in the organism. Insulin possesses glycogenostatic action, i.e. it inhibits glycogenolysis and intensifies the synthesis of glycogen in the liver. It stimulates the conversion of carbohydrates into fat and intensifies the synthesis of proteins from aminoacids. Insulin causes increased consumption of glucose by the tissues which is due to increased entering of glucose into the tissues and its better utilisation by them. Thus, in diabetes there are intensified glycogenolysis and glyconeogenesis, reduced utilization of glucose by the tissues. The conversion of glucose into fat is also disturbed and the synthesis of proteins from amino acids is retarded.

Nonpancreatic insulin insufficiency is due to increased inactivation of insuline (insulinase, proteinases, binding of insulin by proteins, inhibition by nonetherified fatty acids, autoantibodies, antagonists, decreased content or sensitivity of receptors, etc.).

The main manifestations of diabetes are hyperglycemia and glucosuria, polyuria (passage of an excessive amount of urine – up to 5–10 l per day), polydipsia (excessive thirst). Polyuria is conditioned by a plantiful passage of glucose into the primary urine and a resultant increase in its osmotic concentration, which renders reabsorption of water in the renal tubules difficult. Polydipsia follows polyuria and is considered a compensatory phenomenon.

Besides, there are incresed excretion of nitrogen in the urine, the content of fats and lipoids in the blood, hyperketonemia, ketonuria, acidosis.

Intermediate metabolites, mainly ketone acids, may cause diabetic coma. In the main it is characterised by dysfunction of the central nervous system (unconsciousness, sometimes convulsions, hypotension, tachycardia, Kussmaul's respiration) with fatal results if no insulin is administered.

Hypoglycemia

It may be a result of 1) increased insulin secretion (hyperinsulinism) in hyperplasia or tumors (adenoma, insuloma) of pancreas, administration of large doses of insulin, 2) hypofunction of the anterior lobe of the hypophysis and the adrenal cortex in hypophyseal cachexia and Addison's disease, of the thyroid in myxedema, of the medullary substance of the adrenals, 3) insufficient metabolism of glycogen in glycogenoses, 4) mobilisation of large quantities of glycogen from the liver and the muscles, 5) insufficient digestion of glucose (carbohydrate starvation, alimentary hypoglycemia), 6) disturbance of absorption of carbohydrates in the intestine, 7) liver diseases and glycogen deficiency in the liver (toxic hepatitis,liver cirrhosis, action of phosphorus, etc.), 8) kidney's diabetes, 9) insufficiency of mechanisms of regulation of carbohydrate metabolism in newborns.

Hypoglycemia manifests itself mainly in dysfunction of the nervous system. There are general weakness, excessive perspiration, tremor, tachycardia (it is connected with the increased secretion of adrenalin), headache, nausea, impaired memory, sleepiness and periodic paralysis.

Decrease of glucose in the blood to 2,5 mmol per 1l may lead to hypoglycemic coma which is characterised by unconsciousness, periodic respiration, convulsions and sometimes even death.

Setting up the experiment. Discussion of results and formulation of conclusions

To determine the blood sugar content in experimental diabetes in rabbits.

1. In the experiment, take two rabbits, one of which was previously injected with alloxan at the rate of 160–170 mg per 1 kg of body weight to obtain alloxan diabetes.

2. During the lesson, take blood from control and diabetic rabbits and determine the sugar content in it by the orthotoluidine method. The principle of the method: glucose, when heated with orthotoluidine in acetic acid solution, forms a blue-green compound, the color intensity of which is directly proportional to the concentration of glucose.

3. The results of the experiment are drawn up in the form of a protocol (the blood sugar content of a rabbit with alloxan diabetes is significantly higher than that of a control).

During the discussion, pay attention to the role of exogenous factors that disrupt the formation of insulin (alloxan, etc.), which leads to the development of insulin-dependent diabetes mellitus type I. Physiological hyperglycemia is observed with emotional stress, consumption of a large amount of carbohydrates with food; pathological hyperglycemia – in diseases of the endocrine system, diabetes, tumors of the adrenal cortex and pituitary gland, hyperfunction of the thyroid gland, severe disorders of liver function, organic lesions of the central nervous system.

In humans, this type occurs due to the interaction of genetic and immune mechanisms. In the pathogenesis of type II diabetes (non-insulin-dependent) insulin resistance and pancreatic dysfunction are important

Forming conclusions based on the experiment

The introduction of alloxan into the rabbit's body causes the development of alloxan diabetes, which is evidenced by an increase in blood sugar (hyperglycemia) compared to the blood sugar in a control (intact) rabbit.

Tasks for independent work on the topic "Pathology of carbohydrate metabolism"

Students are offered to evaluate glycosylated hemoglobin and glycemic profile (glucose tolerance test). It is necessary to define syndromes of impaired carbohydrate metabolism (impaired glucose tolerance, diabetes mellitus) and explain the mechanism of occurrence. Analysis of errors with an explanation of the correct answers.

List of questions and works to be studied:

1. Violation of absorption of carbohydrates.
2. Concept of glycogenesis, glycogenolysis, gluconeogenesis. their violation.
3. Hyperglycemia, its types. Glucosuria, its mechanisms. Experimental hyperglycemia and glucosuria.
4. Insulin deficiency (pancreatic and extrapancreatic).
5. Concepts in diabetes. Etiology and pathogenesis of diabetes.
6. Forms of diabetes mellitus. Violations of various types of metabolism in diabetes.
7. Experimental models of diabetes.
8. Pathogenesis of diabetic coma.
9. Hypoglycemia, its types. Hypoglycemic coma.

List of practical skills that must be mastered:

1. To characterize the main causes of disorders of carbohydrate metabolism.
2. Characterize the syndromes of hypoglycemia and hyperglycemia, explain the causes, pathogenesis.
3. Explain the mechanism of development of clinical manifestations of the main syndromes of hypoglycemia and hyperglycemia.
4. Explain the causes and mechanisms of metabolic disorders in diabetes (hydrocarbon, lipid, protein, water-salt, acid-base).
5. Explain the mechanism of development of the main clinical signs of diabetes.
6. Explain the mechanism of development of diabetes complications (early, late).
7. Evaluate the results of laboratory studies of carbohydrate metabolism disorders (blood plasma glucose, glycosylated blood hemoglobin -HbA1c, serum C-peptide, blood insulin level, glucose tolerance test, determination of glucose and acetor in urine).

KROK-1 situational tasks to determine the final level of knowledge

1. Patient L., 46 years old, complains of dry mouth, thirst, frequent urination, general weakness. A biochemical blood test revealed hyperglycemia and hyperketonemia. In the urine – glucose, ketone bodies. Diffuse changes in the myocardium on the ECG. The patient reliably has:

A. Diabetes.
B. Alimentary hyperglycemia.
C. Acute pancreatitis.
D. Diabetes insipidus.
E. Ischemic heart disease.

2. A 25-year-old boy complains of dry mouth, thirst, weight loss, despite a high appetite. During examination: height 170 cm, weight – 50 kg, blood glucose level – 10.5 mmol/l, glucosuria. For which of the following conditions are these symptoms most characteristic?

A. Renal diabetes. *C. Alimentary glycosuria.* *E. Diabetes insipidus.*
B. Diabetes. *D. Steroid diabetes.*

3. Patient A., 18 years old, started to lose body weight after having rubella, she notes a constant sensation of dry mouth, thirst, increased appetite, frequent urination. Objectively: the daily amount of urine is 6 l, blood glucose is 17.8 mmol/l, glucose and acetone are found in the urine. What is the most likely pathogenetic mechanism that caused an increase in the patient's glucose level?

A. Increased destruction of insulin.
B. Increase in gluconeogenesis.
C. Decreased insulin production.
D. Damage to insulin receptors of cells.
E. Increased production of glucocorticoids.

4. An experimental animal (rat) was induced with experimental diabetes by intravenous administration of alloxan. What is the mechanism of action of this substance?

A. Activation of insulinase.
B. Binding of zinc.
C. Formation of antibodies to insulin.
D. Damage to beta cells of pancreatic islets.
E. Activation of counterinsular hormone production.

5. The patient was brought to the clinic in an unconscious state, with the smell of acetone coming from his mouth. Blood sugar – 25 mmol/l, ketone bodies – 0.57 mmol/l. Such a condition can develop with a deficiency of which hormone?

A. Somatotropic hormone. *C. Glucocorticoids.* *E. Insulin.*
B. Thyroxine. *D. Aldosterone.*

6. A 9-year-old girl was hospitalized in the department with a diagnosis of type I diabetes. Laboratory examination revealed a high level of ketone bodies. What is the main mechanism of disease development?

A. Insulin deficiency. *D. Excess of somatostatin.*
B. Insulin excess. *E. Violation of complexation of insulin with receptors.*
C. Glucagon excess.

7. Hyperglycemia of 19 mmol/l was detected in a patient with diabetes, which is clinically manifested by glucosuria, polyuria, and polydipsia. Which of the presented mechanisms is responsible for the development of glucosuria?

A. Non-enzymatic glycosylation of proteins. *D. Polydipsia.*
B. Threshold glucose reabsorption. *E. Dehydration of tissues.*
C. Polyuria.

8. Glucosuria and hyperglycemia were found in the patient during the examination. Complaints of dry mouth, itchy skin, frequent urination, thirst. The diagnosis was made: diabetes mellitus. What causes polyuria in this patient?

A. By increasing the filtration pressure.
B. By reducing the oncotic pressure of plasma.
C. An increase in the osmotic pressure of urine.
D. A decrease in cardiac output.
E. An increase in plasma oncotic pressure.

9. A 45-year-old woman has no symptoms of diabetes, but an elevated blood glucose level (7.2 mmol/l) is determined on an empty stomach. What is the next test to be performed?

A. Determination of glucose in urine.
B. Determination of residual nitrogen in the blood.
C. Determination of blood glucose.
D. Determination of glucose tolerance.
E. Determination of glycosylated hemoglobin.

10. A girl with diabetes is waiting for a donor kidney. What complication of diabetes is the cause of chronic renal failure?

A. Retinopathy. *C. Atherosclerosis.* *E. Microangiopathy.*
B. Macroangiopathy. *D. Neuropathy.*

11. A woman complains of deteriorating eyesight. The examination revealed obesity, fasting hyperglycemia. What complication of diabetes can cause vision loss or blindness?

A. Microangiopathy. *C. Atherosclerosis.* *E. Glomerulopathy.*
B. Macroangiopathy. *D. Neuropathy.*

12. An unconscious woman was brought to the intensive care unit by ambulance. During the clinical examination, the blood glucose level was 1.98 mmol/l, Hb – 82 g/l, erythrocytes – 2.1×10^{12} g/l, ESR – 18 mm/h, leukocytes – 4.3×10^{9} g/l. The patient probably has:

A. Diabetes. *C. Galactosemia.* *E. Renal diabetes.*
B. Hypoglycemia. *D. Lack of somatotropic hormone.*

13. A patient with diabetes was admitted to the hospital in an unconscious state. Kussmaul breathing, blood pressure 80/50 mm Hg, with the smell of acetone from the mouth. Accumulation of what substances in the body can explain the occurrence of these disorders?

A. Lactic acid. *C. Ketone bodies.* *E. Complex carbohydrates.*
B. Modified lipoproteins. *D. Carbonic acid.*

14. A 53-year-old man was taken to a hospital in an unconscious state. Objectively: dry skin, frequent shallow breathing, no smell of acetone, pulse 126 bpm, blood pressure 70/40 mm Hg. Art., the blood glucose content is 48 mmol/l, the urine reaction to acetone is negative. For which of the listed conditions are the most characteristic symptoms in the patient?

A. Toxic coma. *C. Lactacidemic coma.* *E. Collapse.*
B. Hyperketonemic coma. *D. Hyperosmolar coma.*

15. The patient was found to have a violation of glucose reabsorption in the proximal part of the tubules with the development of glucosuria, while hypoglycemia occurs in the blood plasma. What is the name of this violation?

A. Diabetes.
B. Renal glycosuria.
C. Phosphate renal diabetes.
D. Extrarenal glycosuria.
E. Renal glycosuria. Galactosemia.

16. During the examination of a patient with type 1 diabetes mellitus, a violation of protein metabolism was revealed, which is manifested by amino-acidemia in a laboratory blood test, and clinically by a slowdown in wound healing and a decrease in the synthesis of antibodies. Which of the listed mechanisms causes the development of aminoacidemia?

A. Increase in proteolysis.
B. Hyperproteinemia.
C. A decrease in the concentration of amino acids in the blood.
D. Increase in oncotic pressure in blood plasma.
E. Increase in low-density lipoproteins.

17. A patient who complains of polyuria has sugar in his urine. The content of sugar in the blood plasma is normal. What is the mechanism of glucosuria in the patient?

A. Violation of glucose filtration in the glomerular part of the nephron.
B. Violation of glucose reabsorption in nephron tubules.
C. Hyperproduction of glucocorticoids by the adrenal glands.
D. Insufficient production of insulin by the pancreas.
E. Insulin resistance of cell receptors.

18. In a 15-year-old patient, the fasting glucose concentration is 4.8 mmol/l, an hour after the sugar load is 9.0 mmol/l, after 2 hours it is 7.0 mmol/l, and after 3 hours it is 4.8 mmol/l. These indicators are characteristic of such a disease:

A. Itsenko-Cushing diseases.
B. –.
C. Hidden diabetes.
D. Type II diabetes.
E. Type I diabetes.

19. The patient was brought to the clinic in a comatose state. There is a history of type II diabetes for 5 years. Objectively: breathing is loud, deep, in exhaled air the smell of acetone is felt. The content of glucose in the blood is 15.2 mmol/l, ketone bodies – 100 μmol/l. What complications of diabetes are characterized by such clinical manifestations?

A. Hyperglycemic coma.
B. Hyperosmolar coma.
C. Hepatic coma.
D. Ketoacidotic coma.
E. Hypoglycemic coma.

20. The patient was diagnosed with diabetes mellitus accompanied by hyperglycemia. The concentration of which blood plasma protein will allow retrospectively (4–8 weeks before the examination) to assess the level of glycemia?

A. C-reactive protein.
B. Albumins.
C. Ceruloplasmin.
D. Fibrinogen.
E. Glycosylated hemoglobin.

Standards of correct answers to the KROK-1 task

1	2	3	4	5	6	7	8	9	10
A	*B*	*C*	*D*	*E*	*A*	*B*	*C*	*D*	*E*
11	12	13	14	15	16	17	18	19	20
A	*B*	*C*	*D*	*E*	*A*	*B*	*C*	*D*	*E*

Recommendations for registration of work results

1. Written answer to test tasks (basic level of knowledge).

2. The results of the experiment are formed in the form of an experiment protocol with the determination of relevant conclusions.

3. Protocol for solving situational tasks with an explanation of the correct answers. (final level of knowledge).

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Topic 12. Pathology of fluid and electrolyte balance. Edema.

Justification of the topic: Disorders of water metabolism are typical metabolic disorders in the body, accompanied by a lot of serious diseases, as well as appear in healthy people who are in emergencies related to a limited or complete cessation of water flow. Variations in water content are one of the most dangerous disorders of homeostasis, which adversely affect the functions of all systems and is often the cause of complications and death of various diseases. Knowledge and systematic study of water balance should enter into an obligatory scheme of clinical research for many diseases, which will properly diagnose and implement a rational therapy to correct these violations.There are two forms of water metabolism disorders: dehydration and fluid retention (hyper-hydration). A variation of an excessive accumulation of extracellular fluid is swelling. The study of swelling can reveal the basic mechanisms of its development, and show the pathogenic nature of the localization of edema in vital organs (lungs, larynx, brain).

Purpose of the lesson:

General - be able to characterize a violation of water exchange as a typical metabolic disorders, swelling like a typical pathological process, to classify and explain the basic pathogenetic mechanisms of edema.

Specifically:

Know:

1. Classify forms of violation of water metabolism (dehydration, hyper-hydration).
2. Formulate a definition of "swelling".
3. Give etiologic and pathogenetic classification of edema. Analyze the pathogenetic mechanisms that underlie the different types of edema.
4. Modeled pulmonary edema by intraperitoneal injection of adrenaline, select physiological indicators to assess the degree of its development, and analyze the mechanism.
5. Determine the amount of pulmonary factor. Show by neural mechanisms anesthesia's role in the pathogenesis of pulmonary edema.
6. To substantiate on the basis of the data obtained pathogenetic therapy in edema of various etiologies.

Be able to:

1. Determine the concept of "water balance", its size, and components.
2. The mechanism of regulation of the water balance, to explain the role of hydrostatic, osmotic, and oncotic pressure in the mechanisms of transcapillary water exchange.
3. To show the role of neuroendocrine regulation in maintaining water balance.

Practical experience:

1. Modeled pulmonary edema by intraperitoneal injection of adrenaline, select physiological indicators to assess the degree of its development, and analyze the mechanism.

2. Determine the amount of pulmonary factor. Show by neural mechanisms anesthesia's role in the pathogenesis of pulmonary edema.

The graphological structure of the topic "Pathology of fluid and electrolyte balance. Edema." is attached.

Material and methodological support of the topic "Pathology of fluid and electrolyte balance. Edema.":

1. Lectures;
2. Methodical instructions for teachers;
3. Methodical instructions for students;
4. Set of test tasks to determine the basic level of knowledge;
5. Set of situational tasks to determine the final level of knowledge;
6. Set of KROK-1 tasks;
7. Set of schemes and tables (presentation);
8. Set of forms with a blood test
9. Video films;
10. For the experiment (experimental animals – white mice, injections, scissors, pincers, hemostatic clamp, weigh balance, 0.1 % solution of adrenaline, 10 % solution of urethane.).

Oriented map of students' work on the topic "Pathology of fluid and electrolyte balance. Edema."

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the initial level of knowledge	10	Written answer to test tasks	Test tasks	Study room
2	Analysis of theoretical material	35	Analysis of theoretical material based on control questions of the topic, situational tasks, tasks of KROK-1	Topic control questions, KROK-1 tasks, situational tasks	
3	Practical part (conduct experiment)	30	Introduction and preparation for setting up the experiment. Setting up the experiment. Discussion of the results of the experiment and formulation of conclusions	White mice, injections, scissors, pincers, hemostatic clamp, weigh balance, 0.1 % solution of adrenaline, 10 % solution of urethane	
4	Determination of the final level of knowledge and skills. Summarizing the results	15	Determination of the final level of knowledge and skills. Summarizing the results	KROK-1 tasks, situational tasks	

Disturbances in water metabolism include: changes in the total volume of water in the organism and the pathologic redistribution of water between the blood and the tissues (edema and dropsy).

CHANGES IN THE TOTAL VOLUME OF WATER IN THE ORGANISM

They are expressed in changes of the water balance, i.e. relation between, on the one hand, consumption of water by the organism and the formation of water in the organism in the processes of metabolism, and, on the other hand, excretion of water.

There are negative and positive water balance.

A negative water balance means a reduction of the total volume of water in the organism. It is observed when insufficient water is consumed or an excess of water is excreted and is called dehydration, or hypohydration, or hypohydria, or hydropenia, or exicosis.

A positive water balance means an increase of the total volume of water in the organism. It is a result of retention of water in the organism (reduced excretion of water) and is called hyperhydration, or hyperhydria.

Hypohydria and hyperhydria may be isotonic (isoosmotic), hypotonic (hypoosmotic) and hypertonic (hyperosmotic) ones.

In isotonic forms of hypo- and hyperhydria only the volume of extracellular fluid is changed. In hypo- and hypertonic forms the relation between extracellular and intracellular fluids is changed too.

Hypohydrias

The common causes of hypohydrias are:

1) absolute or water and mineral starvation (minimal daily necessity in water of adult man is about 1,5 l),

2) loss of water and mineral salts – diabetes mellitus and insipidus, renal diseases with polyuria, long application of sodiumuretic diuretic drugs, insufficiency of adrenal cortex (accompanying with polyuria because of decreased reabsorption of water); diarrhea, gastric and intestinal fistulas, vomiting; burns, inflammation of serous membranes (because of strong exudation); overheating (because of intensive perspiration); hyperventilation; loss of the blood; hypersecretion of parathyroid hormone and hypervitaminosis D (because of polyuria and vomiting caused by hypercalciumemia),

3) loss of the salts – in compensation of the lost fluids by fresh water or glucose.

The Kinds of Hypohydria

1. Isotonic One. It is observed in loss of isotonic fluids – strong vomiting and diarrhea, polyuria, extensive exudative burns, in the beginning of the acute loss of blood, etc.

The volume of extracellular fluid decreases only.

It is expressed in hypovolemia (reduction of blood volume) and anhydremia (hemoconcentration). The blood pressure is there of reduced, and collapse is possible. Together with disturbance of microcirculation it leads to hypoxia. Besides, hypotension leads to olyguria, hypernitrogenemia and acidosis. Hypoxia and hypernitrogenemia affect the nervous system. The disturbances of consciousness, hallucinations, disorders of respiration and heart activity, increased temperature of body, coma are observed. The loss

of water correspondent to 10 per cent of the body weight is dangerous to life and the loss of 20 per cent is lethal.

The restoration of the volume of extracellular fluid: the ample drinking of water, in the strong cases the intravenous infusion of the isotonic solution of sodium chloride, glucose, blood substitute fluids.

2. Hypoosmotic (Anhydremic) One. It is observed in the primary negative sodium balance - repeated diarrhea, repeated vomiting (the loss of salts with secrets), increased perspiration, if the lost water is replaced by drinking of water without addition the salts.

Because of hypoosmolarity of the extracellular fluid the transition of water into the cells happens. It results in strong anhydremia. Therefore the disturbances of blood circulation (systemic circulation and microcirculation) and their consequences are expressed stronger than in previous variant of hypohydria. The important role play the initial shifts in acid-base balance, as the repeated vomiting results in alkalosis (because of loss of chlorides and hydrogen), and repeated diarrhea leads to acidosis (because of loss of sodium and hydrocarbonates).

It is necessary to notice that diabetes insipidus does not result in disturbances of water metabolism, if the loss of fluid is compensated, as the urine has the low relative density.

For prevention and elimination of this form of hypohydria the reception of water with addition of the salts is necessary, in the strong cases the intravenous infusion of hypertonic solutions is needed.

3. Hyperosmotic One. It is observed in the primary negative balance of water – in the insufficient receipt of water, hyperventilation, profuse perspiration, hypersalivation (sweat and saliva are hypotonic in relation to the tissue fluid), as well as in diarrhea, vomiting and polyuria, if the insufficient compensation of water happens.

Because of hyperosmolarity of the extracellular fluid the dehydration of the cells is happened.

There are olyguria, loss of the body weight, the strong thirst, the increased protein decomposition, intoxication, the increased body temperature, disturbances of consciousness, coma.

Despite of cell dehydration, the volume of extracellular fluid is reduced (hypohydria), therefore hemoconcentration is observed.

For restoration of the osmotic concentration of the extracellular fluid and elimination of cell dehydration the ample receipt of water, the intravenous infusion of hypotonic sodium chloride solution or isotonic (5 %) glucose solution are necessary. In strong perspiration the reception of water with 0,5% of sodium chloride is expedient to prevent this form of hypohydria.

Hyperhydrias

The common causes of hyperhydria are: the redundant consumption of water, glomerulonephritis and other diseases resulting in the disturbances of the secretory function of the kidneys, heart insufficiency, nephrotic syndrome,

liver cirrhosis, starvation accompanied by the secondary hyperaldosteronism and hypoproteinemia, and, hence, by retention of water in the organism, shock, etc. Accompanied by the increased vascular permeability and, thus, strengthened output of water into the tissues, diseases accompanied by increased secretion of vasopressin and insulin.

The Kinds of Hyperhydria

1. Isotonic One. It is not often observed - in the first time after infusion a lot of isotonic solution of sodium chloride, in large edemas.

The volume of extracellular fluid is increased only.

The redundant amount of fluid arriving into the organism is usually not detained in blood and passes into the tissues. Therefore in all causes of this form of hyperhydria mainly the volume of extracellular fluid is increased.

To eliminate this form of hyperhydria it is necessary to stop the infusion of isotonic solution, and surplus of the fluid will be fast removed from the organism. As to edemas, the measures on their elimination are necessary (improvement of blood circulation, etc.).

2. Hypoosmotic one (water poisoning). It is observed in the primary positive balance of water – disturbances of the renal functions (the renal insufficiency, reflex anuria after operations); in adrenal insufficiency (accompanied by olyguria), hypersecretion of vasopressin after trauma, operation or application of vasopressin (olyguria), especially in combination with redundant reception of water or infusion of glucose solution.

Because of hypoosmolarity of the extracellular fluid the transition of water into the cells happens. The volumes of extracellular and intracellular fluids are increased, but the specific significance has the increased amount of water in the cells.

There are hydremia, an increased body weight, nausea which increased after reception of the fresh water, vomiting which does not give a relief, humidity of the mucous membranes, apathy, somnolence, headache, muscle twitching, convulsions, in the strong cases – lung edema, ascitis, hydrothorax, coma.

For liquidation of this form of hyperhydria it is necessary to restrict the consumption of water, in the strong cases - the intravenous infusion of the strongly hypertonic solutions of sodium chloride in the strongly limited volume of fluid.

3. Hyperosmotic One. It is observed in the primary positive sodium balance – infusion of the hypertonic solutions of sodium chloride, use the salt (marine) water for drinking.

Because of hyperosmolarity of the extracellular fluid dehydratation of the cells happens, and the phenomena similar to hyperosmotic hypohydria become.

For liquidation of this form of hyperhydria it is necessary to stop the infusion of hypertonic solutions or reception of salt water.

EDEMA AND DROPSY

Edema (oedema) is an redundant accumulation of fluid in the tissues (mainly in intercellular substance), due to disturbed water metabolism between the blood and the tissue.

The positive water balance promotes development edema.

Dropsy (hydrops) is accumulation of fluid in serous cavities. The dropsy of subcutaneous connective tissue is referred to as anasarca, peritoneal cavity – ascites, pericardial cavity – hydropericardium, pleural cavity – hydrothorax, cerebrospinal cavity – hydrocephalus, in the sac of the tunica vaginalis of the testis – hydrocele.

Edema is a typical pathologic process which is met in many diseases.

The fluid in edemas is called transudate. It is characterised by low specific gravity and negligible protein content (in comparison to exudate). The amount of protein in the transudate varies with the kind of the edema on its etiology and, accordingly, some difference in pathogenesis.

According to their etiology edemas are distinguished as: congestive – in obstruction of veins (thrombi and emboli), their constriction by tumors, etc; cardiac (in insufficiency of the heart and hemocirculation); renal (nephritic – in glomerulonephritis, and nephrotic – in nephrotic syndrome); hepatic – in hepatic cirrhosis; starved – in qualitative starvation; cachectic – in severe anemia, malignant tumors, tuberculosis, Simmond's disease, etc; inflammatory; allergic; toxic – in various poisonings, at points stung by certain insects, etc; endocrine – in hypothyrosis, hyperinsulinism, hyperaldosteronism, increased secretion of vasopressin, Simmond's disease; neurotrophic – edemas of limbs in hemiplegia and syringomyelia, edema of the face in neuralgia of the trigeminale nerve, Quincke's edema in injures to or constriction of nerves, edemas of the skin in hysterias.

In pathogenesis of edema the following factors take part:

1. Mechanical – increased hydrostatic (hydrodynamic) pressure of the blood.

2. Physicochemical – mainly decreased colloid osmotic (oncotic) pressure of the blood and increased of the tissues, partly the same changes of osmotic pressure.

3. Membranogenic – increased vascular permeability.

4. Lymphogenic – disturbed outflow of lymph.

5. Neurogenic and endocrine – disorders of the nervous and hormonal regulation of the water and salt metabolism (mainly the secondary hyperaldosteronism).

The role of leading factor in pathogenesis of the edema is determined by its etiology.

The classification of edemas according to their pathogenesis:

1. Hydrodynamic: congestive (purely mechanical), partly – cardiac.

2. Hypooncotic, or hypoproteinemic: nephrotic, hepatic, starved, cachectic.

3. Membranogenic: inflammatory, allergic, toxic, partly – neurotrophic, partly – congestive, cardiac, nephritic, starved, cachectic (due to hypoxic and dystrophic increase of vascular permeability).

4. Lymphogenic:

– purely lymphatic (in elephantiasis), partly – cardiac (in right-ventricular insufficiency), partly – all of the hypoproteinemic edemas because of dynamic lymphatic insufficiency in hypoproteinemia.

5. Neuro-endocrine: partly – neurotrophic; endocrine; partly – cardiac, nephritic and nephrotic (due to significance in their pathogenesis of the reflex renin-adrenal mechanism of retention of water, or secondary hyperaldosteronism, increased secretion of vasopressin).

Setting up the experiment. Discussion of results and formulation of conclusions

- **Experimental edema of lungs and the study of the influence of CNS in its development.**

Weigh the animal. Observe the condition of the animal, depth and rate of respiration, colour of skin. Inject intraperitoneally into one of the mice 0.3 ml solution of urethane. Within 15 minutes watch for the development of narcosis. Simultaneously inject intraperitoneally into mouse N 1 (in a state of narcosis) and mouse N 2 (control mouse) 0.3 ml 1 % solution of adrenaline. Compare the state of both animals. Watch for changes in behavior, respiration, skin colour, foaming in the mouth. After the death of one mouse, watch the second in a period of ten minutes. Cut open the animals, take the lungs out, describe the external appearance, weigh and calculate the lung coefficient.

Method of calculating lung's coefficient: Cut the skin of the neck along linea mediana, find the trachea and place a hemostatic clamp on it. Cut open the thoracic cavity, take out the lungs and the heart. Separate the heart and large vessels from the lungs, take off the clamp from the trachea and remove the trachea. Weigh the lungs and calculate the relative percentage of the weight of the lungs to the body weight.

Table

Mouse №1					Mouse №2			
Without of narcosis					With narcosis			
Time	Behavior	Sound react	Colour skin	Respiratory rate	Behavior	Sound react	Colour skin	Respiratory rate
	Injection of 0,5 ml 0,1 % solution of adrenalin							

Discussion of the results of the experiment

Point to the main edema development mechanisms: hydrodynamic, physico-chemical factors and permeability of the capillary wall. Emphasize on the importance of nervous and humoral factors in the regulation of water exchange. Describe in detail the changes that occur in the body during

injection of large doses of adrenaline.adrenaline pulmonary edema develops in conditions of pronounced hypertension in a large circle of blood circulation, with the accumulation of blood in the area of the small circle and increased blood pressure in the vessels of the small circle circulation. An important link in the mechanism of adrenaline edema are pulmonary vascular receptors, the fibers from which go to part of the vagus nerve, the efferent link is represented sympathetic neurons in the thoracic region. Vagotomy, removal sympathetic nodes on the neck, the introduction of urethane either prevents adrenaline edema, or weakens its course.

Formulation of conclusions based on the experiment

The animal (without anesthesia) develops changes characteristic for pulmonary edema – shortness of breath, cyanosis, foaming from mouth, etc. In an animal in a state of urethane anesthesia, the same changes develop more slowly and they are weaker expressed. Without anesthesia, the animal dies earlier. Pulmonary the coefficient is greater in an animal without anesthesia.

Tasks for independent work on the topic "Pathology of fluid and electrolyte balance. Edema."

The student is offered to investigate the results of a clinical blood analysis of a patient with a disorder of water-electrolyte metabolism. It is necessary to determine the signs and type of violation. Be able to explain the mechanism of occurrence. Analysis of errors with an explanation of the correct answers

List of questions and works to be studied:

1. Positive and negative water balance. Hyperhydria and hypohydria. Their types.
2. What is oedema. Etiology and pathogenesis.
3. The role of neuro-humoral mechanisms in the pathogenesis of oedemas.
4. Types of oedemas. The specific role of pathogenic factors in the mechanism of different types of oedemas.
5. The mechanism of adrenaline oedema of the lungs.
6. Anasarca. Types.

List of practical skills that must be mastered:

1. Modeled pulmonary edema by intraperitoneal injection of adrenaline, select physiological indicators to assess the degree of its development, and analyze the mechanism.

2. Determine the amount of pulmonary factor. Show by neural mechanisms anesthesia's role in the pathogenesis of pulmonary edema.

Situational tasks KROK-1 to determine the final level of knowledge

1. A 45-year-old woman complains of strong general weakness, dyspnea, palpitation, feet edema, increased size of abdomen. On examination: serious condition, respiration rate 32 per min, cyanosis of face, lips, edema of feet, limbs, ascites, edema of anterior abdominal wall. Pulse 124 per min, BP 150/90 mm Hg. Liver is increased. Total serum protein – 70 g/L. What is the driving member of edema pathogenesis in the patient?

A. Increase of permeability of vessel wall.
B. Increase of hydrostatic pressure in capillaries.
C. Increase of oncotic pressure of interstitial fluid.
D. Hypoproteinaemia.
E. Disorder of lymphatic drainage.

2. On examination in patient the expressed swelling was found out in the field of the left forearm. It developed after a bee sting. Name leading pathogenetic mechanism of the edema?

A. Hydrodynamic. *C. Osmotic.* *E. Membranogenous.*
B. Colloid. *D. Lymphogenous.*

3. The liquid was received from the patient with heart decompensation at a puncture of a belly cavity, density ratio – 1012 albumine – 10 g/l, globuline – 2 g/l transparent citreous color, fibrinogen is not present, single red blood cells, 1–3 leukocytes in sight. Name leading pathogenetic mechanism of the edema?

A. Hydrodynamic. *C. Lymphogenous.* *E. Osmotic.*
B. Membranogenous. *D. Colloid.*

4. Gastric resection was done to a 35-years-old patient after ulcerous genesis stenosis of pylorus. In 3 days after operation patient complains of intolerable thirst. Objectively: dryness of tongue and mucous membrane of mouth, BP 110/70 mm Hg; hemoglobin, hematocrit and total serum protein are normal. What alteration in water metabolis is likely to take place in this case?

A. Extracellular hyperhydration. *D. Intracellular dehydration.*
B. Intracellular hyperhydration. *E. Total dehydration.*
C. Extracellular dehydration.

5. 40-years-old patient complains of total weakness, breathlessness, palpitation, feet swellings, increasing of belly. Objectively: resperation rate 32 per min, cyanotic face, ascitis, liver is increased, pulse 124 per min, BP 170/90 mm Hg. Total serum protein 70 g/L. What is the leading pathogenesis factor in the patient?

A. Increasing of oncotic pressure if transcellular fluid
B. Increasing of permeability of vessel wall.
C. Increasing of hydrostatic blood pressure in capillars.
D. Disorder of lymphatic drainage.
E. Lipoproteinemia.

6. In a patient, who used plant food for a long time, swellings have appeared. What is the direct cause of this condition?

A. Hypoaminoacidemia. *D. Hypoglycemia.*
B. Hypoproteinemia. *E. Anemia.*
C. Decreasing of blood amount of microelements.

7. Dehydration appears in patients with diabetes incipidus and in patient with forced perspiration or stomach secretion. In both cases debit of water excesses debit of electrolytes. Changes of what of the following rates will have the same directions in those pathologies?

A. Urine osmolalityю
B. Concentration of sodium in blood.
C. Concentration of sodium in urine.
D. Blood osmolarity.
E. Circulatory volume.

8. Patient has severe nephropathia with massive edematous syndrome complicated with chronic bronchiectasis dicease. The following characteristics have been found by taking measurements: heavy proteinuria, cylindruria, heavy serum protein decrease, hyperlipemia, hypokaliemia and other. What is the initial and significal event in swelling pathogenesis in this patient?

A. Blood oncotic pressure decrease.
B. Blood hydrodynamic pressure increase.
C. Extracellular fluid pressure increase.
D. Limphatic flow block.
E. Microvessels permeability i.ncrease.

9. Lung edema appeared in a patient with hypertensive crisis. What is the main factor in the pathogenesis of this condition&

A. Blood pressure increase.
B. Pulmonary vessels permeability increase.
C. Pulmonary vessels hydrodynamic pressure increase.
D. Pulmonary vessels resistance increase.
E. Blood oncotic pressure decrease.

10. What process is not important in the pathogenesis of swelling?

A. Tissue oncotic pressure increase.
B. Blood oncotic pressure increase.
C. Tissue osmotic pressure increase.
D. Blood osmotic pressure decrease.
E. Capillar hydrostatic pressure increase.

11. Thirst appeared in 'hot shop' worker as a result of forced perspiration. Worker quenched thirst with water without salt. What kind of water-salt alteration could be in this case?

A. Isoosmolar hypohydration.
B. Hyperosmolar hyperhydration.
C. Hyperosmolar hypohydration.
D. Hypoosmolar hypohydria.
E. Hypoosmolar hyperhydria.

12. Clinical signs of lung edema appeared in a patient with left-heart failure. What pathogenic mechanism is the initial in this case?

A. Colloid-osmotic.
B. Hydrodynamic.
C. Lymphagenic.
D. Membranogenous.
E. Congestive.

13. A 72-years-old patient 8 years has essential hypertension. Last 3 weeks he has such sighs of enterocolitis as intensive and frequent diarrhea. Swellings on the face and limbs appeared. What is the cause of swellings?

A. Dehydration.
B. Na reabsorbtion decrease.
C. Arterial hypertension.
D. Hypoproteinemia.
E. Venous pressure increase.

14. Swellings are marked in a patient as a result of kidney disease. There is significance amount of protein in urine analysis. What mechanism could explain swellings appearing in this patient?

A. Lymphatic oncotic pressure decrease.

B. Kidney filtration pressure decrease.

C. Blood oncotic pressure decrease.

D. Interstitial oncotic pressure decrease.

E. Blood osmotic pressure increase.

Standards of correct answers to the task КROK-1

1	2	3	4	5	6	7	8	9	10	11	12	13	14
B	*E*	*A*	*D*	*C*	*B*	*D*	*A*	*C*	*B*	*D*	*B*	*D*	*C*

Recommendations for registration of work results

1. Written answer to test tasks (initial level of knowledge).

2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.

3. Protocol for the study of the results of the patient's blood analysis.

4. Protocol for solving situational tasks with an explanation of the correct answers.

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Topic 13. Pathology of acid-base balanse

Justification of the topic: Acid-base balance is one of the most important homeostasis signs. Due to its prevalence and lack of symptoms of acid-base state and balance deviations, are often skipped and revealed only by resuscitators in far gone often critical cases. Knowing and systematic study of acid-base balance has to be necessary and added to the scheme of clinical study in different diseases. This will allow to diagnose correctly and to carry out rational therapy to correct those deviations.

Purpose of the lesson:

General. To be able to characterize acid-base balance disorders as typical changes of metabolism, to classify and to define the main pathogenetic mechanisms of the main types of disorders.

Specifically:

Know:

1. Formulate the concept of "acid-base state", "acidosis" and "alkalosis".
2. Classify its forms.
3. Analyze the pathogenetic mechanisms forming different types of acid-base disorders.
4. Estimate acid-base indexes in different types of alkalosis and acidosis.
5. Substantiate using given data pathogenetic therapy of different types of acid-base disorders.

To be able to:

1. Define the "acid-base state" concept, indexes, determining it
2. Show mechanisms of regulation (disorders compensation) of acid-base balance.
3. Evaluate indicators of acid-base balance, to explain the mechanism of violation and justification of the clinical conclusion.

The graphological structure of the topic "Pathology of acid-base balanse" is attached.

Material and methodical support of the topic "Pathology of acid-base balanse".

1. Lectures;
2. Methodical instructions for teachers;
3. Methodical instructions for students;
4. Set of test tasks to determine the basic level of knowledge;
5. Set of situational tasks to determine the final level of knowledge;
6. Set of KROK-1 tasks;
7. Set of schemes and tables (presentation);
8. Set of forms with a clinical blood test;
9. Video films;

Oriented map of students' work on the topic
"Pathology of acid-base balanse"

No	Stage of lesson	Academic time, min	Educational guide		Place holding a class
			Educational tools	Equipment	
1	Determination of the basic level of knowledge	10	Written answer to test tasks	Test tasks	Learning room
2	Analysis of theoretical material	65	Analysis of theoretical material based on control questions of the topic, situational tasks, tasks of KROK-1	Topic control questions, KROK-1 tasks, situational tasks	
3	Determination of the final level of knowledge and skills. Summariz-ing the results	15	Determination of the final level of knowledge and skills. Summarizing the results	KROK-1 tasks, situational tasks	

VIOLATION OF ACID-BASE BALANCE.

Acid-base balance, (ABB) – the ratio of the concentration of hydrogen (H) and hydroxyl (OH) ions in biological environments.

pH – the value of the reaction of the biological system (which is numerical) is equal to the negative logarithm of the concentration of H ions (pH = -H):

- *pH – 7.0 reaction of neutral water*
- *pH < 7.0 acidic reaction of the solution*
- *pH > 7.0 alkaline reaction of the solution.*

Under the physiological conditions of the body, the active reaction of the blood is weakly alkaline and fluctuates within the range of pH 7.35–7.45. Deviations of [H+] from the optimal range lead to disturbances in metabolism, vital activity of cells (up to their death), tissues, organs and the body as a whole. pH shift in the range:

±0.1 – causes breathing and blood circulation disorders;

±0.3 – loss of consciousness, violation of hemodynamics and lung ventilation;

±0.4 and more – death of the organism.

Falling of pH to 6.95 leads to coma and death, increasing to 7.7, titanic convulsions and cardiac arrest in the systole phase occur.

Therefore, any changes in the active reaction of the blood beyond the permissible limits can lead to irreversible damage. It is clear that even within these limits, complex automatic systems that regulate COD are included to maintain pH at a constant level.

Indicators of evaluation of ABB

Main indicators of blood:

- ph,
- pCO_2,
- standard bicarbonate of blood plasma – sb (standart bicarbonate),
- buffer bases of capillary blood – bb (buffer base),
- base excess of capillary blood – be (base excess).

Additional indicators of blood and urine:

• KB – blood ketone bodies,

• LA – lactic acid of the blood,

• Ta – titratable acidity of urine

• urine ammonia.

Acidosis is a typical form of bos disorder characterized by a relative or absolute excess of acids in the body. In acidosis, there is an absolute or relative increase in [H+] and a decrease in ph below the norm (conditionally – below the average value of ph, taken as 7.39).

Alkalosis is a typical form of kos disorder characterized by a relative or absolute excess of bases in the body. In blood with alkalosis, there is an absolute or relative decrease in [h+] or an increase in ph (conditionally – higher than the average value of ph, taken as 7.39).

Causes of ABB disorders

• ***Endogenous:*** due to disturbed functions of both chemical buffer systems and physiological mechanisms of maintaining optimal BOS in the body (disorders of vital activity of various organs and tissues).

• ***Exogenous***: due to the excessive intake of acidic or alkaline substances into the body (drugs used with incorrect dosage and/or treatment regimens; toxic substances; food products). Acidosis often develops in people who use synthetic diets (containing amino acids with acidic properties). Consumption of large amounts of alkaline mineral waters and milk can lead to the development of alkalosis.

Compensation for violations of the ABB

The determining parameter of the degree of compensation of ABB violations is the pH value.

Compensated ABB shifts are disorders in which blood pH does not deviate beyond the normal range: 7.35–7.45. 7.39 is conditionally accepted as the average (neutral) value. Deviation of pH in the ranges:

7.38–7.35 – compensated acidosis;

7.40–7.45 – compensated alkalosis.

With compensated forms of ABB violations, changes in the absolute concentration of the components of the hydrocarbonate buffer system (H_2CO_3 and $NaHCO_3$) are possible. However, the $[H_2CO_3]/[NaHCO_3]$ ratio remains within the normal range (20/1).

Uncompensated ABB violations - violations in which blood pH exceeds the normal range:

pH 7.34 and below – uncompensated acidosis;

pH 7.46 and above – uncompensated alkalosis.

Uncompensated acidosis and alkalosis are characterized by significant deviations of both the absolute concentration of H_2CO_3 and $NaHCO_3$, as well as their ratio.

VIOLATION OF THE ABB

Based on the criteria of "causes and mechanisms of development", copd disorders are divided into gas, non-gas and mixed (combined) disorders.

Gas (respiratory) disorders ABB are characterized by a primary change in the content of CO_2 in the body and, as a result, the concentration of carbonic acid in the ratio: [HCO3'] / [H_2CO_3]. With gas acidosis, the denominator of the ratio (that is, the concentration of carbonic acid) increases, with gas alkalosis, it decreases.

Compensation. Usually, gas acidosis and alkalosis remain compensated for a long time. This is due to the activation of physiological mechanisms of compensation (mainly due to a mobile decrease in the volume of alveolar ventilation – an increase in gas acidosis and a decrease in gas alkalosis), and the effects of buffer systems.

RESPIRATORY (gas) acidosis

Respiratory acidosis is characterized by a decrease in blood pH and hypercapnia (an increase in blood pCO2 of more than 40 mmHg). At the same time, there is no linear relationship between the degree of hypercapnia and clinical signs of respiratory acidosis. The latter are largely determined by the cause of hypercapnia, the features of the underlying disease, and the reactivity of the patient's body.

Compensated acidosis, as a rule, does not cause significant changes in the body. Uncompensated acidosis leads to significant disturbances in the vital activity of the body and the development of a complex of characteristic changes in it.

Causes of respiratory acidosis:

• A decrease in the volume of alveolar ventilation occurs as a result of the accumulation of excess CO_2 in the blood and the subsequent increase in the concentration of carbonic acid in it. At the same time, the ratio [HCO_3] / [H_2CO_3] decreases due to an increase in the value of the denominator, which is a characteristic feature of respiratory acidosis (obstruction of the respiratory tract, impaired lung distensibility, increased functional "dead" space, impaired breathing regulation).

• Increased formation of endogenous .

Reasons:

- activation of catabolic processes (fever, sepsis), prolonged convulsions of various genesis,
- with parenteral administration of a large amount of carbohydrates (glucose).

• Excessive intake of CO_2 into the body (with the subsequent formation of carbon acid) is observed when a gas mixture is supplied for breathing with an inadequately increased CO_2 content, when a large number of people are in a closed space.Прояви респіраторного ацидозу

■ The danger of bronchospasm in conditions of acidosis lies in the possibility of the formation of a vicious pathogenetic circle "bronchospasm of

increasing pCO_2 – rapid decrease in pH – strengthening of bronchospasm – further increase of pCO_2"

■ Bronchospasm.

The mechanism of bronchiole spasm: increased cholinergic effects in conditions of significant acidosis due to:

• increased release of acetylcholine from nerve terminals,

• increased sensitivity of cholinergic receptors to acetylcholine.

■ Expansion of brain arterioles, development of arterial hyperemia of its tissue, increase of intracranial pressure.

Causes: prolonged significant hypercapnia and hyperkalemia.

Mechanism: decrease in basal muscle tone of brain arteriole walls in conditions of long-term elevated pCO_2, pH and hyperkalemia.

Manifestations of increased intracranial pressure: headache and psychomotor agitation, then drowsiness and inhibition; compression of the brain leads to increased activity of vagus nerve neurons, causes: arterial hypotension, bradycardia, sometimes cardiac arrest. Spasm of arterioles and ischemia of organs (Except for the brain!).

Reasons:

• hypercatecholaminemia observed in conditions of acidosis.

• hypersensitivity of α-adrenoblockers of peripheral arterioles.

Manifestations of arteriolar spasm: multiple organ dysfunction (renal blood flow and GFR decrease and BCC increases), which significantly increases the load on the heart. With chronic respiratory acidosis (respiratory insufficiency) can lead to a decrease in the contractile function of the heart to HF. Violation of the flow of blood and lymph in the vessels of the microcirculatory channel.

Reasons:

• Spasm of arterioles in tissues and organs (except the brain!).

• HF, which leads to a decrease in perfusion pressure of blood in arterioles and violation of its outflow through venules.

Manifestations: in many patients, microhemocirculation disorders become one of the main pathogenetic links in the development of multiorgan disorders.

Hypoxemia and hypoxia

Reasons:

- Hypoventilation of the lungs.
- Violation of lung perfusion in connection with heart failure.
- A decrease in the affinity of Hb to O2 (a consequence of hypercapnia).
- Violation of biological oxidation processes in tissues (caused by impaired microhemocirculation, hypoxemia, decreased activity of tissue respiration enzymes, and in severe acidosis and glycolysis).

Imbalance of ions: Increased content of K+ ions in the intercellular fluid, hyperkalemia, hyperphosphatemia, hypochloremia.

Reasons

- Hypoxia and disruption of the energy supply of cells.
- An increase in the concentration of H+ in the extracellular fluid.

At the same time, the entry of H+ into the cells is accompanied by the exit of K+ from them.

Consequences (manifestations): Significant hyperkalemia causes a decrease in the excitability threshold of cells, including cardiomyocytes. This often leads to cardiac arrhythmias, including fibrillation.

Compensation of respiratory acidosis is aimed at neutralization of excess H+, formed during the dissociation of carbonic acid.

1. Urgent compensation of respiratory acidosis is implemented with the participation of chemical agents buffer systems of the body, Cl-, HCO of the exchange mechanism of erythrocytes.

- Hemoglobin buffer of erythrocytes is the most capacious mechanism of respiratory acidosis compensation - excess H+ is bound by unoxygenated Hb of erythrocytes.
- The protein buffer system of cells reduces H+ in the extracellular fluid as a result of exchange for intracellular K+, which is accompanied by hyperkalemia.
- Protein and phosphate buffers of bone tissue are activated with a significant decrease in pH.
- The protein buffer of the blood plasma makes a certain contribution to the neutralization of H+ in the blood,
- Accept it with anionic ligands of proteins and release Na+ into the plasma (with the development of hypernatremia).
- The HCO3' anions leave erythrocytes in exchange for plasma SG, fill its bicarbonate buffer and thereby contribute to the elimination of acidosis.

2. Long-term compensation of respiratory acidosis is realized by the kidneys. (it takes 3–4 days to achieve the effect). With respiratory acidosis, the following are activated in the kidneys: acidogenesis, ammonogenesis, secretion of $NaH_2PO_4K^+$, Na^+ -xchange.

The specified mechanisms simultaneously ensure the reabsorption of hydrocarbonate into the blood and replenish the consumption of the hydrocarbonate buffer system.

Indicators of respiratory acidosis

The main pathogenetic factor: an increase in pCO2 in the blood.Typical changes in ABB indicators in gas acidosis (capillary blood):

> pH decreases.

> [H+] decreases.

> pCO_2 increases – the main violation.

> $[HSO_2]$ increases – a compensation reaction.

RESPIRATORY (gas) alkalosis

Respiratory alkalosis is characterized by an increase in pH and hypocapnia (a decrease in blood pCO_2 to 35 mmHg or more).

The cause of gas alkalosis is hyperventilation of the lungs, which causes hypocapnia, a decrease in the level of CO_2 and the development of gas (respiratory) alkalosis. The ratio $[HCO_3^-]$ / $[H_2CO_3]$ increases due to a decrease in the denominator, $[H^+]$ decreases, and blood pH increases.

Gas alkalosis develops in: neurotic and hysterical states; CNS damage (concussion, stroke, neoplasm); lung diseases (pneumonia, BA); with hyperthyroidism; about severe fever; drug intoxication (salicylates, sympathomimetics, progestogens); renal failure; painful or thermal irritation; Violation of ventilator mode, leading to hyperventilation; altitude and mountain sickness.

The main manifestations of gas alkalosis

- Violations of central and organ-tissue blood circulation.

Reasons: a) increase in the tone of the walls of the arterioles of the CNS, which leads to its ischemia. b) decrease in the tone of the walls of arterioles in organs and tissues (except the brain!).

Manifestations: arterial hypotension (due to deposition of blood in dilated vessels, reduction of BCC, venous pressure, volume of blood flowing to the heart and, as a result, reduction of shock and cardiac output).

The indicated chain of circulatory changes reduces blood supply to tissues and organs, including the heart, which further worsens systemic circulatory disorders, which closes the hemodynamic vicious circle in gas alkalosis.

- **Hypoxia**

Reasons: a) lack of blood circulation, increased affinity of Hb to O_2, which reduces the dissociation of $HbCO_2$ in tissues, violation (in conditions of respiratory alkalosis) of PVC carboxylation and its transformation into oxaloacetate, restoration of the latter into malate. Increasing energy deficit creates conditions for the development of metabolic acidosis. b) inhibition of glycolysis in conditions of hypoxia: reduction of pCO_2 to 15–18 mm Hg. accompanied by inhibition of the activity of many enzymes of glycolysis.

- **Hypokalemia** develops largely due to the transport of K^+ from the intercellular fluid into the cells in exchange for H^+.
- **Muscle weakness** – hypodynamia, intestinal paresis, paralysis of skeletal muscles caused by hypokalemia.
- **Heart rhythm disturbances** – paroxysms of tachycardia, extrasystole due to hypokalemia (with K+ in the blood plasma of 2 mmol/l, cardiac arrest develops during systole).
- **Hyperventilation tetany** due to: reduction of K+ in intercellular fluid (due to increased K+ binding by albumins), decrease of H+ concentration in intercellular fluid. Blood pH is an important factor that regulates the binding of Ca_2+ by albumins: a decrease in H+ (with alkalosis) activates the fixation of Ca_2+ by proteins.

Compensation of respiratory alkalosis is provided by: 1) a decrease in the concentration of HCO_3 in the blood plasma and other biological fluids and 2) an increase in pCO_2 and, as a result, the concentration of H_2CO_3

1. Urgent compensation of respiratory alkalosis

- ✓ *Reduction in the volume of alveolar ventilation* in connection with the inhibition of neuron activity when blood pCO_2 decreases. The emergency mechanism is activated in case of alkalosis, which develops as a result of hyperventilation, and determines the restoration of the level of carbon dioxide in the body.

✓ *Activation of intracellular buffer systems*: bicarbonate, protein, hemoglobin, phosphate, which ensures the release of H+ from cells into the intercellular fluid and then into the blood in exchange for K+ and Na+.

✓ *Activation of glycolysis* with intensive formation of lactic acid and pyruvic acid, which leads to a decrease in blood pH (a decrease in the concentration of H+ and an increase in HCO_3 activates glycolytic reactions).

✓ The release of intracellular Ca^{2+} into the intercellular fluid in exchange for HCO_3. This ensures a decrease in the concentration of bicarbonate both in the interstitium and in the blood plasma and, as a result, a decrease in pH.

✓ Activation of extracellular buffer systems does not play a significant role in the elimination of gas alkalosis due to their low capacity for H+ generation.

2. Long-term mechanisms of compensation of respiratory alkalosis are implemented mainly by the kidneys:

✓ **Inhibition of acidogenesis** in connection with the increased concentration of HCO3 in the epithelium of the distal parts of the nephrons (activation of kaliuresis).

✓ By **increasing the excretion of Na_2HPO_4** from the blood into the urine

✓ **Inhibition of ammonogenesis.** The latter occurs when glutaminase activity is suppressed under conditions of alkalosis and the amount of glutamate entering the mitochondria decreases.

Indicators of respiratory alkalosis

The main pathogenetic factor: a decrease in pCO_2 in the blood.

Typical directions of changes in ABB indicators (capillary blood) with gas alkalosis:

> pH increases,

> [H] decreases,

> pC02 decreases – the main violation,

> [HSOz] decreases – a compensation reaction.

NON-GAS DISORDERS ABB

Non-gaseous (non-respiratory) disorders of cop are characterized by a primary change in bicarbonate content in the ratio: [HCO3] / [H_2CO_3]. In non-gaseous acidosis, the numerator of the ratio (i.e., the concentration of hydrocarbons) decreases, and in non-gaseous alkalosis, it increases.

The reasons for the development of non-gaseous disorders of the cos: metabolic disorders, impaired excretion of acidic and basic compounds by the kidneys, loss of gastric and intestinal juice, introduction of exogenous acids or bases into the body.

Types of non-gaseous disturbances of cos: metabolic, excretory and exogenous acidosis and alkalosis.

METABOLIC ACIDOSIS is one of the most frequent and dangerous forms of ABB disorders, which can be observed in HF, many types of hypoxia, impaired liver and kidney functions in the neutralization and excretion of acidic substances, depletion of buffer systems.

Causes of metabolic acidosis.

✓ Metabolic disorders that lead to the accumulation of an excess of non-volatile acids and other substances with acidic properties:

✓ lactic acidosis and increased pyruvic acid level (hypoxia, long-term intensive physical work, liver damage); organic and inorganic acids (affecting large arrays of tissues and organs); ketoacidosis (due to acetone, acetoacetic, β-oxybutyric acids in diabetes, prolonged starvation; alcohol intoxication; large burns).

✓ Insufficiency of buffer systems and physiological mechanisms for neutralization and

✓ Removal of excess non-volatile acids from the body.

Indicators of metabolic acidosis.

The main pathogenetic factor: depletion of HCO_3- (hydrocarbonate buffer) in connection with the accumulation of non-volatile compounds.

Typical directions of changes in ABB indicators in all non-gaseous acidosis:

> pH decreases,

> [H] increases,

> [NSOz] decreases – the main violation.

> pC02 decreases – compensation reaction.

COMPENSATION OF METABOLIC ACIDOSIS

1. Urgent mechanisms for eliminating metabolic acidosis:

- **activation of the hydrocarbonate buffer system** of intercellular fluid and blood plasma, which is able to eliminate even significant acidosis;
- **activation of the hydrocarbonate buffer of erythrocytes** and other cells;
- **observed in conditions of significant accumulation of non-volatile acids** in the body;
- **activation of bicarbonate and phosphate buffers of bone tissue**;
- **increasing the activity of the respiratory center**. The "buffer power" of the external breathing system in conditions of metabolic acidosis is approximately 2 times greater than that of all chemical buffers. However, the functioning of this system alone is absolutely not enough to normalize the pH without the participation of chemical buffers.

2. Long-term mechanisms of compensation of metabolic acidosis are implemented mainly by the kidneys and, to a much lesser extent, with the participation of buffers of bone tissue, liver, and stomach.

• **Renal mechanisms**. During the development of metabolic acidosis, the following are activated:

✓ ammonogenesis (main mechanism), acidogenesis, secretion of monosubstituted phosphates (NaH_2PO_4), Na+, K+ exchange mechanisms.

In total, the renal mechanisms ensure an increase in the secretion of H+ in the distal part of the renal tubules and the reabsorption of bicarbonate in the proximal part of the nephron.

• **The participation of bone tissue buffers** (hydrocarbonate and phosphate) in chronic acidosis is also preserved.

• **Hepatic compensation mechanisms** consist in the intensification of ammonia formation and gluconeogenesis, detoxification of substances with the participation of glucuronic and sulfuric acids and their subsequent removal from the body.

The chronic course of metabolic acidosis is characterized by an increase in the production of hydrochloric acid by the lining cells of the stomach. Thanks to the activation of the mentioned mechanisms, metabolic acidosis can be compensated: pH does not decrease below 7.35. However, with the insufficiency of buffer systems and physiological mechanisms to eliminate the shift of the ABB, the pH of the blood decreases beyond the norm, and significant disorders of the body's vital activity are possible, including the development of a coma.

METABOLIC ALKALOSIS

Metabolic alkalosis is characterized by an increase in blood pH and an increase in bicarbonate concentration. The concept of metabolic alkalosis is the most controversial in the pathophysiology of ABB:

✓ part of alkalosis is the result of the accumulation of an excess of alkalis in connection with a disorder of the excretory function of the kidneys (NH). Therefore, these conditions refer to the excretory renal forms of alkalosis.

✓ part of alkalosis is due to the loss of the body's acidic content (due to gastric HCl during vomiting or due to gastric fistula) is also isolated gastric alkalosis.

✓ the category of alkalosis arising from enteral or parenteral entry of an excess of bases into the body is known as "exogenous alkalosis".

In clinical practice, states that arise as a result of disturbances in the exchange of Na+, Ca_2+ and K+ ions are justifiably called metabolic alkalosis. They are considered below.

Causes of metabolic alkalosis:

• **Primary hyperaldosteronism** is the result of primary impression of the glomerular zone of the cortical substance of the adrenal glands: its tumor (adenoma, carcinoma) or hyperplasia.

• **Secondary hyperaldosteronism** is the result of stimulation of aldosterone production by the glomerular zone of the adrenal cortex of extra-adrenal origin, i.e. for the second time (increased angiotensin II in hypertension or hypovolemia); blockade or decrease in the synthesis of glucocorticoids and androgens (compensatory increase in aldosterone); hyperplasia of the UA (Bartter's syndrome); increase in ACTH content in the blood (stimulates the synthesis of corticosteroids)

• **Hypofunction of the parathyroid glands** is accompanied by a decrease in the content of Ca^{2+} in the blood (hypocalcemia) and an increase in the concentration of Na_2HPO_4 (hyperphosphatemia).

Mechanisms of development of metabolic alkalosis include several links.

The main pathogenetic links include redundant ones:

• secretion of H^+ and K^+ by the kidney tubule epithelium into the primary urine,

• reabsorption of Na^+ from primary urine into the blood,

• H+ accumulation in cells with the development of intracellular acidosis,

• Na+ retention in cells,

• hyperhydration of cells in connection with an increase in osmotic pressure caused by excess of Na+.

These effects are realized through a cascade of exchange reactions (including due to the change in the activity of Na^+, K^+-ATPase and as a result – the metabolism of Na+ and K+), controlled by aldosterone. Therefore, this type of ABB violation is called metabolic alkalosis.

Compensation of metabolic alkalosis is aimed at reducing the concentration of hydrogen carbonate in blood plasma and other extracellular fluids. However, there are practically no sufficiently effective mechanisms for eliminating alkalosis in the body.

1. Urgent mechanisms of elimination of metabolic alkalosis

❖ Cellular compensation mechanisms

✓ activation of metabolism (formation of non-volatile organic acids: MK, PVC, ketoglutaric, etc.);

✓ acids increase the content of H+ in cells, enter the extracellular fluid (where they reduce the concentration of HCO_3), and also enter the blood plasma (where they also remove excess HCO_3 anions).

✓ the effect of a protein buffer that releases H+ into the cytosol and then into the interstitial fluid in exchange for Na+.

✓ transport of an excess of HSO_3 ions from the intercellular fluid into the cytoplasm in exchange for an equivalent amount of Cl- (acts in the erythrocyte).

The relative role of cellular mechanisms in reducing the degree of metabolic alkalosis is quite significant: about 30 % alkali.

❖ Extracellular buffer systems are not essential in eliminating alkalosis, because the main buffer of blood plasma and extracellular fluid under these conditions is protein, and the dissociation of H+ from protein molecules is small.

❖ A decrease in the volume of alveolar ventilation is the result of an increase in the content of bicarbonate in the body's liquid environment. In this connection, pCO_2 increases, the concentration of carbonic acid and H+ is formed during its dissociation. As a result, the pH decreases.

2. Long-term mechanisms of compensation of metabolic alkalosis

Long-term compensation of metabolic alkalosis is carried out with the participation of the kidneys: they remove excess NSOZ- from the body. However, the value of this mechanism is limited as the degree of alkalosis increases (in connection with the increase in the reabsorption threshold of bicarbonate).

Indicators of metabolic alkalosis

The main pathogenetic factors: an increase in NCO_3 (hydrocarbonate buffer), hypokalemia.

Typical directions of changes in ABB indicators in all non-gas alkalosis:

• pH increases,

• [H] decreases,

• [HCO3] increases - the main violation.

• pCO2 increases - compensation reaction.

Excretory disorders abb is the result of a violation of the excretion of acids or bases from the body with the development of acidosis or alkalosis

Excretory acidoses

Mechanisms of excretory acidosis compensation

It is important that with renal excretory acidosis, the renal mechanisms of eliminating excess non-volatile acids from the body are ineffective. This significantly complicates the patient's condition, since other mechanisms of long-term compensation of excretory acidosis (activation of hepatic metabolic and excretory processes, bicarbonate and phosphate buffers of bone tissue, increased synthesis of hcl- in the lining cells of the stomach) are not always able to eliminate excess h+ in the body.

The mechanisms of excretory acidosis compensation are similar to those in metabolic acidosis. They include immediate (cellular and non-cellular buffers) and long-term reactions.

Excretory alkalosis

The main causes of the development of excretory alkalosis

• loss of hcl by the body of the stomach, vomiting of gastric contents or its suction through a gastric (gastric) tube, excretory alkalosis.

• increased excretion of na+ from the body by the kidneys, which is combined with the retention of bicarbonate. Reasons - taking diuretics (mercury, furosemide, ethacrynic acid) – renal excretory alkalosis

Mechanisms:

• hypovolemia and hypokalemia;

• the presence of " inhibition of Na+ and water reabsorption. As a result, na+ is excreted from the body, and the content of alkaline bicarbonate anions in the blood plasma increases;

• excretion together with Na+ and Cl-, which causes hypochloremia (hypochloremic alkalosis - a variant of excretory renal alkalosis);

• development of poorly absorbed anions" in the glomerular filtrate – anions of nitrate, sulfate, metabolic products of some antibiotics, which are poorly reabsorbed in the proximal part of the tubules of the nephron. Accumulation of poorly reabsorbable anions in primary urine is accompanied by increased excretion of K+ by the kidneys and the development of hypokalemia, activation of transport of H+ into cells from the intercellular fluid, release of h+ into primary urine and reabsorption of HCO_3. All these changes cause progressive renal alkalosis

• hypovolemia (with repeated blood loss, vomiting, diarrhea, increased sweating) and a decrease in bcc activates the raa system. In this connection, secondary hyperaldosteronism develops, which is accompanied by the

removal of K+ and Na+ from the body and the reabsorption of hco3, which increases the degree of alkalosis.

• increased release of K+ from the body by the intestines, caused by the abuse of laxatives, frequent enemas

Mechanisms of development:

✓ intensive excretion with intestinal content of K+ leads to hypokalemia, which stimulates the transport of H+ into cells from the intercellular fluid and the development of alkalosis, both intracellular and in blood plasma - secretory intestinal (enteral) alkalosis.

✓ loss of K+ and fluid causes the development of hypovolemia, which is accompanied by secondary hyperaldosteronism.

✓ hyperaldosteronism increases the excretion of H+ and K+ from the body, that is, excretory renal alkalosis develops.

Therefore, secretory intestinal alkalosis is formed at first, which is later potentiated by the development of renal alkalosis.

Mechanisms of compensation of excretory alkalosis

The mechanisms of compensation for excretory alkalosis are the same as for metabolic alkalosis. They are aimed at reducing the content of bicarbonate in blood plasma. These mechanisms are implemented due to the inclusion of urgent reactions (consisting in the activation of cellular and non-cellular mechanisms, as well as in the increase of alveolar ventilation) and long-term processes aimed at reducing the level of bicarbonate in the blood plasma.

Exogenous disorders of abb develop as a result of ingestion of exogenous agents with acidic or basic properties

Exogenic acidosis is a consequence of the entry into the body of non-volatile acids or compounds with acidic properties.

Causes of exogenous acidosis

• Reception of acid solutions (hydrochloric, sulfuric, nitric) either by mistake or with the purpose of poisoning.

• Long-term use of foods and drinks containing a large amount of acids (citric, malic).

• Use of drugs containing acids and/or their salts (salicylic acid, aspirin, ammonium chloride, calcium chloride).

• Transfusion of preparations of donor blood preserved with sodium citric acid.

• An increase in the concentration of H+ in the body due to excessive intake of acid solutions, which leads to the rapid depletion of buffer systems.

• Release of excess H+ in connection with the dissociation of acid salts (NaH_2CO_3, NaH_2PO_4 and $NaHCO_3$, sodium citric acid).

• Secondary metabolic disorders in tissues and organs under the influence of exogenous acids.

• Damage to the liver and kidneys, which is observed with a significant increase in the concentration of H+ in blood and other biological fluids. The development of kidney and liver failure potentiates the degree of acidosis.

The mechanisms of compensation of exogenous acidosis are the same as those of metabolic acidosis.

Exogenous alkalosis – a relatively rare disorder of ABB – is, as a rule, a consequence of getting into the body or an excess of bicarbonate in the composition of buffer solutions, or alkalis in the composition of food and drink.

Causes of exogenous alkalosis

•Introduction for a short time of an excess of HCO_3-containing buffer solutions; observed in the treatment of acidosis (lactic acidosis or ketoacidosis in patients with diabetes). Rapid administration of alkaline buffer solutions to patients with reduced renal excretion (DM) is especially dangerous.

• Long-term use of foods and drinks containing a large amount of alkali (gastric ulcer disease due to the intake of a large amount of alkaline solutions and milk; flour products, seasonings, drinking alkaline mineral waters).

The mechanism of development of exogenous alkalosis usually includes two links:

1) the main (primary) link– an increase in the concentration of HCO_3 introduced into the body

2) additional (secondary) - increased formation and/or impaired excretion of endogenous bicarbonate.

Compensation mechanisms for exogenous alkalosis are identical to those for metabolic alkalosis

Mixed disorders of abb

In clinical practice, signs of mixed (combined) forms of ABB disorders are often observed in the same patient, i.e. gas and non-gas acidosis or alkalosis at the same time. Examples:

• **Heart failure**: mixed acidosis: gaseous (due to impaired alveolar perfusion and pulmonary edema) and non-gaseous: metabolic (as a result of circulatory hypoxia) and excretory renal (due to hypoperfusion of the kidneys).

• **Brain injury or pregnancy**: mixed alkalosis: gas (caused by hyperventilation of the lungs) and non-gas – secretory gastric (due to repeated vomiting of gastric contents).

General characteristics of non-gaseous discharges of abb

1. **Non-gaseous acidosis** (the most characteristic manifestations of non-gaseous acidosis):

• *Increase (compensatory) of alveolar ventilation* (in all acute and in most cases of chronic acidosis). With severe acidosis, "acidotic breathing" can be registered – deep and noisy breathing, periodic Kussmaul breathing. The reason: an increase in the content of H+ in the blood plasma is a stimulus for DC neurons. However, as pCO2 decreases and the degree of NS damage increases, DC excitability decreases: periodic breathing develops.

• *Increasing depression of the nervous system* – drowsiness, retardation, sopor, coma (acidosis with diabetes). Reasons: disturbances in the energy supply of brain neurons, caused by a decrease in its blood supply; imbalance of ions from changes in the physicochemical and electrophysiological properties of neurons of the respiratory center, leading to a decrease in their excitability.

• *Insufficiency of blood circulation* - arterial hypotension, collapse. Reasons: decrease in vascular tone (caused by hypocapnia), decrease in cardiac output.

• *A decrease in blood flow in the brain*, myocardium and kidneys increases the impairment of the functions of the nervous system and the heart, and also causes oliguria (reduced diuresis).

• *Hyperkalemia* is caused by the transport of excess H+ ions into the cell in exchange for K+ in the intercellular fluid and blood plasma.

• *Hyperosmia* - hyperosmolar syndrome caused by an increase in the concentration of K+ in the blood (as a result of damage to cells and an increase in the content in the blood plasma due to the "displacement" of Na+ from their connection with protein molecules by an excess of H+).

• *Edema.* Reasons: hyperosmia of tissues, hyperonkyia of tissues as a result of increased hydrolysis of proteins, increased permeability of the walls of arterioles and precapillaries in conditions of acidosis; decrease in fluid reabsorption in microvessels due to venous stasis (CH);

• *Loss of Ca ions* by bone tissue with the development of osteodystrophy. Reason: Consumption of bicarbonate and calcium phosphate of bone tissue for buffering excess H+ in blood and other body fluids. The process regulates PTH, namely: the stimulus for its increase is a decrease in the concentration of Ca2+ in the blood due to its inclusion in buffer systems. As a result, osteoporosis, osteodystrophy, and rickets develop in children. The specified changes in calcium metabolism and the state of bone tissue were called the "retribution phenomenon" for compensation of non-gaseous acidosis.

2.Non-gas alkalosis (the most characteristic manifestations of non-gas alkalosis):

• *Hypoxia.* Reasons: hypoventilation of the lungs, due to a decrease in [H+] in the blood and as a result - a decrease in the functional activity of the inspiratory neurons of the respiratory center; an increase in the affinity of Hb to O2 due to a decrease in the content of H+ in the blood, which is due to a decrease in the dissociation of HbO_2 and the supply of O_2 to tissues.

• *Hypokalemia.* Reasons: increased excretion of K+ by the kidneys (in conditions of hyperaldosteronism); activation of the exchange of Na+ for K+ in the distal parts of the kidney tubules (in connection with the increase in primary urine K+); loss of K+ (due to vomiting).

• *Consequences*: transport of H+ into the cell with the development of acidosis in it; metabolic disorders, especially inhibition of proteosynthesis; deterioration of neuromuscular excitability.

• *Insufficiency of central and organ-tissue blood flow* – arterial hypotension. Reasons: decreased tone of arteriole walls (in connection with impaired energy supply and ion exchange), cardiac output, hypovolemia.

• *Violation of microcirculation up to signs of capillary-trophic insufficiency*. Reasons: disorders of central and organ-tissue blood flow; violation of the aggregate state of blood in connection with hemoconcentration (most pronounced with repeated vomiting and polyuria).

• *Deterioration of neuromuscular excitability* – muscle weakness, disturbances of peristalsis of the stomach and intestines. Causes: hypokalemia and changes in the composition of other ions in the blood and intercellular fluid, cell hypoxia.

• *Disorders of the functions of organs and tissues*, up to their insufficiency. Causes: hypoxia, hypokalemia, impaired neuromuscular excitability.

Tasks for independent work on the topic «Violation of acid-base balance»

The student is offered 2-3 results of research on indicators of ABB. It is necessary to determine the disorder (acidosis, alkalosis, the degree of compensation and decompensation, etc. Be able to explain the mechanism of occurrence. Analysis of errors with an explanation of the correct answers.

List of questions and works to be studied:

1. Concepts of "acid-base state", "acidosis", "alkalosis".
2. Mechanisms of ABB regulation. The main indicators of ABB assessment.
3. Classification of violations of the ABB. Types of violations of the ABB.
4. Acidosis: definition, types, causes, pathogenetic mechanisms of development.
5. Compensatory mechanisms of acidosis. Clinical manifestations.
6. ABB indicators in various types of acidosis.
7. Alkalosis: definition, types, causes, pathogenetic mechanisms of development.
8. Compensatory mechanisms of alkalosis. Clinical manifestations.
9. ABB indicators in different types of alkalosis.
10. Pathogenetic therapy of various variants of ABB violation.

List of practical skills that must be mastered:

1 Determine the concepts of "acid-base state", "acidosis", "alkalosis".

2. Describe the pathogenetic mechanisms of development and compensation of ABB violation.

3. Identify the ABB indicators in various types of alkalosis and acidosis.

4. Identify on the basis of the received data, the pathogenetic therapy of various variants of ABB violation.

Situational tasks KROK-1 to determine the final level of knowledge

1. A patient suffering from a respiratory failure has the blood pH level of 7.35. Hypercapnia was diagnosed on the basis of his $PaCO_2$ rate measurements. An increase in his urine pH was found when measured. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

2. A patient has the following results of laboratory examinations: pH = 7.32, $PaCO_2$ = 38 mm Hg, SB = 19 mEq/L, BB = 36.0 mEq/L, BE = 6 mEq/L, blood lactic acid = 26 mg%, daily urine TA – 45 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

3. A patient with food toxicoinfection accompanied by profuse diarrhea suffers a severe condition attended with impairment of consciousness and Kussmaul's breathing. The blood test showed the pH level of 7.3. A substantial drop of base fund (i.e. a base deficit) in blood is observed. The urine is in a strong acid condition; containing excessive phosphates and ammonium salts. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

4. A patient with pylorostenosis suffers from a frequent vomiting with caused him to feel worse. He appeared to feel apathetic and weak, with the muscles' tone increased and cramps sometimes to occur. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

5. A patient suffering from the mountain disease which develops has the compensatory hyperventilation in his lungs. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

6. Hypercapnia was found in patient's blood when tested for CO_2 content which caused a bronchial asthma attack. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

7. A solution of glucose containing sodium bicarbonate is being infused intravenously to a patient. The following characteristics have been found by taking measurements: pH =7.43, $PaC0_2$ = 61,0 mmHg, SB = 31.5 mEq/L, BB = 59.0 mEq/L, and BE = +8.5 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

8. The following lab test data were obtained: pH = 7.28, $PaC0_2$ = 35 mmHg, SB = 16.5 mEq/L, BB = 35 mEq/L, BE -9.0 mEq/L, daily urine TA = 8.0 mEq/L/day, urine H^+ = 17 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

9. The following lab test data were obtained: pH = 7.35, $PaC0_2$ = 52 mmHg, SB = 26.5 mEq/L, BB = 45 mEq/L, BE = +3.0 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

10. The following changes in a patient's blood composition occurred as a cause of severe blood loss: pH = 7.19, $PaC0_2$ = 25 mmHg, SB = 11.0 mEq/L, BB = 26 mEq/L, BE = -17.0 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

11. A patient suffers from a prolonged loss of intestinal juice caused by bowel fistula. The following changes in blood composition are observed: pH = 7.25, $PaC0_2$ = 36 mmHg, SB = 14.0 mEq/L, BB = 24.0 mEq/L, BE = -8.0 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

12. The following blood composition changes were observed in a patient with concussion of the brain ("brain-shaking") accompanied by frequent vomiting attacks and dyspnea: pH = 7.56, $PaCO_2$ = 30 mmHg, SB = 27.0 mEq/L, BB = 50 mEq/L, BE = +3.0 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

13. A patient suffers from hyponatremia and polyuria caused by nephrosis, (he keeps taking the Diacarb medication). The following data of his blood lab tests were obtained: pH = 7.30, $PaC0_2$ = 36 mmHg, SB = 17.0 mEq/L, BB = 42 mEq/L, BE = -8.0 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

14. The following data have been obtained during the blood lab tests: pH = 7.36, $PaCO_2$ = 36 mmHg, SB = 19.5 mEq/L, BB = 39 mEq/L, BE = -5.0 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

15. A patient suffers from severe vomiting and tetany attacks. The following data have been obtained during the blood lab tests: pH = 7.50, $PaCO_2$ = 36 mmHg, SB = 28.0 mEq/L, BB = 57 mEq/L, BE = +5.6 mEq/L. Which of the following types of acid-base balance disorders is likely to take place in this case?

A. Metabolic alkalosis. *C. Excretory alkalosis.* *E. Respiratory alkalosis.*
B. Metabolic acidosis. *D. Respiratory acidosis.*

16. A 19-vear-old young man has been examined in a nephrological hospital. Increased potassium content was detected in secondary urine of the patient. Such changes have been most likely caused by the increased secretion of the following hormone:

A. Glucagon. *C. Testosterone.* *E. Oxytocin.*
B. Aldosterone. *D. Adrenalin.*

17. 30 minutes after drinking mango juice a child suddenly developed a local swelli-ng in the area of the soft palate, which impeded swallowing and, eventually, res ration. Mucosa of the swollen area was hyperemic and painless. Blood test revealed moderate eosinophilia. Body temperature was normal. Anamnesis states that the elder sister of the child has been suffering from bronchial asthma attacks. What kind of edema has developed in the child?

A. Inflammatory. *C. Cardiac.* *E. Allergic.*
B. Hepatic. *D. Alimentary.*

18. Due to recurring vomiting a patient has lost significant amount of gastric juice, which led to development of acid-base dysbalance. What type of acid-base dysbalance has developed?

A. Metabolic acidosis. *C. Gaseous acidosis.* *E. Gaseous alkalosis.*
B. Nongaseous alkalosis. *D. Nongaseous acidosis.*

19. Ketoacidosis that develops due to accumulation of ketone bodies in blood serum is a primary complication of diabetes mellitus. What acid-base disbalance develops during this condition?

A. Respiratory alkalosis. *C. Respiratory acidosis.* *E. –.*
B. Metabolic alkalosis. *D. Metabolic acidosis.*

20. A patient suffers from disrupted patency of the airways at the level of small and medium-sized bronchial tubes. What changes of acid-base balance can occur in the patient?

A. Respiratory acidosis. *D. Acid-base balance remains unchanged.*
B. Metabolic alkalosis. *E. Metabolic acidosis.*
C. Respiratory alkalosis.

Standards of correct answers to the situational tasks

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
D	*B*	*B*	*A*	*E*	*D*	*C*	*B*	*C*	*B*	*B*	*C*	*B*	*D*	*A*	*B*	*E*	*B*	*D*	*A*

Recommendations for registration of work results

1. Written answer to test tasks (basic level of knowledge).
2. The results of the experiment are drawn up in the form of an experiment protocol with the determination of relevant conclusions.
3. Protocol for the analysis of ABB indicators.
4. Protocol for solving situational tasks with an explanation of the correct answers.

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Subject plan

Навчальне видання

ЗАГАЛЬНА ПАТОФІЗІОЛОГІЯ

Методичні вказівки
для практичних занять з підготовки іноземних студентів
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