ПЕРМСКИЙ
МЕДИЦИНСКИЙ
УНИВЕРСИТЕТ АКАДЕМИКА ВАГНЕРА

A COURSE OF LECTURES ON PATHOPHYSIOLOGY FOR FOREIGN MEDICAL STUDENTS

PART 1

Education edition

ПЕРМЬ
2025

Federal State Budgetary Educational Institution
of Higher Education "Academician Ye.A. Vagner
Perm State Medical University"
of the Ministry of Healthcare of the Russian Federation

A COURSE OF LECTURES ON PATHOPHYSIOLOGY FOR FOREIGN MEDICAL STUDENTS

In two parts

Part 1

Approved by the Central Coordination Methodological Council of FSBEI HE Academician Ye.A. Vagner PSMU MOH Russia as a manual

Perm
2026

UDC 616-001-092(077)
LBC 52.5 я 73
A 18

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A 18 **A course** of lectures on pathophysiology for foreign medical students : manual in two parts. Part 1 / *E.I. Samodelkin, I.L. Gulyaeva, O.O. Lyamova, L.V. Sivakova* ; FSBEI HE Academician Ye.A. Vagner PSMU MOH Russia. – Perm, 2026. – 0.97 MB. – 1 electron. wholesale disk (CD-ROM). – System. requirements: PC, Intel(R) Celeron(R) processor and higher, frequency 2.80 GHz; Super VGA monitor with resolution. 1280×1024 display 256 or more colors; 1024 Mb RAM; Windows XP and higher; AdobeAcrobat 8.0 and higher; CD drive; keyboard; mouse. – Text (visual): electronic.

ISBN 978-5-7812-0802-9
Part 1. – ISBN 978-5-7812-0803-6

The training manual presents modern outlooks on pathophysiology, characterizes the pathophysiological experiment, advantages and disadvantages of the experimental method, relationships of pathological physiology with other disciplines, peculiarities of regulation of functions of the human organism in a disease.

Printed by the decision of Central Coordination Methodological Council of FSBEI HE Academician Ye.A. Vagner PSMU MOH Russia. Protocol no. 3 from 21.05.2025.

UDC 616-001-092(077)
LBC 52.5 я 73

ISBN 978-5-7812-0803-6 (Part 1)
ISBN 978-5-7812-0802-9 (general)

CONTENTS

PREFACE

The importance of fundamental training of doctors can't be overestimated. In terms of the new conception of specialists' training, introduced within the framework of current curriculum, pathophysiology is considered to be one of the most important components of successful high-quality education of future doctors.

The presented course of lectures, from our point of view, meets the above mentioned purposes and is designed to provide an independent work of foreign students studying at a medical university. It is aimed to ease studying of pathophysiology and to help students to understand complex questions, the knowledge of which is necessary for every doctor.

This course of lectures should become the basis for self-guided training of students studying in the English language, who are not, unfortunately, supplied with a full range of necessary text-books on the very subject.

The course of lectures is devoted to the main questions of general pathophysiology, typical pathological processes, applied pathophysiology and is aimed to piece out the shortage of the necessary text-books.

The authors would like to thank the following people for their feedback and comments during the development of the guide:

Academician V.A. Chereshnev

Professor I.F. Elkin

Professor A.I. Plaksin

Professor V.N. Kaplin

Lecture 1. GENERAL NOSOLOGY

Topics discussed in this lecture:

1. Pathophysiology as a science and an academic discipline, its subject, objectives and methods of investigations.
2. Characteristics of the pathophysiological experiment, experimental method advantages and disadvantages.
3. Relationship of Pathophysiology with other disciplines.
4. General nosology.

Pathophysiology is the science that studies, mainly in animal experiments, general patterns of occurrence, development and termination of diseases and pathological processes in humans.

It explores vital functions of an organism during illness and is called *general pathology*.

The subject of Pathophysiology is the general laws, primarily of a functional character, which exist at the level of cells, organs, systems and the whole sick organism. They determine the origin and course of a disease, the mechanisms of resistance, pre-disease, recovery and disease outcome.

General laws are derived from the study of pathological processes, states and pathogenesis of various diseases and syndromes.

Pathophysiology was established as an experimental science. However, at the same time clinical Pathophysiology studying pathophysiology questions in the clinic with the help of harmless methods of research was developing too.

Therefore, Pathophysiology is a methodological science. Using Pathophysiology a physician learns the general laws of disease development and how to solve complex situations on their basis.

Any science should have its object and its method.

The subject of Pathophysiology is a sick person, and the method is a pathophysiological experiment which allows to reproduce models

of human diseases and pathological processes in animals and, therefore, to investigate the problems of Pathophysiology.

Pathophysiology solves six problems:

1) tudying problems of general pathology, creating the general doctrine of illness – *general nosology*;

2) studying causes of a disease and establishing the general doctrine of causation in pathology – the laws which regulate disease causes – *general etiology*;

3) studying general mechanisms of occurrence, development and termination of diseases and pathological processes – *general pathogenesis* (it's the main aim);

4) studying *typical pathological processes* (there are a lot of various combinations of about 20 processes) – the foundation of a disease;

5) studying general laws of disturbance and restoration of the activity of specific physiological systems and organs – *private pathophysiology* (the most important is to study the *indicators of* the system or organ *failure*);

6) studying new methods of treatment – *establishing the doctrine* about the *principles of pathogenetic therapy and influencing mechanisms of disease development* on the basis of knowledge of pathogenesis.

Methods:

1. Pathophysiological experiment on an animal.

2. Pathophysiological experiment on a sick person (less common).

The structure of the pathophysiological experiment (acute and chronic) and its features. There are three phases of the experiment:

1) studying of the initial background;

2) obtaining of a "*model*" of the disease and studying of its pathogenesis, disease mechanisms;

3) pathogenetic therapy (regulation of pathogenesis mechanisms).

The advantages of the experimental method over the clinical one:

1) in the experiment (in contrast to a clinic) you can always determine the initial level and quantify the changes, but a doctor cannot do that in a clinic;

2) there are unlimited possibilities of studying the causes – as there is a rigid connection between the existing causal factor and a developing disease (modeling – it is the studying of a cause);

3) in the experiment there is an opportunity to study the mechanisms of the earliest phases of a disease hidden from clinical observation, those which are usually the trigger mechanisms;

4) as we can use different techniques in the experiment, there are unlimited possibilities for studying the pathogenesis – the deepest, intimate mechanisms of pathology;

5) the experiment gives you unlimited possibilities of scientific substantiation of developing new methods of treatment.

The experiment uses different methods: biophysical, physiological, biochemical, morphological, immunological.

There are various types of acute (vivisection) and chronic experiments (the method of conditioned reflexes, implantation of electrodes into tissue, creating a fistula).

The difficulties and disadvantages of the experimental method:

1) selection of animals for experimental research;

2) not all diseases can be simulated in an animal experiment;

3) it is difficult to transfer experimental data into a clinic;

4) it is difficult to create a model of a disease;

5) ethical problems.

Clinical Pathophysiology has its principal features, as different manifestations of mediation of biological processes by the social ones are the most important element in the life of a healthy and a sick person.

The main unit of mediation is the nervous and other regulatory systems as well as labor activity that, along with other factors, differs a man from an animal.

Pathophysiology connects biological disciplines with clinical ones. The basis of Pathophysiology as a science is biology, normal physiology and biochemistry.

Pathophysiology is associated with morphological disciplines (anatomy, histology, pathological anatomy), because studying of cell function in isolation from its structure is impossible.

A close connection with normal physiology does not mean identity. A variety of cell, organ and whole organism metabolism disorders in pathology has not "the prototype" of these disorders in a healthy body.

Depending on the cause of a disease, the reactivity of an organism and the influence of external environment there are a lot of combinations of functional disorders and reactive changes generated in the body.

In case of a disease a number of changes are caused by developed in the evolution process and consolidated by the heredity forms of response of cellular elements, organs, physiological systems in pathological conditions.

Pathophysiology as an academic discipline. Preparing a practitioner Pathophysiology equips him with the knowledge of the general laws of disease development, general principles of disease control, right methodology of the analysis of a disease and pathological processes.

Pathophysiology aims to teach students to apply science at a patient's bedside, to understand the mechanism of a disease and recovery processes basing on the general laws of organs and systems activity.

Consequently, Pathophysiology equips a physician with the correct method of finding truth by the shortest route and by the simplest ways allowing him to analyze the pathology quickly and cost-effectively – i.e., it is a methodology.

The advantages of Pathophysiology. Every disease consists of a small number of pathological processes, which have the general laws of development.

Therefore, a smart doctor can fully analyze any disease, and small details will not present any difficulties (for example, fever and inflammation develop by the same laws in any location; they are intertwined and form different combinations).

General nosology – the general doctrine of a disease, the most important elements of which are: 1) damage; 2) reaction; 3) pathological process; 4) pathological condition; 5) disease.

Reaction is a phenomenon of counteracting to damage, aimed at its eliminating and restoring the initial state. Between a damage and response, there is a certain conformity: in case of a relatively weak damage the level of reaction meets or exceeds the level of damage. In case of a severe damage the reaction, level may be lower than the damage level.

A doctor evaluates the level of damage not according to the damage itself, but according to the response to it. In case when the reaction level is enough – it is good, otherwise it must be strengthened.

Types of reactions: initially genetically formed *protective-adaptive* reactions (coughing, sneezing, vomiting) and those formed on the basis of physiological reactions (increasing of body temperature and blood pressure) provide adaptation to the damage.

Pathological reactions are protective-adaptive too, but due to the unusual quantity or quality, they lead to the appearance of a secondary injury (fever, pus). There are two criteria that distinguish protective-adaptive reactions from the pathological ones: the presence of a secondary damage and / or necessity to the body.

The pathological process is a combination of damage events, protective-adaptive and pathological reactions.

A typical pathological process is a natural combination of elements in the same strict sequence (always in the same order, independently of the localization of a pathological process and its type).

Characteristic features of the pathological process are dynamism and the presence of phases.

If a pathological process stops at some point of its development – it is already a pathological condition (process with no changes).

Due to its structure, a pathological process is closer to the concept "disease", the process includes component parts, but a disease is a more complex phenomenon.

General biological signs of healthof disease

Structural and functional completeness of a healthy organism	The presence of a number of pathological processes with structural and functional disturbances of organs
Homeostasis, that means the constancy of characteristics of the internal environment, the ability to maintain continuity and the optimal level of reaction	Homeostatic disturbance (at least partial)
The balance of the organism and the environment, organism independence On the environment	Disturbance of organism adaptation to changing environmental conditions, a reduction in the biological and social activity

When diagnosing a disease you should always evaluate these three disease criteria. In addition to biological indicators, indicators of adaptability to the environment should be taken into account. You can easily do that using exertion with functional tests, but it should be done cautiously.

Disease is a complex phenomenon, which consists of several main elements. The disease always has two sides: the damage and the response to it.

The most important constituent element of the disease is *disturbance of homeostasis* and interaction of the organism with the external environment. In case of a disease there is a change in the number of homeostatic indicators that are normally held in the body very firmly, and their shift leads to death (for example, pH). Although it should be noted that most of the values may fluctuate to some extent (for example, body temperature, biochemical or cellular composition of blood).

Homeostasis is the maximal efficiency of functioning of an organism, the ability to a more complete adaptation to changing environmental conditions.

Homeostasis is useful in a healthy body, and it is broken in a disease.

Losing homeostasis the body loses its normal regulation mechanisms. The adaptation to the external environment becomes defective (for example, a child with a fever is very sensitive to hypoxia).

The term "disease" is used:

1) to identify a particular human disease – a disease as a nosological unit;

2) to identify the generalized concept of the biological and social phenomenon. Disease is a form of existence of an organism, qualitatively different from health. However, at the same time the health and disease are in close unity, since they represent though different but inseparably interconnected forms of life.

TEST TASKS FOR THE LECTURE 1

Choose the correct answer

1.1. ORGANIZER OF THE FIRST CHAIR OF PATHOPHYSIOLOGY IN RUSSIA

1) Bogomolets
2) Voronin
3) Pashutin
4) Podvysotsky
5) Focht

1.2. WHAT IS NOT INCLUDED IN THE CHARACTERISTIC OF A DEFENSE-ADAPTIVE RESPONSE

1) occurs in response to damage
2) has a protective character
3) eliminates the damage
4) is adequate to the damage in quantity and quality
5) includes the damage

1.3. WHAT IS NOT INCLUDED IN THE CHARACTERISTIC OF PATHOLOGICAL REACTION

1) occurs in response to damage
2) has a protective character
3) causes secondary damage
4) is aimed at eliminating damage
5) includes damage

Lecture 2. GENERAL ETIOLOGY

Topics discussed in this lecture:

1. The concept of etiology.
2. Damage and its types.
3. Indicators of cell structures damage.

General etiology is the general doctrine of causality in pathology. When considering human disease etiology we find some difficulties, which arise because many pathogenic factors can influence the body simultaneously or sequentially, each of them can cause damage and so it is very difficult to determine which of them is the true cause (UVR, trauma, cold, germs, emotions).

Etiology theories:

1. Monocausality means one cause. According to this theory, the action of one specific pathogenic factor is enough for the occurrence of a disease. This factor determines the picture of a disease, and the disease follows its features, it is like the imprint of the damaging effect of the factor. The merit of this theory – the discovery of the material substrate of a disease, its particular culprit.

2. In contradiction to monocausality there is another theory – conditionalism. According to it, a disease occurs under the action of many equally important factors, and their combination should be regarded as the cause of the disease. Conditionalism does not allocate only one specific host factor but emphasizes a combination of equal factors.

3. A variant of conditionalism - analysis of risk factors of a disease, when each factor is quantified in the origin of a disease. In the analysis of a large number of cases of a particular disease, we can ascertain the relative frequency of the factors in the genesis of the disease.

4. Polyetiologism – as an approach to the analysis of etiology. Specific forms of a disease may be caused by a variety of specific factors (tumor causes: exposure to radiation, chemical carcinogens, biological agents).

5. Dialectical materialism means that a disease occurs under the influence of many factors; among which we identify the main causative factor and conditions. Characteristic features of the causative factor are:

1) necessity;

2) it causes a new phenomenon – a consequence;

3) it gives to the disease specific characteristics, which mostly concern the initial injury.

The cause of a particular disease is a dialectical process of interaction of the etiological factor with the organism under certain conditions leading to damage. Conditions themselves do not define the specificity of a disease, but their action is necessary for the appearance of specific causative interaction. There are external and internal conditions, contributing and preventing, sufficient and modifying ones.

Sufficient conditions are those without which the causative agent does not cause a disease. These factors determine the interaction of the causative factor with the body, facilitate or, on the contrary, resist this interaction, but lack the main feature of the etiological factor – its specificity.

Thus, *general etiology* is the doctrine of causes and conditions of a disease; in a narrow sense, the term "etiology" refers to the cause of a disease or pathological process. The cause of a disease is the interaction of the organism with the etiological factor in certain conditions – as the initial *trigger of the disease*.

The main component elements of a disease are damage, response and pathological process.

Pathophysiology of damage (damage mechanisms). A disease is the life of a damaged body. The basis of any disease is the damage and the response to this damage. Damage is a violation of homeostasis caused by the action of the etiological factor in certain conditions.

This may be a violation of *morphological* homeostasis that is a violation of the anatomical integrity of tissues and organs, resulting in a violation of their functions, violation of *biochemical* homeostasis –

abnormalities of the content of various substances in the body (hyperglycemia → diabetes → diabetic coma, hypoglycemia → hypoglycemic coma). Violation of the *functional* homeostasis is a pathological deviation of the functions of various organs and systems in the form of *increasing* or *decreasing*.

Types of damage, damage classification:

1. In time:

1) primary one, caused by the direct action of the etiological factor: burn, acid, alkali, electric current, microbes – determine the specificity of the damage;

2) secondary one – as a consequence of excessive or distorted, inadequate response to the initial damage.

2. Specific and nonspecific.

3. According to the nature of the process: acute and chronic.

4. According to the degree of manifestation: reversible – necrobiosis, paranecrosis and irreversible – necrosis.

5. According to the outcome: complete or incomplete recovery or death.

Acute injury is the result of immediate homeostasis changes under the influence of strong damaging factors – acute developing ischemia of cells, which manifests itself in:

a) a sharp decline in the number of macroergs;

b) disturbance of lipid peroxidation;

c) reduction of the membrane potential and cell death.

Acute swelling of cells is reversible. Signs of swelling disappear in case of ischemia termination. Irreversible acute swelling is accompanied by a decrease in macroergs of purine bases and leads to cell death due to the inability to continue life. Death is accompanied by cell necrosis, irreversible changes in cell structures as a result of autolysis of proteins, carbohydrates, lipids by lysosomes enzymes – hydrolases.

Death of cells can occur without necrosis under the influence of such fasteners as formaldehyde, glutaraldehyde, which rapidly destroy tissue enzymes and prevent necrosis.

Chronic injury – slowly developing cell ischemia leads to:

1) accumulation of lipids as a result of the decrease of their peroxidation;

2) deposition of pigments (e.g., lipofuscin – the pigment of cell aging, which gradually accumulates and determines the duration of a cell life).

Injury levels. Modern medical science tries to learn the essence of pathology from the point of view of the injury appearance at the following eight levels:

I – the behavior of electrons and protons in the body.

II – the behavior of atoms in the form of oxygen ions in the body, H^+, Na^+, Ca^{++}, P^+, K^+, Fe^{++}.

III – molecular level:

1) damage to protein molecules;

2) violation of lipid peroxidation;

3) violation of the activity of enzymes: their blockade or pathological activation. At the molecular level in the damage mechanisms a great role is played by damage mediators: 1) histamine; 2) serotonin; 3) catecholamines; 4) leukokinins, interleukines; 5) lymphokines; 6) fibronectin; 7) Hageman floating mediators; 8) complement; 9) prostaglandins; 10) nucleotides.

Damage of cell membranes. Cell membrane is a layer of phospholipids containing protein molecules and lipoproteins. Protein molecules perform three functions: 1) enzyme; 2) pumping or transporting; 3) receptor.

Packaging of structures is carried out by hydrophobic bonds. The damage of these structures primarily influences protein molecules, their ability to maintain hydrophobic cell homeostasis is impaired. There is also the impairment of: 1) enzymatic activity; 2) permeability (intact cell membrane does not pass colloidal paints); 3) electrical conductivity; 4) charge.

All this leads to disruption of ion homeostasis, sodium ions accumulate in the cell, outside the cell K^+, Ca^{++}, there is a threat of cell

lysis, water discharge in tissue injury, swelling of brain tissues. For one day 3–4 liters of fluid turn into lymph.

Pathophysiological indicators of damage to cells and subcellular structures:

1) the general indicator is a violation of the nonequilibrium state of a cell with its environment: the cell composition and power do not correspond to the environment – a cell has a higher power, another ionic composition, the amount of water is more by 10 times, K^+ – by 20–30 times, glucose – by 10 times greater than in the environment, but Na^+ in the cell is less by 10–20 times;

2) the damaged cell loses its *nonequilibrium* and moves closer to environmental indicators, and a dead cell has exactly the same composition due to simple diffusion. *Equilibrium* of the organism with the external environment is provided by *cell disequilibrium with the environment*. The loss of nonequilibrium due to damage leads to cell loss of K^+, water, glucose, entropic potential, energy dissipation into the environment (entropy is energy potential equalization).

Non-specific manifestations of alteration:

1) acidosis;

2) increase of osmotic pressure in the cell;

3) accumulation of water in the free state;

4) changes in the composition of colloidal protoplasm.

Damage at the cellular level can be specific. This specificity is determined by the etiological factor. For example, in case of mechanical damage such specific factor is the damage of the structure of tissues, cells and intracellular formations: compression, crush injury, contusion, sprain, rupture, fracture, wound. In case of thermal damage, its specific manifestation is denaturation and coagulation of protein-lipoid cell structures.

Dystrophic changes: protein dystrophy – cloudy swelling, granular degeneration, fat decomposition, infiltration, destruction of the nucleus:

karyolysis – dissolution, karyorhexis – decay, karyopyknosis – shrinkage. There is the development of necrobiosis, necrosis, damage of cell structures, cytoplasm vacuolization, loss of organelle detectability, rupture of histocytoplasmic membranes.

The transition from the cellular level of damage is considered to be damage of the functional element of an organ. The structure of the functional element of an organ includes:

1) parenchymal cell that provides the specificity of the organ: in the liver – a hepatocyte, in the nervous system – a neuron, in the muscle – a muscle fiber, in the glands – glandular cells;

2) connective tissue components: fibroblasts and fibrocytes, hyaline and collagen fibers – connective tissue framework that serves as a supporting unit;

3) nerve structures:

– receptors – sensory nerve endings – the beginning of the afferent part of the reflex arc;

– effector nerve endings that regulate a variety of functions: muscle contraction, salivation, tears, gastric juice;

4) microcirculatory bloodstream;

5) lymph capillaries.

Microcirculation is the blood circulation in the area of: 1) arterioles; 2) precapillaries; 3) capillaries; 4) postcapillaries; 5) venules.

Precapillaries end with the precapillary sphincter. Its contraction let the blood go in venules by passing the capillaries. In this case, blood goes through arterio-venous shunts. There is an abnormal blood storage, stasis in capillaries, hypoxia.

This system of microcirculation provides the functional element of the organ with oxygen and nutrients and removes carbon dioxide and metabolic products, ensures the movement of biologically active substances and neurotransmitters (catecholamines, biogenic amines, hormones, kinins, prostaglandins, ions, enzymes.

V – tissue level – studied well enough. I.I. Mechnikov showed the role of RES or endothelial-macrophage system in defense reactions of the organism.

VI – organ level – i.e. the study of the functions of organs, their specificity and behavior:

1) in its body;

2) isolated from the organism - preserved;

3) transplanted into another organism.

The most severe changes in the organism that may lead to death occur in case of a cardiac, renal and hepatic failure. Advances in studies of the organ level lead to the fact that modern medicine stands at the threshold of a fundamentally new stage of development of *transplantation therapy*.

VII level. The study of physiology and pathology of specialized functional systems. The general mechanisms of their pathology are damages to various parts of functional systems, namely:

1) the receptor-sensing system – an afferent link of the reflex regulation of a function;

2) the central regulation unit represented in the CNS by various centers: respiratory, vasomotor, food center;

3) the executive body or working organs.

Their damage manifests in specific forms of a disease (e.g., stomach ulcers, pneumonia, myocarditis).

VIII – organism level – studies physiology and pathology of the organism as a whole. Damage at the organism level is manifested in the form of a disease. This is the most difficult and most important level. Prevention has always been considered the ideal of medicine. Learning prevention mechanisms is the main task of medicine. And if recovery is recognized as the basic idea of clinical medicine, prevention, i.e. maintaining health of the entire organism at the organism level, is the main idea of *preventive medicine*.

TEST TASKS FOR THE LECTURE 2

Choose the correct answer

2.1. THEORY ABOUT THE CAUSES AND CONDITIONS OF DISEASE

1) pathogenesis
2) sanogenesis
3) etiology
4) thanatogenesis
5) carcinogenesis

2.2. THEORY ABOUT THE MECHANISMS OF ORIGIN AND DEVELOPMENT OF PATHOLOGICAL PROCESSES

1) etiology
2) pathogenesis
3) sanogenesis
4) thanatogenesis
5) carcinogenesis

2.3. THE BASIC THEORY OF CAUSATION IN PATHOLOGY

1) polyetiology
2) conditionalism
3) constitutionalism
4) monocausalism
5) dialectical materialism

Write a detailed answer

During the first 30 minutes of the pilot's stay at an altitude of 8.000 m, a break occurred cabin sealing. The pilot showed signs of high-altitude decompression-on-line disease: general weakness, dizziness, nausea, tachycardia, increasedblood pressure, increased blood pressure shortness of breath, paresthesia, pruritus, musculoarticular and chest pain, severe pain, visual impairment. Explain the mechanism of origin of these symptoms.

Lecture 3. GENERAL PATHOGENESIS

Topics discussed in this lecture:

1. The concept of pathogenesis.
2. Elements of pathogenesis.
3. The role of neuromechanisms in disease pathogenesis.
4. Features of regulation of body functions in disease.

Pathogenesis is a doctrine about the mechanisms of origin, development and termination of diseases and pathological processes.

The doctrine of pathogenesis is based on general beliefs about the disease, analysis of the role of a causative factor in pathology; the main cause and cause-effect relationships; general and local changes in the whole organism and is associat

Often an etiological factor interacts with the body during a short period of time (a split second) as a trigger mechanism: directed action of electric current, acids, high temperatures. However, developing as a result of this pathological processes form burn disease which runs for a long period, and the consequences of burns require different treatments. The pathogenesis in the action of such extreme etiological factors is determined by internal pathogenic factors manifesting at the moment of interaction of the etiological factor with tissues and organs, resulting as well from their destruction and formation of biologically active substances.

Pathological factors include:

1) stimulation of nerve receptors and conductors;

2) excretion of biologically active substances from damaged tissues (histamine, serotonin, adenine nucleotides);

3) impact of humoral factors of the response, not always adequate, reaction of the neuroendocrine system on the body (accumulation of mediators of nervous excitement, glucocorticoids, catecholamines).

Elements of pathogenesis: the primary (main) element of pathogenesis – a trigger factor and a pathogenetic chain.

The main element (the trigger factor) of pathogenesis is the phenomenon that determines development of a process with its characteristic specific features under the influence of damage. A pathogenetic chain starts with the main element and development of pathogenesis is impossible without it.

The chain of pathogenesis is a consecutive inclusion of leading mechanisms of a disease, linked by cause-effect relationships.

The leading factors of pathogenesis are included later than the main element. Pathogenesis includes the core mechanisms characterizing specificity of the disease, and the task of a doctor is to determine the pathogenesis of the disease in a variety of different manifestations.To illustrate this let's analyze the scheme of development of the pathogenesis of acute blood loss: the etiological factor (blood loss) causes the trigger factor – *the main element* (decrease of CBV) and the response to a decrease of the circulating blood volume: reflexive VAS-oconstriction, increasing of blood and fluid ejection from the depot, increased reactions of the cardiovascular and respiratory systems and others.

But if protective and adaptive reactions are not enough, hypoxemia and tissue hypoxia develop and lead to metabolic disorders, acidosis arises → disturbance of the central nervous system (especially the respiratory and vasomotor centers) → aggravation of hypoxemia → damaging of cells and subcellular structures → accumulation of unoxidized products and a further violation of the functions of various body systems.

The most important mechanism of development of a disease is violation of the regulation of homeostasis and, in particular, violation of the mechanism of feedback functioning. This is the basis of the formation of *vicious circles of pathogenesis* – the closure of the pathogenesis chain in a circular type, when a pathological deviation of the level of functioning of an organ or system begins to support and strengthen itself as a result of positive feedback.

Thus, in case of a blood loss the pathological deposition of blood, the output of its liquid part from the vascular bed increase blood volume deficit, it results in increased hypotension, which, in turn, through baroreceptors activates the sympathoadrenal system, enhances vasoconstriction, centralization of blood circulation, abnormal deposition of blood and a further increase of hypoxia in the CNS, decrease of excitability of the respiratory and vasomotor centers.

Early diagnosis of the initial stages of the formation of a vicious circle and prevention of its formation is very important for successful treatment of a disease.

The outcome of the disease depends on the ratio of adaptive and compensatory mechanisms with pathological phenomena caused by destructive influence of etiological factors: inadequate, inappropriate responses of the body.

There are excessive responses depleting the body or closure of vicious circles of pathogenesis, elimination of which is possible only due to complex treatment.

In many cases, pathology is aggravated by a too active and inadequate reaction of the body (e.g. allergic reactions, pain shock). Excessive stimulation of sensory nerves causes their local destruction, not life-threatening, but the organism can die of shock.

Kinds of therapy:

1. Causal therapy – the most effective form of therapy aimed at eliminating the etiological factor, but its capabilities are limited, because usually the action of the etiological factor is short.

2. Pathogenetic therapy is focused on the mechanisms of pathogenesis of a disease; it is the leading method in modern conditions. Pathogenetic therapy is very important, its main task is to choose the methods and tools that can eliminate or weaken the effect of the main element and leading factors of pathogenesis and strengthen compensatory processes in the body.

3. Symptomatic therapy – does not focus on the pathogenesis, but only on eliminating the symptoms bothering the patient (e.g.,

a headache is present in many diseases and its eliminating does not affect the pathogenesis, it is only an external effect, something should be administered to a patient to convince him of quick recovery).

Principles of pathogenetic therapy:

1. Pathogenetic therapy should be dynamic, changing and correspond to the phase of the pathogenesis of a disease.

2. The most effective pathogenetic therapy is directed to the trigger (main) element of the pathogenesis. If you eliminate it in time, the disease stops. Pathogenetic therapy should be started as early as possible, its success depends on early diagnosis, until the pathogenesis chain has developed.

3. Medical intervention should be necessary and urgent in the following cases:

– under the influence of extreme factors (as in this case protection is always not enough); c) in case of insufficiency of protective-adaptive mechanisms, even with a relatively small damage (for example, in immunodeficiency microbial action leads to severe consequences);

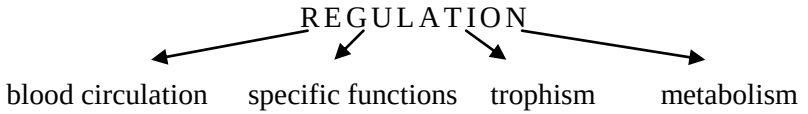
– in case of the formation of a vicious circle – it must be immediately broken, otherwise it can lead to death of the whole body or its part, where the vicious circle has developed.

4. A physician should not interfere if there is no possibility to influence the damage with sufficient protective and adaptive reactions, because the body is capable of self-healing. There are natural recovery mechanisms, which are optimal.

Nature treats, the doctor only helps healing. Attempts to enhance reactions when they are sufficient and correspond to the damage are dangerous because there is a risk of pathologic reactions and a secondary damage. When defensive reactions are externally intensified, the body loses this ability for future (vaccination stops the natural immune process, the immunity decreases and allergies develop). Suppressing of symptoms leads to disease prolongation (for example, when fever is decreased the body’s protection eliminates).

The role of neuromechanisms in the pathogenesis of diseases. In case of damage, the body develops different reactions. The main regulatory mechanisms are *nervous* and *hormonal regulation mechanisms*. They are responsible for reactions of the whole organism:

DAMAGE → of an organ, of a tissue	IRRITATION → of nerve receptors	REACTIONS + of the nervous system	REACTIONS of the endocrine system



Neural mechanisms – triggering in protective-adaptive reactions (trigger), and hormonal – start later than the neural ones and support a nervous reaction, as the executive part of the neuroendocrine regulation.

The most important forms of participation of the nervous system in the pathogenesis of diseases and pathological processes are *excitation* and *inhibition*.

Excitation – the universal reaction of the nervous system, on its basis protective and adaptive mechanisms are regulated and hormonal reactions are triggered. At the beginning of the action of damaging agents, there is diffuse generalized excitation, covering all levels of the nervous system. Depending on the strength and duration of the action of the damaging agent, excitation diffusion will be different: under the influence of a relatively weak damaging agent, excitement will last longer, and in case of a greater agent, general excitement will be short – seconds.

Excitation can be motor, psycho-emotional, sometimes there is an increase of the working capacity and irritability – this phase precedes the disease. Normally, excitation in the CNS is transmitted through a vector, and in pathology there is a risk of irradiation against the vector. There are the following types of excitation: the physiolog-

ical dominant, the pathological dominant and the determinant.

Inhibition plays an important role in protecting the nervous system**.** Inhibition forms are also different:

1. Active, regulating, central inhibition (as a defense mechanism) – development of a complex of various inhibitory processes associated with the excitatory ones, their interaction provides the analysis of the factors influencing the body and organization of adaptive behavior to preserve the *homeostatic equilibrium* with the external environment. It reduces the sensitivity of nerve structures to abnormal irritation caused by damage, protecting them from overstimulation. A characteristic feature of central inhibition is keeping of an adequate response to stimuli of different strengths. So, the level of good breeding is also determined by active inhibition.

2. Protective inhibition occurs under the influence of a very long and strong excitation or injury and is characterized by phases, changes in response to stimuli of different strengths or biological significance. Its phases: equalizing, paradoxical, narcotic (inhibitory), ultraparadoxical (develops only in the cerebral cortex).

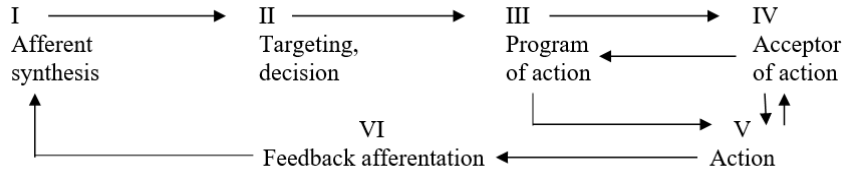
Inhibition starts in the cerebral cortex and with the action of a stimulus comes down to lower (but more stable) levels, and release – from the bottom to the top.

The role of inhibition is double:

1) protection of nerve cells from death;

2) reduction of adaptation and possible death of the organism.

The theory of functional systems (P.K. Anokhin). The body constantly has to choose the most appropriate solution:



I. Afferent synthesis – the right stimulus is selected from the variety of them and a certain wave of nervous activity is formed = isorithm.

II. The group of nerve cells starts working in isorithm – a personal decision.

III. Action program – the dominant is formed: 1) many nerve centers work in isorithm, although some nerve centers continue working at their own pace; 2) high excitability of nerve cells and centers; 3) the possibility to keep excitement for a long time; 4) the ability to sum stimuli (even non-specific) which enhance the initial excitement; 5) vector direction of excitation from the dominant center to a strictly defined group of muscles = action.

IV. Acceptor of action is not formed for a specific movement; it contains the parameters of the results of the future action - the perfect image of the action outcome. While the action continues muscles send constant throbbing to the acceptor, and practice matches with theory - that is, with an acceptor. If the result has completely coincided with the acceptor – the action stops, if it hasn't – the acceptor sends impulses to muscles causing them to correct the action. At the same time the acceptor sends impulses to the program – to correlate the correct action.

V. The action itself is the only visible manifestation of the activity of the functional system. The number of afferent receptors is five times greater than the efferent ones. Motor cells of the motion analyzer are scattered throughout the cerebral cortex, though are mostly situated in the anterior central gyrus and have the lowest threshold of excitation. The following pyramidal and extra-pyramidal tracts come from them:

– α-large motor neurons (pyramidal tract = voluntary movements);

– b-small motor neurons (extra-pyramidal = involuntary movements);

– γ-motor neurons – impulses to proprioceptors of muscles, tendons and ligaments.

VI. Afferent sensitive way through the posterior horns of the spinal cord, carrying information to the γ-motor neurons about muscle condition = reafference. Thus, the system is called *functional, self-regulated, closed* because it is created only for the implementation of a specific action, after which it breaks.

Features of regulation of body functions in disease lie in the fact that physiological parameters go beyond homeostatic boundaries for a long time – to a higher or lower level. Regulation of functions in disease, of course, exists, but it is not homeostasis.

In a disease functions are governed by the type of *emergency regulation*, it allows you to save a life or protect tissues from death, but adaptive reactions of the whole organism decrease. This is the only option to save the life in these conditions.

In a disease there are the same standards of functional activity as in a healthy organism, the body does not acquire any new features. In a disease:

1. Parameters go beyond homeostatic ones, but reaching life-threatening borders indicators do not go beyond them due to protective and adaptive reactions, which ensures adaptation to damage.

2. The ability of homeostatic regulation is disturbed, but the ability to survive is preserved. *The method of regulation, allowing preserving life at the cost of adaptation to the environment, is called emergency regulation.* New connections appear, the body donates its part in order to preserve the whole (redistribution of blood, tachycardia, shortness of breath, protective inhibition of the CNS, blood shunting).

3. Emergency regulation is uneconomical for the body, depletes its energy and plastic resources, but this is the only way to survive.

TEST TASKS FOR THE LECTURE 3

Choose the correct answer

3.1. WHICH THEORY STATES THAT THE ACTION OF ONE SPECIFIC PATHOGENIC FACTOR IS SUFFICIENT TO CAUSE DISEASE?

1) dialectical materialism
2) polyetiologism
3) monocausalism
4) conditionalism

3.2. THEORY ABOUT THE MECHANISMS OF ORIGIN AND DEVELOPMENT OF PATHOLOGICAL PROCESSES

1) etiology
2) pathogenesis
3) sanogenesis
4) thanatogenesis
5) carcinogenesis

3.3. WHAT IS NOT INCLUDED IN THE CHARACTERISTIC OF A DEFENSE-ADAPTIVE REACTION?

a) arises in response to damage
b) includes damage
c) has a protective character
d) eliminates the damage
e) is adequate to the damage in quantity and quality

Lecture 4. ROLE OF HORMONAL MECHANISMS IN THE PATHOGENESIS OF NON-ENDOCRINE DISEASES

Topics discussed in this lecture:

1. Definition, concept, reasons and types of stress-reactions.
2. Characteristics of rapid stress.
3. Characteristics of a long-term stress, its stages.
4. Morphological, biochemical and hematological changes in stress.
5. Pathogenesis and pathological forms of stress-reaction.

Stress is a universal nonspecific neurohormonal reaction of the organism in the form of tension of nonspecific adaptative mechanisms caused by damage or life-threatening agents. Stress reveals itself in the form of increased resistance.

Stressors classification (a stressor is an agent causing stress):

1) all kinds of agents causing extremal damage (hypoxia, hypothermia, trauma, radiation energy, intoxication), i.e. all extreme factors;

2) signals of danger to the human organism causing negative emotional conditions (fear, mental discomfort), i.e. all negative emotional agents.

Types of stress. Classification:

1) depending on the reason (stressor):

– biological (physical) stress caused by extremal agents;

– emotional stress caused by negative emotions;

2) depending on the speed of mechanism activation:

– urgent stress appears immediately (seconds). Its aim is to find a quick solution of the danger situation. The mechanism of urgent stress is excitation of the sympathoadrenal system;

– long-term stress turns on later (hours). Its aim is long resistance to the stressor. The basis of a long-term stress is involving pituitary gland hormones and adrenal cortex hormones into the reaction.

Characteristics and pathogenesis of the urgent stress-reaction. *Urgent stress* is an immediate organism reaction appearing in response to extremal agent attacks. The aim of this stress-reaction is a short raise of resistance which mechanism is connected with the sympathoadrenal system. The urgent stress was described by Kennon. The idea of urgent stress is to run away from the danger or remove it. It's a reaction "strike or run". The physiological processes are targeted to reinforce muscular and brain activity by activation of blood circulation or breathing system. *Adrenalin* forms chaotic stress. *Noradrenalin* forms urgent stress by brain structures activation. But urgent stress can't provide a long-term adaption to the stressor because of the lack of sympathoadrenal resources.

Pathogenesis of the urgent stress-reaction:

1) activating of the urgent stress is done by hypothalamus centers with further activation of the sympathoadrenal system and finally catecholamines ejection (adrenalin, noradrenalin). Activating the stress hormones function by reinforcing blood circulation and metabolism.

2) hemodynamic stress-providing mechanisms: tachycardia, increase of minute cardiac output, increased arterial pressure, quick blood circulation, redistribution of blood to the brain, muscles, heart; increased blood clotting and gas exchange.

3) metabolic stress-providing mechanism:

– formation of glucose from glycogen under the influence of glucagon. As a result – hyperglycemia in the brain, muscles;

– reinforced fatty aids splitting process connected with the release of energy;

– reinforced gas exchange, widening of bronchi;

– isometric muscles reduction.

Characteristics and pathogenesis of the long-term stress – general adaptation syndrome (GAS). GAS – is a general nonspecific neurohormonal organism reaction in response to the extremal agents attack aimed at a long-term increase of body resistance. The mechanism

of GAS is based on the activity of hypophysis and adrenal cortex adaptive hormones.

GAS was found and described by Hans Selye.

The first stage is anxiety (mobilization). It consists of two phases – shock and anti-shock. The *shock phase* is characterized by a threat to all vital functions of the organism because of the developing hypoxia, decreased blood pressure, hypothermia, hypoglycemia. The organism is prone to destruction and may die if the activity of adaptive hormones is switched off.

The *anti-shock phase* is characterized by the activation of the adrenal glands, release of corticosteroids, the resistance increases and thus leads to the second stage of GAS. During the second stage **(resistance**) the resistance level is high for a long time and is enough to fight against stressors. The resistance is not specific.

If the stressor stops its activity the resistance returns to normal and the organism survives. If the stressor is strong and continues alteration the third stage is possible.

The third stage (*exhaustion*) is characterized by all signs of the shock phase: resistance decreases, the organism is susceptible to the damaging activity of stressors up to death.

Morphological stress triad:

1) hypertrophy of the adrenal glands;

2) involution of thymic-lymphatic system (reduction in size of the thymus, lymph nodes, spleen);

3) bleeding ulcers of the gastrointestinal tract.

Hematological stress changes:

1) lymphopenia – lysis, disintegration of lymphocytes. Lymphocytes move to tissues and provide the release of energy and plastic substances (RNA, DNA, protein). The output of lymphocytes to tissue provides immune protection;

2) eosinopenia is a sign of defense: eosinophiles move to tissues providing histamine distraction and, thus, reduce tissue damage;

3) neutrophilic leukocytosis: all neutrophils from the bone marrow are spewed to blood: it provides non-specific protection against some bacteria.

Biochemical stress changes:

1) general metabolism changes:

– the first phase is catabolic (breakdown of proteins, fats, carbohydrates, disintegration and lysis of cells in the lesions and throughout the body). In case of a one-time action of a stressor the first phase lasts for not more than three days;

– the second phase is *anabolic*. There is an increased protein synthesis, activation of cell proliferation, replacement of dead cells with new ones;

2) hyperglycemia is a result of gluconeogenesis. Glucose is synthesized from proteins under the influence of adrenal cortex hormones;

3) breakdown of fats with the release of energy and its usage in metabolism, cell nutrition;

4) delay of water and sodium in the organism.

The characteristics of adaptive hormones of the anterior pituitary lobe and adrenal cortex:

1. ACTH (adrenocorticotropic hormone) – peptide, catabolic. It activates the release of glucocorticoids and mineralocorticoids;

2. Glucocorticoids are steroid catabolic hormones (corticosterone, cortisone, hydrocortisone and others).

Glucocorticoids: regulate protein and carbohydrate metabolism; stimulate gluconeogenesis; stabilize cell membranes – reduce membrane permeability, preventing cellular damage;

3. Mineralocorticoids (deoxycorticosterone, aldosterone) are steroid hormones regulating water-salt metabolism, delay body's sodium and water, excrete potassium.

Hormones influence on inflammation. Glucocorticoids are anti-inflammatory hormones decreasing an inflammation process. Mineralocorticoid hormones are inflammatory hormones increasing an inflammation process.

The pathogenesis of the general adaptation syndrome (GAS). The launching factors: adrenalin; 2) cerebral cortex; 3) pituitary chemoreceptors → reticular formation → excitation of the hypothalamus centers and releasing of release-factors → activation of the anterior lobe the pituitary gland and the release of hormones (ACTH, GH) → reinforcement of secretion of adrenal cortex hormones (glucocorticoids, mineral-corticoids) → increase of the general organism resistance due to hormones activity in all kinds of metabolism.

The therapeutic usage of adaptive hormones (glucocorticoids) in case of other medicines insufficiency.

a) in case of a pathological course of inflammation;

b) to suppress allergies;

c) for immunosuppression;

d) to enhance protection in extreme conditions.

Forms of stress:

Eustress is the optimal course of the GAS – the exact matching of the reaction to the level of damage.

Distress is a negative course of the GAS. It should be fought.

Forms of distress:

1. Emotional distress. Stressors have a long-term action; there are severe somatic diseases (hypertension, atherosclerosis, coronary heart disease, peptic ulcer and duodenal ulcer, bronchial asthma and other allergic diseases, allergic dermatitis), neuroses (psychosomatic diseases).

2. Distress connected with pathology of hormonal mechanisms. There are three variants of this kind of stress:

1) glucocorticoid insufficiency which is manifested in the form of inability to answer to stressors, decreasing organism functions, even up to shock:

– in extremal situations there is a lack of glucocorticoids which leads to their deficit (the lack of glucocorticoids occurs in the anxiety-phase especially);

– in extremal situations there is a large number of glucocorticoids but cell receptors are not susceptible to them;

– after a long glucocorticoid therapy the synthesis of our own glucocorticoids is reduced;

– congenital child glucocorticoid insufficiency is often accompanied by thymic-lymphatic status;

2) excessive glucocorticoid activity is manifested in the form of exhaustion, decreased resistance to infection, hypertension, hyperglycemia (diabetes) and it occurs in case of excessive secretion of glucocorticoids:

– in slow destruction;

– in excessive sensitivity of receptors to glucocorticoids;

– in a long-term therapy with these hormones;

3) excessive mineral-corticoid activity is manifested in the form of activation of inflammation (arthritis, myocarditis, periarteritis, sclerosis processes of vessels – nephrosclerosis, arterial hypertension). It occurs in conditions that exacerbate the increased action of mineral-corticoids (hypothermia, excess intake of sodium chloride and proteins, some other diseases in patient's anamnesis).

Methods of stress-reaction determining:

1. Determining the concentration of ACTH, glucocorticoids and mineral-corticoids in blood.

2. Determination of hormone metabolism products in urine (17-hydroxy-ketosteroids).

3. Studying of weight dynamics (especially in children). During the anxiety stage the weight decreases, during the stage of resistance it increases.

4. Determination of eosinophils concentration in blood (eosinopenia).

5. Torn's sample. An injection of ACTH causes a 2-time drop in the number of eosinophils in blood if the adrenal cortex functions normally.

6. Determining the emotional stress degree by studying the muscle tonus. The higher is the tonus, the higher is the stress-level.

7. Determining catecholamines concentration.

TEST TASKS FOR THE LECTURE 4

Choose the correct answer

4.1. WHAT IS INCORRECT IN THE CHARACTERIZATION OF OAS

1) is a general nonspecific response
2) has a sympathoadrenal mechanism
3) is aimed at increasing resistance
4) lasts for several hours, days
5) occurs in response to the action of a stressor

4.2. ANTI-INFLAMMATORY HORMONES

1) mineralocorticoids
2) glucocorticoids
3) STH
4) thyroxine
5) insulin

4.3. MINERALOCORTICOID HORMONE

1) aldosterone
2) corticosterone
3) ACTH
4) TSH
5) TTG

Write a detailed answer

Patient Z., 25 years old, was admitted to the clinic with complaints of mustache and beard growth and menstrual disorders. The examination revealed: thin, dry skin, pronounced obesity of the trunk; blood pressure-150/95 mm Hg. Ultrasound data: bilateral adrenal hypertrophy. The ACTH level was increased by 1.8 times.

1. What endocrine gland function is impaired in the patient?
2. What is the name of the disease?

Lecture 5. PATHOPHYSIOLOGY OF REACTIVITY AND RESISTANCE, BIOLOGICAL BARRIERS

Topics discussed in this lecture:

1. Definition of reactivity.
2. Mechanisms of reactivity
3. Major manifestations of reactivity, management methods.
4. External and internal barriers of the body.
5. Blood-brain barrier.

Reactivity (Reactio – opposition) is the ability of the body, elaborated in the process of evolution, to respond, in the form of changing, to different impacts of the environment, thus ensuring its adaptation to constantly changing conditions of existence – the ability to react.

Reactivity mechanisms depend on the level of development of the organism and its four correlative systems:

1. Metabolites: universal – CO_2, H_2O, lactic acid, NH_3, urea, glucose.

2. Parametabolites:

– sub-group - proteinogenic amines: histamine, tyramine, serotonin;

– sub-group - polypeptides;

– sub-group - kinin systems;

– sub-group - necrohormones;

– sub-group - hypothalamus neurosecretions: releasing factors.

3. Hormones produce a generalized effect through blood (thyroxine, insulin, epinephrine).

4. The nervous system. It is a complex system of various analyzers which provide the adequacy of reactions, hormones production and connection with external environment.

Speaking about the *role of the nervous system*, it is necessary to consider that *specific features* of reactivity and resistance of the organism are determined by the presence of the second signal system

and the influence of social environment. A word as a powerful irritant causes not only mental, but also vegetative shifts.

A word treats – a word hurts:

1. A psychic trauma can be the cause of diseases (corticifugal, corticovisceral diseases).

2. A psychic trauma can aggravate the course of diseases, especially chronic ones.

3. A word can cause sophisticated reactions - psychoses and neuroses, especially in the state of inhibition.

Reactivity is the same property of all living bodies, like metabolism, reproduction and growth. It is influenced by the environment: barometric pressure, radiation, illumination, monotony. The correlation between reactivity and resistance is of great biological importance. The knowledge of these correlations is widely used in practice to control vital processes.

Forms (species) of reactivity manifestations:

1. Anabiosis – the earliest and the most primitive form of response of lower animals and single-cell organisms. In this case the life-sustaining activity almost completely stops, but the resistance to adverse influences increases.

2. Animal winter hibernation – lowering of functions.

3. In humans, the passive protection – tolerance – resistance to damage, which should provoke a reaction.

4. Actively responding to different damaging agents – the most varied and optimal form of response.

5. Adaptation – fitting.

6. Compensation: supplementing – compensatory mechanisms when climbing; vicariation – functional reserve or reserve strength.

Reactivity control methods. Improvement: 1) vitamin fortification; 2) pyrogen- therapy; 3) ultraviolet irradiation; 4) therapeutic physical training; 5) protective excitement when moving; 6) caffeine; 7) pantocrine; 8) ginseng; 9) Apilac; 10) rhodiola rosea.

Decrease: 1) anesthesia; 2) narcosis; 3) blockade; 4) sleep; 5) hypothermia; 6) tranquilizers and bromine.

It is very important to estimate reactivity according to:

1) the *quantity*: hyperergy, normergy hypoergy and anergy;

2) the *quality*:

– positive anergy in vaccinated organisms, immunity, completed phagocytosis;

– negative anergy in case of exhaustion, starvation, cachexia, the elderly;

– species areactivity (e.g., in frogs to tetanus).

Individual reactivity depends on the constitution. Moreover, not only the morphological structure of the body but its functional features are of great importance. The role of the nervous system and its typological features are extremely important, too.

Factors causing violation of the condition of regulatory systems and changes of individual reactivity:

1. Violations of the higher nervous activity – neuroses caused by an extreme irritant, error, nervous activity overstrain.

2. Influence of an additional irritant on the nervous system during the main reaction.

3. Opened by academician A.D. Speransky phenomenon of the second attack on the nervous system, which reproduces the pathological process which is already finished.

4. Intoxication of the central nervous system, reduced lability, perversion of reactivity.

5. Violation of the trophic function.

6. Violations of autonomic innervation – the adaptive-trophic function of the nervous system. Removal of the cervical sympathetic ganglia leads to a decreased resistance to infection and hyperthermia. The parasympathetic nervous system increases the production of antibodies, the sympathetic one – increases phagocytosis. There is an increase in the sensitivity of denervated structures to hormones, alka-

loids, ions, alien proteins due to the increase of cell membrane permeability, which has a compensatory value – adaptation.

7. Condition of internal secretion glands.

8. A great role in individual reactivity is played by inhibitory stimulation caused by proprioceptive inflow (muscles, joints). Hence, the role of physical education and sport and the negative impact of hypokinesia are great.

Body resistance (Resisteo – resistance) – resistance of the organism to the effects of various damaging factors, the ability to resist them by maintaining homeostasis. During the process of phylogeny, the body of humans and animals acquired some functional properties ensuring its existence under the conditions of continuous interaction with the environment. Many environmental factors (physical, chemical, biological) could disrupt life activity and even lead to death if the organism didn't have sufficient resistance – hypoplasia or weakening of protective mechanisms and adaptive reactions.

The ability to withstand damaging influences is ultimately determined by the reaction of an organism, as a whole, to these impacts.

Body resistance is one of the main manifestations of reactivity. The concept of body resistance encompasses a wide range of phenomena. In some cases, it depends on the properties of different organs and systems not related to reactions.

For example, the barrier properties of many structures, preventing penetration of microorganisms, alien substances through them, are largely determined by their physiological characteristics.

The question of the relationship between *reactivity and resistance* is also extremely important. The reliability of different human tissue structures is judged according to resistance. Ideally: when reactivity is normal – resistance is optimal (for example, skin has a great resistance to the action of electric current, B-radiation and microbes; bones and ligaments – great resistance to deformation under mechanical influence).

In addition to such relatively passive resistance mechanisms, adaptive reactions maintaining homeostasis in case of harmful environmental impacts or changes in the body (specific resistance) are also very important. Resistance can vary depending on different factors (fasting, cooling, hypokinesia, over-training of athletes).

Physiological barriers of the body. Physiological barriers of the body are one of the mechanisms of resistance, which serves to protect the body or its parts, to prevent violation of permanence of the internal environment when the body is exposed to factors that can destroy this stability – physical, chemical and biological properties of blood, lymph and tissue fluids.

Conditionally, we distinguish external and internal barriers. The external barriers include:

1. Skin, protecting the body from physical and chemical changes in the environment, which is also involved in thermoregulation.

2. External mucous membranes, possessing strong antibacterial protection, excreting lysozyme.

The breathing apparatus has a powerful defense; it constantly faces a huge number of microbes and various atmospheric substances surrounding us. Respiratory system protection mechanisms: 1) emission (coughing, sneezing, movement by epithelial cilia); 2) lysozyme; 3) antibacterial protein-immunoglobulin-A secreted by mucous membranes and immune organs (immunoglobulin-A deficiency causes inflammatory diseases).

The *digestive barrier*: 1) emission of microbes and toxic products by mucous membrane (e.g., in uremia); 2) bactericidal activity of gastric juice, lysozyme and immunoglobulin-A; 3) alkaline reaction of the duodenum.

Internal barriers regulate the flow of blood into organs and tissues, necessary energy resources and timely outflow of products of cellular metabolism, which ensures the constant composition, physical-

chemical and biological properties of tissue (extracellular) liquid and preserve them at a certain optimal level.

The *histohematic barriers* include all barriers between blood and organs. The most specific of them are blood-brain, haematoophthalmic, haemato-labyrinth, haemato-pleural, haemato-synovial and placental.

The structure of histohematic barriers is largely determined by the structure of an organ in which they are located. The main element of histohematic barriers is blood capillaries. The endothelium of capillaries in different organs has characteristic morphological features. Differences in the mechanisms of implementation of the barrier function depend on the structural characteristics of the basic substance (noncellular formations that fill spaces between cells).

The *main substance* forms membranes which, in the form of protofibrils, envelop macromolecules of fibrous protein composing the frame of fibrous structures. Directly under the endothelium there is the basic capillary membrane which includes a large number of neutral mucopolysaccharides. The basal membrane is the main amorphous substance, fibers constitute the barrier mechanism, in which the main reactive and labile link is the main substance.

The blood-brain barrier (BBB) – a physiological mechanism selectively regulating metabolism between blood and the central nervous system and preventing penetration of alien substances and intermediates into the brain. It provides a relative stability of composition, physical, chemical and biological properties of the cerebrospinal fluid and adequate microenvironment of separate neural elements.

The morphological substrate of the BBB is anatomical elements located between blood and neurons: capillary endothelium cells overlap each other without spaces, like a tiled roof; three-layered basal membrane and glial cells; vascular plexus, brain lining and natural basic substance (complexes of protein and polysaccharides).

A special role is played by glial cells. Perivascular astrocyte feet, adjacent to the exterior surface of capillaries, can selectively extract the necessary nourishing substances from the bloodstream (squeezing capillaries-slow blood flow) and return metabolic products to the blood.

The permeability of the BBB in different parts is not the same and can be changed in different ways. It is determined that the brain has "barrier-free zones" (area postrema, neurohypophysis, pituitary gland stalk, epiphysis and grey tubercle), where substances can easily enter through bloodstream.

In some parts of the brain (the hypothalamus) the permeability of the BBB with respect to biogenic amines, electrolytes, some alien substances is higher than in other divisions that provides timely humoral information to the highest autonomic centers.

The permeability of the BBB varies in different conditions of the organism: during menstruation and pregnancy, in case of any change of the environment and body temperature, diet violating and vitamin deficiency, fatigue, insomnia, different dysfunctions, injuries, nervous disorders.

In the process of phylogenesis nerve cells become more sensitive to changes in the composition and properties of their own environment. High lability of the nervous system in children depends on the lack of active internal inhibition and high permeability of the BBB.

Selective permeability (selectiveness) of the BBB when moving from the blood in the cerebrospinal fluid and the central nervous system is significantly higher than the back one. The study of the protective function of the BBB has a particular importance for identifying the pathogenesis and treatment of diseases of the central nervous system.

Reduced permeability of the barrier contributes to penetration into the central nervous system not only alien substances, but also products of breached metabolism; at the same time increased resistance of the BBB partially or completely closes the path for protective antibodies, hormones, metabolites, mediators.

A clinic offers various methods to increase the permeability of the BBB (overheating or hypothermia, exposure to x-rays, malaria inoculation), or the introduction of drugs directly into the cerebrospinal fluid.

TEST TASKS FOR THE LECTURE 5

Choose the correct answer

5.1. THE ABILITY OF AN ORGANISM TO RESPOND TO ENVIRONMENTAL INFLUENCES

1) resistance
2) areactivity
3) reactivity
4) excitability
5) neoplasia

5.2. SPECIFICALLY PATHOLOGIC HYPERREACTIVITY

1) immunity
2) allergy
3) hormone production
4) leukocytosis
5) leukopenia

5.3. RESISTANCE OF THE ORGANISM TO THE ACTION OF PATHOGENIC FACTORS

1) reactivity
2) excitability
3) areactivity
4) resistance
5) hyperreactivity

Lecture 6. PATHOPHYSIOLOGY OF THE IMMUNE SYSTEM

Topics discussed in this lecture:

1. The concept of the immune system, classification of immunopathological processes.
2. B-type of the immune response (humoral response).
3. T-type of the immune response (cell-mediated immunity).
4. Phenomena of transplantation immunity.
5. Types of immunological tolerance.
6. Forms and mechanisms of primary immunodeficiency.
7. Mechanisms of secondary immunodeficiencies.

The *immune response* is a way of protecting the organism from living bodies and substances which carry alien genetic information. The target of the immune system is the preservation of antigenic and structural homeostasis of the organism.

Genetic control of the immune response is regulated by immunoreactivity genes and the major histocompatibility complex.

Intra-system regulation is based on the effects of lymphokines and monokines, humoral factors of the thymus, interferon and prostaglandins, activity of T-suppressor and T-helper cells. Such conditions as decreased development of the functional state of the immune system, organism damage or a disease are studied by the field of immunology – immunopathology.

Classification of immunopathological processes:

1. Protective-adaptive reactions:
   1) B-type of the immune response (humoral response);
   2) T-type of the immune response (cell-mediated immunity);
   3) immune tolerance (IT).
2. Pathological reactions of the immune system – phenomena of allergy and autoimmune aggression.
3. Immune deficiency:
   1) primary (inherited) immunodeficiencies (PI);
   2) secondary immunodeficiency or immunosuppression.

Mechanisms and forms of B-type immune response (humoral response). The inductive phase starts with antigen phagocytosis. This process is called processing – the absorption and digestion of antigen with its division into separate antigenic structures. The basic part of the absorbed antigen is destroyed. The other part is recycled. 10 % of the recycled antigen appears on the macrophage membrane in the shape of equally oriented repeating antigenic determinants – "antigenic cartridge clip".

This cartridge clip reacts with antigen-recognizing receptor of T-helper cells. T-receptors-capping takes place (the formation of a "cap" from receptors on the membrane of lymphocytes in case of contact with antigen cartridge clip on the membrane of macrophages). This cooperation is a specific activating signal. In addition, the macrophages begin to secrete IL-I (interleukin-1). Under the influence of these two signals T-helper cells are activated, proliferate and differentiate in producers of IL-2.

IL-2 is a nonspecific activating signal for T-helper cells; the specific signal is the same. T-B-helper cells are essential as a source of IL-4, IL-5 and a source of antigen-specific helper factors.

The next *phase (productive)* is the activation and proliferation of resting B-lymphocytes with receptors for the given particular antigen. Activation is caused by membrane immunoglobulins' capping and is supported by IL-1, IL-2 and IL-4.

The precursors of plasma cells are formed. They produce IgM. Some of these cells are switched from IgM synthesis to IgG synthesis. The memory cells are formed at the same time. Under the influence of IL-2, IL-5 and IL-6 intermediate forms of B-lymphocytes develop (proliferate and differentiate) to plasma cells which secrete IgM or IgG.

The *effector phase* of the humoral immune response is the accumulation of the sufficient number of IgM, IgG, IgA or IgE, and their transport to the place of antigen localization.

When antigen and antibody meet a specific cooperation of the active center of immunoglobulin molecule and antigenic determinant takes place. As a result of this cooperation the immune complex is formed.

The consequences of the immune complex formation can be different, so there are the following effector functions of antibodies:

1) neutralization of toxins, viruses;

2) agglutination and precipitation of bacteria, soluble antigens;

3) opsonization;

4) complement-dependent lysis of target cells;

5) antibody-dependent cellular cytotoxicity;

6) degranulation of assistive effector cells;

7) strength and time regulation of the immune response by the type of feedback: IgM via FC-part reinforces clonal expansion of T-helper cells. IgG through the FC -part reinforces clonal expansion of T-suppressors.

There are some types of the humoral immune response: it can be primary and secondary. The primary one is characterized by a long-term inductive phase (3–5 days), the initial accumulation of IgM modifying to IgG then IgA, the limited duration of peak production of IgG.

Secondary immune response is characterized by a shortened inductive phase due to the presence of long-living memory cells, predominant accumulation of IgG, the peak of production of antibodies is higher, attenuation of the immune response happens much later.

Forms of the humoral immune response:

1) IgM and IgG production;

2) IgE production;

3) IgA production.

The humoral immune response is significant because of creating:

1) immune response in acute bacterial infections;

2) immunity against soluble and freely moving corpuscular antigens.

To a lesser extent:

1) antiviral immunity;

2) anticancer immunity;

3) transplantation immunity.

Mechanisms and forms of T-type immune response (cell-mediated immunity). There are two main types of T-type immune response:

1. Induced T-cell cytotoxicity (ICC). It is mediated by cytotoxic T-lymphocytes (CTL) – T-killers, which are already "trained" during the intrauterine development. They are able to cooperate with the modified cells without a specific signal from immune cells.

2. The reaction of delayed-type of hypersensitivity is mediated by T-effectors.

Mechanisms of the induced cell cytotoxicity. Originally during the inductive phase the clonal expansion of T-inducers with cytotoxic specificity takes place. Macrophages present antigen to T-inducers and start secreting IL-1. T-inducers are required as a source of IL-2 and IL-6.

Under the influence of these interleukins and specific antigen cooperation on the macrophage surface or its own genetically modified or genetically foreign cells T-cytoxic precursors activate, proliferate and transform into memory cells or differentiate to cytoxic reaction effectors.

During the productive phase of immune response the number of cytoxic T-lymphocytes raises and cytoxic T-lymphocytes move to antigen localization.

The importance of cell-mediated immune response:

1) antiviral immunity;

2) antifungal immunity;

3) chronic bacterial infections immunity;

4) anticancer;

5) transplantation immunity.

Phenomena of the transplantation immunity:

1) transplant rejection (transplanted tissue is rejected by the recipient’s immune system);

2) graft-versus-host disease.

The developing mechanism of these reactions is associated with differences in the specificity of cell transplantation antigens between a donor and a recipient.

The mechanism of transplant rejection. Transplant cell antigens (allo- and xeno-) cause the production of antibodies in the regional lymph nodes and mobilization of T-effectors of induced T-cell cytotoxicity and the reaction of delayed-type of hypersensitivity. An infiltration consisting of T-cells, macrophages and plasma cells appears around the graft tissue. Necrosis of the graft tissue occurs due to a direct cytotoxic effect of macrophages, antibodies and local circulatory disturbances.

The mechanism of transplant rejection reaction. In case of transplantation of suspensions of spleen cells, bone marrow, lymph nodes to a donor T-lymphocytes, especially T-cytoxic, damage host organs and tissues. As a result of aggression of other lymphocytes, young or newborn animals suffer from runting disease (synonyms – "homologous disease"). Immune tolerance (IT) is the lack of the immune response to a specific antigen, i.e. a specific areactivity which is not related to immune system injury (*immunosuppression*). The ability to develop immune response to other antigens is remained. Due to the phenomenon of immunological tolerance the specific elimination of antigen doesn’t occur.

Types of the immune tolerance:

1. Congenital or natural IT develops after the contact with antigen in the embryonic or neonatal period of an individual.

2. Developed IT:

– "low dose" IT;

– "high dose" IT.

Immune tolerance mechanism. Natural IT is managed by clone selection, activation of T-supressors which suppress autoreactive clones of lymphocytes during fetal development. Developed immunological tolerance of a "low dose" is mediated by activation of antigen-specific T-suppressors blocking immune response.

Immunological tolerance of a "high dose" is partly mediated by activation of T-suppressor cells that respond to supraoptimal doses of antigen. Immunological tolerance of a "high dose" can be affected by

the mechanism of "immunological paralysis".

Forms and mechanisms of primary immunodeficiencies. Primary lesion is localized in the immune system and caused by an abnormal genotype which is inherited. Early symptoms of primary ID are the following: skin and mucous membrane lesions in the form of spots of a "coffee with milk" color, eczema depigmentation, neurodermatitis, angioedema.

1. Combined hereditary immunological insufficiency is caused by:

– reticular dysgenesia of bone-marrow defect hematopoiesis when progenitor cells of myelo – and lymphopoiesis don't form;

– agammaglobulinemia of the Swiss type.

2. T-cell immunodeficiency can be:

– syndrome of Di-George which is characterized by hypoplasia of the thymus resulting in disturbed further differentiation of prethymic T-progenitor;

– Nezelof syndrome is characterized by hypoplasia of the thymus due to the impaired process of migration of T-progenitor to the thymus;

– hereditary deficiency of purine-nucleoside phosphorylase enzyme which affects T-cells differentiation in the thymus;

– Louis-Bar syndrome (ataxia-teleangiectasia) is characterized with failed differentiation of T-cells and lack of IgE and IgA.

3. B-cell immunodeficiency occurs because of

– Bruton agammaglobulinemia is caused by impaired differentiation of cells-progenitors of lymphopoiesis to cells-progenitors of B-lymphopoiesis;

– hypoimmunoglobulinemia with macroglobulinemia – no IgG no IgA;

– selected IgA deficiency.

4. A deficiency of myeloid cells leads to:

– chronic granulomatous disease (a genetic defect of hexosaminidase cycle enzyme leads to a decreased microbicide capacity of neutrophils. Neutrophils englobe but do not eliminate microorganisms;

– Wiskott - Aldrich syndrome (impaired ability of macrophages to present antigen);

– Chediak-Higashi syndrome (violation of lysosome structure and functional activity);

– hereditary deficiency of myeloperoxidase;

– "lazy leukocytes" syndrome – a violation of neutrophilic response to chemotactic stimuli.

5. Deficiency of the complement system appears in the forms of:

– deficiency of inhibitors and inactivators which stabilize system. It leads to a the overspend of complement components;

– the lack of initial factors which negates the activation of complement in general;

– deficiency of terminal complement components C5–C9 (disrupted formation of MAC – membrane attack complex).

Main mechanisms of secondary immunodeficiencies. The immune system damage is secondary and may be associated with infections of the immune system, lymphoproliferative diseases, depletion of the immune system.

The reasons of secondary immunodeficiencies are:

1) protein deficiency, disorders of the nervous, hormonal and intracellular regulation;

2) chemical, pharmaceutical and toxic immunosupression;

3) radiation suppression;

4) immunosuppression by hormones and biologically active substances, hypoxia, hypoglycemia;

5) immunosuppression because of the age;

6) depletion of the links in immune reactions because of immunopathological reactions;

7) a true blockade of the RES;

8) lymphoproliferative disease;

9) infectious immunosuppression;

10) reaction of delayed-type hypersensitivity immunodeficiency;

11) surgical immunosuppression.

The main manifestations of immunosuppression:

1) recurrent infections caused by different infectious agents depending on the form of immunosupression. When B-immunity is impaired by recurrent bacterial infections (sepsis, pneumonia), when T-immunity is impaired by viral and fungal infections;

2) tumor growth, lymphoproliferative diseases;

3) a tendency to autoimmunities and allergies;

4) violation of hematopoiesis;

5) pathology of the gastrointestinal tract - disorders of digestion;

6) primary immunodeficiencies are often marked by congenital deformities, pathology of the musculoskeletal system and the nervous system.

Secondary immunodeficiency is often associated with disorders of proliferation and differentiation of cells, decrease of the number of effector cells or their functional inferiority, excess of some humoral factors of regulation and lack of other factors, pathological activation of T-suppressor cells and selective suppression of T-helper potential.

Principles of immunodeficiency pathogenic therapy:

1. Replacement therapy – replacement of a defective immunity part.

2. Prevention of infection complications using antibiotics, non-microbial environment.

3. Correction of metabolism disorders taking proteins, vitamins, minerals.

4. Immune stimulators: T-activin, B-activin and others.

TEST TASKS FOR THE LECTURE 6

Choose the correct answer

6.1. AUTOIMMUNE DISEASES
1) serum sickness
2) lupus erythematosus
3) urticaria
4) anaphylactic shock
5) pollinosis

6.2. AREACTIVE PHENOMENA OF IMMUNITY
1) production of antibodies
2) sensitization of excitable cells
3) innate immunological tolerance
4) graft rejection
5) graft versus host

6.3. CLINICAL FORMS OF IMMEDIATE-TYPE ALLERGY
1) allergic thyroiditis
2) graft rejection
3) contact dermatitis
4) bronchial asthma
5) allergic orchitis

Lecture 7. PATHOPHYSIOLOGY OF ALLERGY

Part I

Topics discussed in this part:

1. The concept of allergy.
2. The concept of allergens.
3. The stages of immediate type allergic reactions.
4. Reagin type of immune destruction.
5. Cytotoxic type of immune destruction.

The *term "allergy"* (allos – different, ergon – action) means any different action in comparison with immune reactions. Allergy itself is the condition of an increased and qualitatively distorted reaction to substances having antigenic specificity and even without it (hapten attaches to body proteins and native antigens – AG – are formed). Allergy differs from immunity by the fact that an allergen does not cause any injury, but in allergy cellular and tissue damage is able to cause the complex of allergen-allergic antibody.

There are two classification types of allergens: exoallergens and endoallergens.

Exoallergens:

1. Infectious exoallergens: bacterial; viruses; fungi.
2. Flowering plant pollen, poplar fluff (wool), dandelion (blowball), ambrosia, cotton.
3. Surface exoallergens (or epiallergens).
4. Domestic exoallergens (library or house dust as a waste product of domestic mite is specific for a particular apartment).
5. Food – especially in children – like cow milk, chicken eggs, chocolate, citrus plants, strawberry, fish, seafood (crab meat), grasses;
6. Medicines – especially medicative sera.
7. Chemical synthetics.

Endoallergens can be:

– natural (primary) endoallergens – eye lens and retina, tissues of the nervous system, the thyroid, testicles;

– acquired (secondary) endoallergens that are induced from the owner's tissues when influenced by external actions (environment).

Infectious:

1) intermediate: tissue damage is caused by a microbe;

2) complex:

– microbe + tissue ≥ result in complex infectious endoallergens;

– virus + tissue ≥ result in complex infectious endoallergens.

Non-infectious: cold; burn; exposure to radiation.

General characteristics of allergic types of reaction

Markers	Immediate reactions type, B-type	Delayed reactions, T-type
Clinical syndrome	Anaphylactic shock, bronchial asthma, hives, Quincke's edema, migraine, serum disease, atopic disease	Autoimmune diseases, transplant rejection, contact dermatitis
Secondary injection	In several minutes	In 4–6 hours
Antibodies in serum	IgM, IgG, IgA, IgE, IgD	No
Passive diffusion	With serum	With lymphocytes
Local cell-mediated response	Polynuclear (pruritic blister)	Mononuclear (doughy swelling)
Cytotoxic effect in tissue culture	Present	No
Deallergization	Effective	Ineffective

There are three stages in general pathogenesis of allergic reactions:

– immunological (formation of antibodies – Ab);

– pathochemical (exudation of substrates of bioactive substances);

– pathophysiological (clinical manifestations).

The immunological stage: when an allergen enters the human body allergic antibodies develop and accumulate there for 2 or 3 weeks – active sensibilization.

Sensibilization can be passive (when ready antibodies are injected with serum at least two hours are necessary for fixation of antibodies on a tissue). Passive sensibilization continues to live for 2–4 weeks. Allergy is strictly specific. All antibodies appear not simultaneously: firstly IgE (immunoglobulin E) "regains" develop, that are basic allergic antibodies. IgE (immunoglobulin E) have close affinity with skin and tissues.

Blocking antibodies – immunoglobulin G (Ab – IgG) – appear in the recovery period, they can be easily connected with antigens (AG) in blood; they also block antigen contact with reagins, so that they play a protective role.

Usually due to IgG hemagglutinin titer you can say something about the titer of reagins as there is a certain relationship between them.

Reaginic type of tissue damage (first type). Immunological stage: due to "Fc" (constant fragment) ends reagins fix on the corresponding receptors of mast cells and basophils, nerve receptors of vessels, smooth muscles of the bronchi, bowels and corpuscular elements of blood. The other end of the molecule Fab (antigen-binging fragment) performs the antibody function by binding to AG (antigen), besides one molecule of IgE can bind two molecules of AG.

IgE synthesize in the lymphatic tissue of mucous membranes and lymph nodes (Peyer's patches, mesenteric and bronchial), so in case of the reaginic type of damage the "SHOCK" ORGANS are the organs of the respiratory system, intestine and conjunctiva. IgE clinically appears as a typical form of bronchial asthma, hay fever, urticarial fever, food and drug allergies and helminthiases.

If the same antigen enters the body, or it is still there after the initial contact, is binds to IgE – antibodies both circulating and fixed on mast cells as well as to basophils. There is cell activation and transition of the process to the pathochemical stage. Activation of mast and basophil cells (degranulation) leads to release of various mediators.

Mediators of immediate type allergy:

1. Histamine.
2. Serotonin.
3. Slowly reacting substance (slow-reacting substance – SRS-A).
4. Heparin.
5. Platelet-activating factors.
6. Anaphylatoxin.
7. Prostaglandins.
8. Eosinophilic chemotactic factor of anaphylaxis and high-molecular neutrophil chemotactic factor.
9. Bradykinin.

Pathophysiological stage. It is established that the action of mediators has adaptive and protective significance. Under the influenced of mediators the diameter and permeability of small vessels increase, chemotaxis of neutrophils and eosinophils enhances, that leads to the development of various inflammatory reactions.

The increase of vascular permeability promotes release of immunoglobulins to tissues, complement, providing inactivation and elimination of the allergen. The forming mediators stimulate secretion of enzymes, superoxide, SRS and other bioactive substances that plays an important role in anthelminthic protection.

However, at the same time mediators have a damaging effect: increased permeability of the microcirculatory bloodstream leads to liquid outflow from vessels with the development of edema and serous inflammation with an increase in the percentage of eosinophils, arterial blood pressure fall and the increase of blood coagulability.

This leads to the development of bronchospasm and the spasm of smooth muscles of the intestine, increased gland secretion. All these effects clinically manifest in bronchial asthma attacks, rhinitis, conjunctivitis, urticarial fever, edema, skin irritation, diarrhea.

Thus, from the moment of AG and AT connection the first stage finishes. Cellular damage and release of mediators is the second stage, and the effects of mediators action is the third stage.

Anaphylactic shock generally occurs in a standard way: firstly, there is a short erectile stage, and in a few seconds, there is the torpid stage:

– a guinea pig mainly has bronchospasm (asthma type shock);

– dogs have the spasm of the hepatic veins sphincter, blood stagnation in the liver and intestines – collapse;

– a rabbit has mostly the spasm of pulmonary arteries and blood stagnation in the right half of the heart;

– a man has all the components: arterial blood pressure decrease due to blood redistribution and disturbed venous return, suffocation attacks, involuntary urination and defecation, skin manifestations, hives (urticarial fever), edema, itching (pruritus).

Atopy (lack of contact places) naturally can be found only in humans and has a strong genetic predisposition.

It does not need a preliminary contact with AG, the readiness to allergy is already formed: bronchial asthma, hay fever, urticarial fever, Quincke's disease, migraine. The pathogenesis of these diseases is similar.

The clinical characteristics mostly depend on the engagement of the target organ (shock-organ), which is mainly determined by the development of smooth musculature and AT fixation on a tissue.

Bronchial asthma (asthma bronchiale) is an attack of breathlessness (asthma attack) with difficult exhaling – bronchospasm, mucosal swelling, excessive mucus secretion and bronchial obstruction.

Pollinosis: allergic rhinitis and conjunctivitis – mucosal edema, lacrimation, often itching caused by plant pollen.

Skin manifestations: Quincke's disease caused by cosmetics and food allergens (deep facial skin layers are injured) and urticarial fever (upper skin layers are injured by creams, ointments, powders).

Migraine (hemicrania): periodic severe one-sided headache – allergic edema of one half of the brain to foods, rarely to medicines.

Second (II) Type of Damage (Cytotoxic). the formed AG-cells of antibodies join other cells and cause their damage or even lysis, because body cells acquire autoallergenic properties under the influ-

ence of various reasons (for example, chemicals or drugs) due to:

1) conformational changes of AG cells;

2) damage of the membrane and appearance of new AG;

3) formation of complex allergens with a membrane, where a chemical compound acts as haptene. Lysosomal enzymes of phagocytic cells, bacterial enzymes and viruses influence cells similarly.

The forming antibodies (AB) relate to IgG or IgM classes. They join their Fab end to the corresponding AG of cells. The damage can be caused by three ways:

1) due to activation of the complement – complement-mediated cytotoxicity, when active fragments generate and damage the cell membrane;

2) due to activation of phagocytosis of cells covered with opsonins – G4 antibodies;

3) through activation of antibody-dependent cytotoxicity.

After connection with a cell has happened, conformational changes occur in the area of "Fc end" of the antibody, to which K-cells join (killers, T-lymphocytes and null cells). The complement system (system of serum proteins) is activated at the pathochemical stage. Lysis of target cells develops under the joint action of the components C5b to C9.

The process involves superoxide anion radical and lysosomal enzymes of neutrophils.

Pathophysiological stage. In the clinic, the cytotoxic type of reaction may be one of the manifestations of drug allergy (medicamentous allergy) in the form of leukopenia (*leukocytopenia*), thrombocytopenia, hemolytic anemia, allergic transfusion-induce reactions, hemolytic disease of newborns due to formation of Rh-positive IgG to foetus' red blood cells in a rhesus-negative mother.

However, the effect of cytotoxic antibodies does not always end with cellular damage – with a small number of AB you can receive the stimulation phenomenon (antireticular cytotoxic serum of A.A. Bogomolets

for stimulation of immune mechanisms, pancreatoxic serum of G.P. Sakharov for treatment of diabetes). Certain forms of hyperthyroidism (thyrotoxicosis) are usually associated with a long-term stimulating effect of naturally formed autoantibodies.

Part II

Topics discussed in this part:

1. Immunocomplex type of damage.
2. Allergic reactions of the delayed type.
3. Diagnosis of immediate allergic reactions.
4. Diagnosis of delayed allergic reactions.
5. Treatment of allergic reactions.

Damage by immune complexes (AG + AT) is called the III type (the synonyms are immunocomplex, Arthus type). Antibodies (AB) of G and M classes (precipitating and capable in vitro of forming precipitate when combined with AG) are formed on the antigen (AG) having a soluble form.

Immune reactions constantly happen in the human body, forming the complex of antibodies and antigens as some antigens always get into the body from outside or they are formed endogenously, but these reactions are the expression of protective response or homeostatic function of the immunity and not accompanied by damage.

However, under certain conditions the complex AG + AB may cause damage and disease progression through complement activation, release of lysosomal enzymes, generation of superoxide radical and activation of the kallikrein-kinin system. A lot of exogenous and endogenous antigens and allergens such as antibiotics, sulfonamides, antitoxic serum, homologous gammaglobulins, foods, inhaled allergens, bacteria and viruses take part in the formation of immune complexes. Immune complex formation depends on the site of entrance or formation of AG. The damaging effect is usually caused by the complexes, which are formed in a slight excess of antigen with the molec-

ular weight of 900,000 – 1 million Daltons.

Pathochemical stage. Under the influence of the complex and during the process of its removal a number of mediators for phagocytosis and digestion of the complex are formed. These are the following mediators: complement, lysosomal enzymes (acid phosphatase, ribonuclease, cathepsin, collagenase, elastase); kinins causing a spasm of smooth muscles and bronchi, vasodilation, leukocyte chemotaxis, painful effect, increased permeability of the microvasculature. There is also a possibility of activation of Hageman factor (XII) and/or the plasmin system and the release of histamine, serotonin, platelet-activating factor that cause platelet aggregation on the endothelium and histamine and serotonin release out of platelets.

Pathophysiological stage: circulating immune complexes deposit in vessels of renal glomeruli and cause different types of glomerulonephritis: alveolitis – in the lungs and dermatitis – in the skin.

In severe cases the inflammation can differ greatly and lead to tissue necrosis, partial or complete thrombosis, hemorrhage.

Initially, neutrophils and actively phagocyting immune complexes dominate in the focus of the disease, releasing lysosomal enzymes and factors, which increase permeability and chemotaxis for macrophages.

Macrophages accumulate in the focus of inflammation and phagocyte destroyed cells, clearing the lesion (damage area). Inflammation finishes with proliferation of cellular elements.

The third type of immunological damage is the leader in development of serum disease, exogenous allergic alveolitis, some cases of drug and food allergies and a number of autoimmune diseases (lupus erythematosus, rheumatoid arthritis).

Serum disease is an immediate type allergy disease caused by introduction of heterologous or homologous sera or serum products and is characterized by the predominant inflammatory damage of blood vessels and connective tissue. This disease develops in 7–12 days after a single dose of massive foreign serum.

Different classes of antibodies are formed in the body in response to AG (mainly precipitating) introduction.

Immune complexes undergoing phagocytosis as a normal immune response are formed. However, due to certain conditions (certain size of the AG/AB complex, slight excess of AG, and other factors) this complex is deposited in a vessel wall, its permeability increases, the complement is activated, mediators are released. The symptoms of serum disease develop in 6–8–12 days: there is fever, papulovesicular skin rash (urticaria/urticarial fever) up to the hemorrhagic form, usually at the site of antigen introduction.

The rash is accompanied by severe itching, hemodynamic disorder. Immune complexes are often deposited in renal glomeruli (glomerulonephritis) with swelling and proliferation of endothelial cells and deep colony-forming cells and narrowing or obliteration of the lumen of glomerular capillaries.

Often, there is an enlarged spleen, heart failure (from angina attacks to myocardial infarction), lung damage (emphysema, acute edema).

There is leukopenia with relative lymphocytosis, sometimes thrombocytopenia, glipoglycemia in blood.

Treatment depends on the form of the disease: anaphylactic shock requires emergency help; doctors prescribe steroids, antihistamines, diuretics - in case of edema.

Characteristics of DHR (Delayed Hypersensitivity Reactions) – T-type allergic response (autoimmune diseases, tuberculin-type reactions and contact dermatitis). The steps are the same.

At the *immunological stage*, a clone of sensitized T-lymphocytes accumulates during 10–12 days. Their cell membrane takes structures plying the role of AT which are able to bind to the corresponding allergen.

Lymphocytes do not need to be fixed, they deposit allergy mediators themselves. When re-application of the allergen happens again, T-lymphocytes diffuse from blood flow to the site of application and connect with the allergen.

Under the influence of the complex immuno-allergy-receptor + allergen lymphocytes irritate (*pathochemical stage*) and release DHS mediators:

1) the factor of skin reactivity;
2) the factor of blast transformation of lymphocytes;
3) the transfer factor (Lawrence factor);
4) the chemotaxis factor;
5) the factor of macrophages migration inhibition (MIF);
6) lymphotoxin;
7) interferon;
8) the factor stimulating the formation of endogenous pyrogens by macrophages;
9) mitogenic factors.

The clinically third stage is the center of allergic exudative inflammation of dense consistency. The leading position among DHSR is taken by autoimmune diseases.

The pathogenesis of autoimmune diseases caused by endoallergens has three possible variants:

1) formation of autoantibodies for primary allergens which enter the blood in case of damage of the corresponding organ (as in the intrauterine period during formation of the immune system they didn't contact with lymphocytes, were isolated by histo-hematic barriers or developed after birth);

2) production of sensibilized lymphocytes against foreign flora that has common specific antigen determinants with human tissues (group A streptococcus and heart and kidney tissue, E. coli (collibacillus) and the tissue of the large intestine, timothy glycoproteins and glycoproteins of the upper respiratory tract);

3) removal of the inhibiting effect of T-suppressors – disinhibition of suppress clones against their own tissues, cell nucleus components, it causes a generalized inflammation of the connective tissue, i.e. collagenosis.

Diagnostics of allergic diseases – a search for a specific allergen – is based on serologic and cellular reactions produced by antibodies or lymphocytes that an allergic person has.

To identify the *reagin type* of sensibilization:

1) radioallergosorbent test (RAST);
2) radioimmunosorbent test (RIST);
3) direct skin test;
4) Prausnitz-Kustner reaction (passive transfer skin test);
5) Shelly's test (basophil degranulation test).

To reveal the *cytotoxic type*:

1) different options of the immunofluorescence method;
2) Coombs' Test;
3) antiglobulin consumption test;
4) radioimmunoassay technique.

To identify the *immune complex* type:

1) different methods of determining of circulating immune complexes;
2) determination of the rheumatoid complex;
3) different ways of determining of precipitating antibodies.

Diagnosis of HSR of the delayed type – identification of the effects of mediators:

1) direct skin test;
2) lymphotoxic effect;
3) reaction of blast transformation;
4) macrophage inhibition test.

Allergy treatment is restoration of the immune system:

1. Etiotropic allergy treatment is prevention, stopping and elimination of the allergen: in case of medicine, food, pollen allergy, household allergens.

Desensitization (fractional, continuous long-term introduction of the allergen to a patient in increasing doses) is specific for HSIT/HIT (hypersensitivity of immediate type).

The aim of *pathogenetic therapy* is to identify the leading type of allergic reaction and to provide a blocking effect on the development of each stage.

The *immunological stage* requires the use of levamisole and thymus hormones that regulate the immune response.

The *pathochemical stage* requires the following: in case of the reagin type – blockage of release of mediators from mast cells: Intal, ketotifen, antihistamines, histaglobulin (histaminopexy) antiserotonin drugs.

In case of the cytotoxic and immune complex types – antienzyme drugs inhibiting the activity of proteolytic enzymes, and, therefore, blocking the complement system and kallikrein, etc.

At the *pathophysiological stage*, treatment depends on the type of allergy.

2. Desensitization is an urgent removal of sensitization to prevent anaphylactic shock. There are three types of it:

1) natural: desensitization appears after suffering from anaphylactic shock (lasts for two weeks);

2) non-specific: introduction of a medicine under anesthesia and corticosteroids;

3) specific desensitization by A.M. Bezredko: repeated divided doses of a preparation are introduced in 30 minutes 2–3 times. The first small doses bind a part of AB (antibodies), having a minimal reaction, and then the main dose is introduced.

3. Non-specific allergy treatment is symptomatic: bronchodilators, antihistamines, anti-inflammatory hormones, anticoagulants with the third type of immune damage.

TEST TASKS FOR THE LECTURE 7

Choose the correct answer

7.1. ENDOALLERGENS
1) bacteria
2) plant pollen
3) drugs
4) chemicals
5) lens of the eye

7.2. CLINICAL FORMS OF IMMEDIATE TYPE ALLERGY
1) allergic thyroiditis
2) transplant rejection
3) contact dermatitis
4) bronchial asthma
5) allergic orchitis

7.3. HORMONES THAT INHIBIT ANTIBODY PRODUCTION
1) mineralcorticoids
2) glucocorticoids
3) STH
4) insulin
5) thyroxine

7.4. CELLS THAT ACCUMULATE AROUND THE GRAFT
1) megalocytes
2) eosinophils
3) basophils
4) lymphocytes
5) reticulocytes

7.5. BIOLOGICALLY ACTIVE SUBSTANCES IN DELAYED-TYPE ALLERGY

1) bradykinin
2) histamine
3) serotonin
4) lymphotaxin
5) acetylcholine

7.6. EXOALLERGENS

1) nerve tissue
2) testes
3) lens of the eye
4) plant pollen
5) thyroid tissue

Write a detailed answer

A 10-year-old patient with a leg injury received 3000 units of tetanus-free tetanus serum for preventive purposes. On the ninth day after the introduction of the serum, the child developed severe pain and swelling of the shoulder and knee joints, and a generalized rash appeared. At the same time, severe weakness, deafness of heart tones, and low A/D were observed. The child was hospitalized.

1. What allergic reaction did the child develop?
2. What type of hypersensitivity does it relate to?
3. What is its pathogenesis?
4. Which mediator mainly determines the development of the pathochemical stage of this reaction?

Lecture 8. PATHOPHISIOLOGY OF INFLAMMATION

Part I

Topics discussed in this part:

1. The concept of inflammation
2. Primary and secondary inflammation
3. Metabolism disorders when inflammation
4. Inflammation mediators
5. Stages of vessels reaction when inflammation
6. An exudate, its variations and functions

An inflammation is a complicated local defense-adaptive reaction of connective tissue, vessels and nervous system of all the organism. It occurs as a result of evolution in high-developed organisms and it manages an answer for alteration, its aim is to isolate damaging agent and to eliminate the effects of alteration.

It's a typical pathological process assosiated with changed matabolism and blood circulation, phagocyte and proliferation. A basis of any inflammation is alteration and defense reactions.

An ability to resist to alteration, an ability to heal wounds, to recover at least some lost tissues is an essential quality of living creatures.

These qualities are determined by the fact that healthy organism react to alteration in form of general and local reactions immediately. These reactions are caused by changes of nervous, hormonal and immune systems functional condition.

They are associated with reactivity changes in all the organism. Local reactions that occur in alteration zone or somewhere near it characterize the process of inflammation.

A biological meaning of inflammation is about to limit, to hesitate, to stop a development of alterative process. Also it's about to clean alteration zone from products of destroyed tissues and to prepare the zone for recovery.

In XVIII Celsus described four main clinical signs of inflammation – redness (rubor), swelling (tumor), pain (dolor) and increased temperature (calor). Galen described the fifth sign – function disorder.

Reasons of inflammation:

1) phisical factors;

2) chemical factors;

3) biological factors;

4) blood circulation disorders;

5) tumors;

6) immune reactions.

There are four stages of inflammation: alteration, exudation, emigration, proliferation.

An alteration is a main aspect, it's a start-mechanism. Alteration can be primary and secondary.

Primary alteration develops as soon as alterative factor affects. It forms in functional element of the organ.

Primary alteration manifestates by specific changes and not specific changes that develop stereotypically and don't depend on qualities and peculiariies OD pathogenic factor effect.

These changes are associated with:

1) alteration of membrane structures;

2) alteration of mitochondrial membrane;

3) lysosomal alteration.

An impairment of cell membrane leads to disorder of cell pumps. Because of this cells lose an ability to change appropriately metabolism to the surrounding environment.

Enzyme systems and mitochondria change too. Cells save non-oxidized products - pyruvic, lactic and succinic acid.

Originally these changes are reversible and can disappear if an ethiological factor stops to affect. Cell restores all its functions.

If an alteration continues and lysosomes are alterated too changes are non-reversible. That's why lysosomes are called start platform of inflammation and they are the first stage to secondary alteration forming.

Secondary alteration is caused by alterative effects of lysosomal enzymes. The processes of glycolysis, lipolysis and proteolysis are inforced. As a result of proteins dissociation number of polypeptides and amino acids increases. When fats dissociate number of fat acids increases. Disorders of carbohydrates metabolism leads to the accumulation of lactic acid.

All these processes leads to physical and chemical impairments of tissues. Hyperosmia with an increased number of K^+, Na^+, Ca^{++}, Cl- develops. Hyperonkia is an increased number of protein molecules due to the collapse of large one into small; H-hyperionia develops as a result of the dissociation of a large number of acids with release of hydrogen ions.

To the conclusion metabolic acidosis develops in association with an increased number of acid metabolic products. The process involves all components of tissue, and the alteration is irreversible, the result of which is cells autolysis.

When inflammation substances are formed. It can inforce or reduce alteration, make effects on inflammation components – regulate microcirculation, exudation, leukocytes migration and proliferation of connective tissue cells. These bio-active substances are called *mediators* or *modulators of inflammation*.

Inflammation mediators differs by the *time of their activity*:

– early and late;

– by the point of application: influence on vessels or on cells;

– by originality: humoral (plasmatic) ans cell.

To act as a source of inflammation mediators can blood proteins, proteins of inter-cellular liquid, all blood cells, neurons, cells and non-cell elements of connective tissue.

There are preformed and again-formed mediators. Preformed mediators are synthesized constantly no alteration needed. They are kept in special depots and go out immediately without any alteration (histamine). A synthesis of others mediators starts after the alteration as a reply reaction. These mediators are called again synthesized (prostaglandins).

Tissue alteration is associated with activation of special proteolitic blood systems. This leads to peptides appearance in inflammation focus. They act as inflammation mediators.

Vasoactive kinins are formed by activated Hageman factor, which also turns non-active plasminogen circulated in blood to active plasmin.

Plasmin splits fibrin (split fibrin is essential for successful wounds healing). Plasmin activates complement system. Complement system – consisted from about 20 proteins – can be activated by to ways despite Hageman factor – classical way (antigen- antibody complex) and alternative (lipopolysaccharides of bacteria cells). C_{3a} and C_{5a} complement components take part in inflammation. They opsonise and lysis bacteria, viruses and pathologicaly changed cells; inforce must cells and basophiles mediators' degranulation.

Complement components cause adgesia, aggregation and degranulation of blood cells, lysis ferments outcome, the formation of free radicals, IL-1, stimuly chemotaxis, leucopoiesis and Ig synthesis. Mediators of plasmatic and cells origin are connected and operate on the principle of autocatalytically reaction with feedback and mutual reinforcement.

Microcurculation disorders in inflammation focus is characterized by changing tonus of microcirculation vessels, inforced out of liquid blood part out of vessels (exudation) and out of blood elements (emigration).

Vessels reaction is characterized by four stages:

1) short vessels spasm;

2) arterial hyperemia;

3) venous hyperemia;

4) stasis.

Vessels spasm occur when alterative agents affect a tissue because of vessels constrictors (they are more sensitive than vessel dilatator). Spasm turns with arterial hypertansia.

Arterial hypertensia is formed by these three ways:

– as a result paralysis of the vasoconstrictors;

– as a result of the impact of mediators with vasodilator activity;

– as a result of the implementation of the axon reflex.

Precapilary sphincters relax; number of functioning capillaries increases and blood flow through the vessels of alterative tissue can be 10 times faster than through the vessels of non-alterative tissue.

Spreading of microcirculation vessels, increased number of functioning capilaries and increased hyperemia of an organ are the first macro signs of inflammation – *hyperemia*.

If an inflammation is in skin, which temperature is below than blood temperature then a temperature of inflammation zone increases. *Heat* develops.

As long as the first time after damage linear and volumetric blood flow velocity in the area of inflammation is large enough, then flowing from the source of inflammation blood contains more oxygen and fewer restored hemoglobin and because of this has bright red colour.

Arterial hyperemia at inflammation persists for a short time (from 15 minutes to 3 hours) and then goes into venous congestion when increased blood circulation in the body combined with the slowdown and even complete cessation of capillary blood flow (except aseptic inflammation).

Venous hyperemia starts with the expansion of precapillary sphincters which are insensitive to vasoconstrictor and vasodilatatory stimulies and venous return is hard. After this, the blood flow in capillaries and bringing arterioles slows down.

The main reason for the development of venous hyperemia is exudation – a liquid part of blood from the microvessels goes into the surrounding tissue. Exudation is accompanied by increased blood viscosity, peripheral resistance to blood flow increases, the flow rate of blood decreases.

In addition, the fluid compresses the veins, which impedes venous return and also increases venous congestion. The development of venous hyperemia is promoted by swelling of blood cells, blood clots, impaired desmosomes, regional standing of leukocytes, formation of microthrombi in the acidic environment.

Blood flow gradually slows down and acquires new quality features due to the increase in hydrostatic pressure in the vessels – blood starts to move partly, in the moment of systole of the heart the blood moves forward, and at the moment of diastole the blood stops.

With further increase in the hydrostatic pressure during systole, blood is moving forward, and at the time of diastole back – i.e. there is a pendulum movement.

Jerky and a pendulum movement of the blood determines the formation of pulsating *pain*. Gradually, the exudation causes the development of stasis – a common phenomenon in inflammation. As a rule, the **stasis** occurs in particular vessels of the venous microvasculature part due to a sharp increase in its permeability. Wherein the liquid part of the blood rapidly passes into the extravascular space and the vessel is filled with lots of formed blood elements.

The high viscosity mass makes it impossible to advance its movement in vessels and stasis occurs. RBCs form "coin bars", the borders between them gradually fade, and formed a solid mass in the lumen of the vessel, *sludge (dirt)*.

Mechanisms of exudation: exudation during inflammation is primarily the result of increased permeability of the microvasculature for proteins due to significant changes in the vascular endothelium.

Changing the properties of endothelial cells of microcirculatory vessels is the main but not the only cause of exudation during inflammation.

The formation of various exudate contributes to the increase of hydrostatic pressure in microcirculatory vessels associated with the expansion of bringing arterioles; increased osmotic pressure of interstitial fluid is caused by accumulation in the extravascular space of onkotic osmotically active products of tissue decay.

The process of exudation is more expressed in venules and capillaries. The exudation forms a fourth sign of inflammation – swelling. The exudate contains fluid part of blood, the formed elements of blood and ruined tissue.

The composition of the exudate distinguish five types of inflammation: serous; catarrhal (mucous); fibrinous; hemorrhagic; purulent (its kind – aharony).

Exudate functions: as a result of the exudation occurs a dilution of bacterial and other toxins concentration, and their destruction by coming from blood plasma proteolytic enzymes. During the exudation to inflammation sourse serum antibodies come, they neutralize and opsonize bacteria and their toxins. Inflammatory hyperemia provides a transition of white blood cells to the focus of inflammation, promotes phagocytosis. The exudate fibrinogen turns into fibrin, its threads provide structure facilitating the transition of leukocytes in the wound. Fibrin plays an important role in the wound healing process.

However, the exudation has negative consequences – swelling tissue may lead to suffocation or for life-danger increasment of intracranial pressure.

Disturbance of microcirculation may lead to ischemic tissue damage. Excessive deposition of fibrin may prevent subsequent recovery of the damaged tissue and contribute to excessive growth of connective tissue. That's why the physician must prove effective control over the development of the exudation.

Part II

Topics discussed in this part:

1. Leukocytes migration to the inflammation focus.
2. Leukocytes functions in inflammation focus.
3. Acute and chronic inflammation.
4. Biological essence of inflammation.
5. Diagnosis of inflammation.

When *arterial hyperemia* turns to venous one leukocytes gradually move from axial layer to the peripheral wall and adhesion to endothelium begins. A "regional standing of leukocytes" ocures and the mass migration of leukocytes to focus of inflammation starts. Leukocytes must get over two barriers: the endothelium and the basal membrane. A layer of endothelium granulocytes pass squeezing between endothelial cells, basal membrane is temporarily dissolved by their proteases.

The entire leukocyte transport process through the vessel wall takes 2–12 minutes and causes no damage to the vessel wall. The main place of emigration of leucocytes are post-capillary venules. In acute inflammation, neutrophils are the first to emigrate monocytes emigrate much later. Eosinophils, basophils and lymphocytes are also able to emigrate. Emigration of leukocytes is associated with the appearance of the special picks in inflammation focus.

The strongest exogenous chemattracings are lipopolysaccharides contained in bacterial endotoxins. The strongest endogenous chemattracings are chemattracings activated during inflammation of complement, especially C5A, leukotriene-B4, platelet-activating factor and kallikrein. Emigration of leukocytes into inflammation focus begins with their adhesion to endothelium of microcirculatory vessels. The adhesion increases as a result of enhanced formation of special RNA molecules and corresponding protein by endothelial cell

The passage of leukocytes through the vascular wall is the result of ability of these cells to move – *locomotion* which also is activated by chemattracings. Within the cytoplasm of white blood cells the concentration of calcium ions increases. This activates microtubular system that forms the internal skeleton of the cells, activates actomyosin complexes, increases the neutrophils secretion of their granular content, including neutrophil proteases that can dissolve the basal membrane of blood vessels.

Chemattracings interaction with surface of leukocytes receptors

is accompanied by activation of different enzymes, including calcium-dependent phospholipase A2, calcium-dependent protein kinases: protein kinase A and protein kinase C. Under the influence of chemattracings at the anterior pole of the cortical gel turns into a solum, i.e. it becomes more liquid. To this liquefied portion of the leukocyte solum from the central part moves. Leukocyte shortens behind and elongates in front parts. The liquefied portion of the cortical gel of the front pole with the force throws back and leukocyte moves forward.

Neutrophilic leukocytes are the most active. Polymorphonuclear leukocytes are the first to come into the focus of inflammation because they are more sensitive, they are much more in blood. They are called cells of "*emergency response*" and cells of one-time usage.

Monocytes are in blood up to three days, then move to tissue and stay there for about 10 days. Part of them transforms into tissue macrophages, another part is in an inactive state and can be activated.

That's why monocytes are called reusable cells. This sequence of output of formed elements of blood outside of vessel were identified by Mechnikov. He called it a "law of emigration" or "*stages of cellular response* in inflammation":

1) polynuclear (eosinophils and neutrophils) up to two days;

2) mononuclear (monocytes and lymphocytes) to 5–6 days;

3) fibroblastic is characterized by accumulation of histiocytes and fibroblasts in inflammation focus.

The most important function of leukocytes in inflammation is phagocytosis - the capture, killing and digesting of bacteria and digestion of products of disintegration of tissues and cells of the body.

During *phagocytosis* there are *four stages*:

1) the stage of phagocyte approach to the object;

2) the stage of phagocyte adhesion to the object;

3) the stage of phagocyte absorption of the object;

4) the stage of the intracellular transformations of the absorbed object.

The *first stage* is about an ability of phagocytes to chemotaxis.

In mechanisms of phagocytes, adhesion and subsequent uptake of an object opsonins play a big role (antibodies, complement fragments, plasma proteins and lysozyme). It is established that certain parts of opsonins molecules bind to the surface of the attacked cell and other parts of the same molecule bind with phagocyte membrane.

The mechanism of absorption is not different from the adhesion. Capture is carried by gradually phagocyte enveloping of microbial cells, i.e. by progressive adhesion of the surface of the phagocyte to the surface of a microbe. It lasts as long as the whole object will not be "plastered" with the membrane of the phagocyte.

As a consequence, absorbed object is inside the phagocyte, enclosed in a pouch formed by part of the membrane of phagocytic cell. This pouch is called phagosome. Forming of a pouch begins the phase of the intracellular transformations of trapped object inside the phagosome, i.e., outside the internal environment of the phagocyte.

The main part of the intracellular transformations of absorbed object is associated with degranulation, i.e. the transition of the content of cytoplasmic granules of phagocytes inside the phagosome.

All obligate phagocytes contains in these granulles a large number of biologically active substances, mainly enzymes that kill and then digest the microbes and other absorbed objects.

In neutrophils, there are 2–3 types of granules that contain lysozyme solventing microbial wall, lactoferrin – a protein that binds iron and provide a bacteriostatic effect, myeloperoxidase, neutral proteases, acid hydrolases, protein binding vitamin B12 and others.

Once phagosome is formed, granules come. The membranes of the granules fuse with the membrane of phagosome and the contents of the granules flows inside the phagosome.

Neutrophils are the first to infiltrate the area of inflammation. They provide effective protection against bacterial and fungal infections. If the wound is not infected then the content of neutrophils in it rapidly decreases and in two days, macrophages dominate in inflammation. Like neutrophils, inflammatory macrophages are

movable cells they protect the body from various infectious agents through phagocytosis.

They are also able to secrete lysosomal enzymes and oxygen radicals, but they differ from neutrophils by qualities that make these cells particularly important in later stages of an acute inflammation and in mechanisms of wound healing:

1. Macrophages live much longer (months, and neutrophils – week).

2. Macrophages can recognize and then engulf and destroy damaged and devitalized cells, including neutrophils.

It is related to their extraordinary role in "cleaning" of an inflammatory exudate. Macrophages are the main cells involved in the dissolution and removal of inflammation of the damaged connective tissue. It is necessary for the next reconstruction of the tissue. They synthesize and secrete neutral proteases: elastase, collagenase, plasminogen activator. All these enzymes destroy an extracellular collagen and elastin fibers of the connective tissue.

Macrophages play a key role in wound healing. Wounds of animals in experiment that were devoid of mononuclear cells does not heal.

This is due to the fact that macrophages synthesize growth factors for fibroblasts and other mesenchymal cells, produce factors that increase the synthesis of collagen by fibroblasts. They are the sources of factors managing different stages of angiogenesis – revascularization of damaged tissue. They produce polypeptide hormones, which are the mediators of an "acute phase response" – IL-1, IL-6 and tumor necrosis factor.

Inflammation can be **acute and chronic. Acute inflammation** develops due to sudden damage like burns, frostbite, mechanic injury, some infections. Its duration usually does not exceed a few hours. Acute inflammation is characterized by severe exudative reaction in which water, proteins, blood cells (mainly white cells) leave the bloodstream and enter the damaged area.

Chronic inflammation develops when the damaging agent acts

for a long time. Chronic inflammation lasts weeks, months and years. It is characterized not by exudation but proliferation of fibroblasts and vascular endothelium, as well as accumulation of special cells in inflammation focus – macrophages, lymphocytes, plasma cells and fibroblasts.

A big part of the most severe human diseases is chronic inflammatory process – leprosy, rheumatoid arthritis, tuberculosis, chronic pyelonephritis, syphilis, liver cirrhosis and so on. Chronic inflammation is accompanied by irreversible damaging of normal parenchyma; the defects are filled with fibrous connective tissue that deforms affected organs.

In the optimal case, stop of the damaging agent is accompanied by attenuation of inflammatory response and complete elimination of all the consequences of inflammatory reactions – i.e. "complete resolution of inflammation".

It means the end of mediators forming and their disappearance from the area of damage, the stop of emigration of leukocytes, recovery of vascular permeability, removal of the fluid, proteins, breakdown products of bacteria and cells (including neutrophils and macrophages).

The disappearance of mediators was due to spontaneous diffusion from inflammation focus and partly due to inactivation of various enzymes (system of inactivation develops during the inflammation). If the increased vascular permeability was not associated with gross damage of endothelial cells, it quickly goes normal after the disappearance of mediators.

A large part of accumulated fluid in the inflammation focus is removed with the flow of lymph. Deposits of fibrin dissolve by fibrinolytic enzymes, enzymes of inflammatory cells and they are removed through the lymph vessels.

May be macrophages leave through the lymph vessels too. Part of the macrophagesthat phagocited and contain non-toxic and non-destroyed substances, can stay fora long time on a place of former inflammation.

Complete resolution of inflammation creates the conditions for full recovery of structure and function of damaged tissues.

However, this happens only in relatively small injuries of organs and tissues, with high ability to regenerate – skin, mucous membranes, the parenchyma of internal organs. Incomplete resolution of inflammation leads to the fact that the restoration is performed with scarring.

The general reaction to inflammation depends on the location, cause, extent of damage of the body, the occurrence of failure of organ function, reactivity and resistance of the organism, immunity status of the endocrine glands, nutrition, constitution, sex, age, earlier illness.

The biological essence of inflammation. I.I. Mechnikov investigated phagocytosis for 25 years. His method of comparative pathology is the study of the process in the evolutionary aspect. He proved that inflammation occurs in all the animal world.

One-cellular organisms have the same mechanisms of fefence and digestion.

Lower multicellular organisms (the sponge) can phagocytose cells. During the formation of the embryonic layers, phagocytosis is assigned to the mesoderm.

In formation of vascular system of open type (cancers) phagocytes deliveres to the inflammation focus easier and faster. And the high-developed animals have phagocytic reaction, which is associated with reaction of vessels, nerves and connective tissue.

This is a reaction of the whole organism, developed during evolution. It has protective-adaptive value; the basis for protection is phagocytosis anything else is just an accessory of the inflammatory response.

Diagnosis of inflammation. It manifestates in redness, fever, swalloing, pain and dysfunction.

Methods of evaluation of functional ability of phagocyte. Determination of functional activity of leukocytes:

1) percentage of phagocytosis (extensive index) – % of phagocytic cells for 100 potential phagocytes;

2) phagocytic number is the number of objects of phagocytosis, that are captured by 100 phagocytes;

3) the phagocytic index or the absorption rate is the number of captured objects of phagocytosis, which is accounted for each phagocytic leukocyte;

4) the total absorption rate is the number of objects of phagocytosis captured by phagocytes in 1 mm^3;

5) completeness of phagocytosis;

6) congo rot index – (intravenously) the speed of paint disappearance from blood after retesting the venous blood in 15–20 min;

7) to estimate the degree of vaccination the antibody titre is used;

8) the cellular composition of the exudate is investigates;

9) determination of the total number of leukocytes and leukocyte formula.

There is a direct relation of inflammatory reaction to the general state (reactivity and resistance that provide manifestation, development, course and outcome of inflammation)

Inflammation can be:

– normergic – good reactivity in healthy individuals;

– hyperergic (very rough) – if you are allergic or choleric;

– hyperergic – positive hypoergy and anergy in the immune system and negative hypoergy and anergy in low reactivity, starvation, depletion of regulatory systems (nervous and endocrine).

TEST TASKS FOR THE LECTURE 8

Choose the correct answer

8.1. ACCORDING TO MECHNIKOV, THE ESSENCE OF INFLAMMATION IS BASED ON

1) temperature rise
2) exudation
3) metabolic disturbance
4) phagocytosis
5) nervous system reaction

8.2. THE MARGINAL STANDING OF LEUKOCYTES BEGINS IN THE STAGE OF

1) arterial hyperemia
2) venous hyperemia
3) exudation
4) spasm
5) stasis

8.3. MACROPHAGES ARE

1) basophils
2) monocytes
3) eosinophils
4) neutrophils
5) red blood cells

8.4. CHARACTERISTIC PHYSICOCHEMICAL SHIFTS IN THE FOCUS OF INFLAMMATION

1) hypo-osmia
2) hypocapnia
3) hypokalemia
4) H-hyperionemia

8.5. PLASMA MEDIATORS OF INFLAMMATION

1) bradykinin
2) leukotrienes
3) prostacyclin
4) histamine
5) prostaglandins

8.6. IN THE DAMAGED TISSUE PREDOMINATE ON THE THIRD DAY OF ACUTE INFLAMMATION

1) monocytes
2) basophils
3) platelets
4) mast cells
5) neutrophils

Lecture 9. FEVER

Topics discussed in this lecture:

1. Definition of fever.
2. Pathogenesis of clinical manifestations of fever.
3. Etiology of fever.
4. Pathogenesis of the feverish reaction.

Fever – febris, pyrexia – is a common change of thermoregulation of higher homoiothermal animals and humans under the influence of pyrogenic stimuli that is expressed in restructuring of thermoregulatory homeostasis of the body to maintain a higher level of enthalpy and body temperature.

Fever is a typical pathological process in which the increase of body temperature does not depend on the ambient temperature.

According to its biological value fever is a protective and adaptive reaction.

The body is usually divided into the core and shell. The core is the brain, chest, abdominal and pelvic cavities.

The core temperature of the body is rigidly fixed within 37° – it means that the core is *homoiothermal*.

The shell temperature depends on the ambient temperature. The body shell is *poikilothermic*.

What mechanisms regulate heat production and heat loss?

It is realized by the *hypothalamic thermoregulatory center*. It consists of three different morphological structures:

1) temperature-sensitive part;
2) temperature-measuring part that determines the body temperature level;
3) two efferent formations;
4) heat production center;
5) heat loss center.

Stages of fever:

1) Stadium incrementi – the stage of body temperature elevation;

2) Stadium fastigii – the stage of high temperature ;

3) Stadium decrementi – the stage of temperature decreasing and returning to its normal level.

Clinical characteristics of the stages: first stage – Stadium incrementi – is characterized by chills accompanied by the feeling of cold.

Pathogenesis of chills – there is a spasm of skin vessels and lowering of skin temperature by 10–12° (except axillary and inguinal regions). This causes the irritation of cold receptors (cold sensation) and the response to cold – muscle tremor.

Subjectively, all this is perceived as a chill. The body temperature rise can be rapid, and the chill can be very severe, and, conversely, it can be slow, gradual, with a slight fever, or even without it.

During the second stage (feeling of fever) – a patient says that he is burning with fever. This feeling is caused by the dilation of skin vessels at a high body temperature.

According to changes of the temperature curve (level of increase), its oscillations during a day the *following types of fever* are distinguished:

1) subfebrile – up to 38°;

2) moderate – 38–39°;

3) high – 39–40°;

4) extremely high – hyperpyretic (41° and above). In fever the body temperature can reach up to 42°.

If this limit is exceeded a patient develops severe disturbances of the central nervous system and there is a threat to the patient's life.

The degree of temperature increase in various diseases depends on:

1) the body reactivity (e.g. cholerics usually have a higher increase of the body temperature);

2) injection of CNS stimulating agents: caffeine, phenamine (while anesthesia and bromides reduce the reaction);

3) the pyrogenic activity of microbes;

4) the intensity of endogenous pyrogens production (it is determined by the number;

5) the functional state of thermoregulatory centers and production of mediators.

Types of febrile (temperature) curves:

1) permanent temperature curve (Febric continua) – variations within not more than 1°;

2) remittent – Febris remitens – or reducing (temperature variations within 1.5–2°);

3) intermittent or alternating – Febric intermitens – it is a regular alternation of normal and increased temperature;

4) recurrent – Febric recurrens – 5–7 days of fever and 3–4 days of normal temperature, i.e. the intervals between febrile and normal periods are usually not identical;

5) exhausting or hectic - Febric hectica – temperature variations during a day reach 3–5° (normal in the morning, 40° in the evening). This fever can be atypical, when temperature is higher in the morning than in the evening.

Pathogenesis of the third stage (temperature decrease) clinically appears as sweating. Sweating is the main kind of heat output during the period of temperature decreasing and its returning to the normal level.

The body temperature can decrease quickly (critical) and slowly (lytic). A rapid temperature drop can be dangerous, especially in elderly patients who have had myocardial infarction or cardiosclerosis.

Crisis can lead to collapse of acute heart failure.

Etiological factors of fever. They are divided into infectious and non-infectious: they are lipopolysaccharides of microbes, their exo- and endotoxins, viruses, rickettsiae, foreign transplant cells, tissue decay products, lymphokines, chemotaxins, allergen-antibody complex, allergens.

Fever is caused by special substances – *pyrogens*. Originally they are divided into:

1. Exopyrogens (of microbe endotoxins – bacterial).

2. Endopyrogens (cell).

Characteristics of endopyrogens: by chemical structure, they are macromolecular lipopolysaccharides.

It is determined that:

1) exopyrogens cause fever indirectly through production of endopyrogens, that is why fever develops within 45–60 minutes, maximally – within 3–4 hours;

2) exopyrogens are not toxic;

3) temperature resistant (to destroy them we need to autoclave them for 1–2 hours at the temperature of 200°);

4) not allergenic;

5) not antigenic;

6) they are haptens, so to acquire antigenic properties they need to connect with proteins of cells and tissues;

7) when injected 5–6 times daily the tolerance to exopyrogens occurs and fever does not develop;

8) exopyrogens cause a number of protective effects.

Endopyrogens: their sources are neutrophils, macrophages and blood lymphocytes – they are leukocyte pyrogens or interleukin-$_{I.}$

Properties of leukopyrogens:

1) they are produced only by living leukocytes, according to the structure they are proteins of albumin type;

2) they are not resistant to heat – destroyed at the temperature which causes protein coagulation (60–70°);

3) temperature reaction to endopyrogens develops within 10–15 minutes. The maximum temperature rise after endopyrogen injection develops in 1–2 hours.

Characteristics of interleukin-$_{I}$:

1) it is produced in micro- and macrophages, it does not cause tolerance, non-toxic, it affects all major regulatory systems of the body and especially those that determine reactivity and resistance – the nervous and endocrine systems;

2) It affects hypothalamus cells and increases production of CRF, triggering a stress response, mobilizes energy resources, so hyperglycemia and lipemia develop.

Endopyrogens cause the same biological effect as exopyrogens, enhancing protective properties of the organism:

1) intensify phagocytosis;

2) increase production of glucocorticoids;

3) enhance tissue regeneration, which leads to the formation of tender scars (are used in case of CNS damage to prevent complications (epilepsy, paresis, paralysis);

4) enhance liver detoxification;

5) improve microcirculation processes – that's why pyrogens are used in a mild course of chronic gastric ulcer to promote healing and scarring of ulcers, in renal hypertension to improve microcirculation in the kidneys (in the nephron, glomeruli) and reduce production of renin.

Leukopyrogens are generated during stimulation of leukocytes:

1) in inflammation;

2) effects of toxins;

3) under the influence of blood vessel wall roughness, in leukocyte contact with microbes even in the circulatory bed;

4) in pH change to the acid side (acidosis).

Characteristics of lymphocyte and macrophage pyrogens. Blood, alveolar and peritoneum macrophages during phagocytosis produce the same substance as neutrophils – interleukin-$_{1.}$

Lymphocytic pyrogen is produced by sensitized lymphocytes in allergy while contact with an allergen.

The pathogenesis of febrile reactions – the mechanisms of heat accumulation in the body. Measuring of the amount of heat in the body by direct calorimetry shows that the increase in heat production does not exceed 25 %.

Only at the stage of high temperature, the increase of heat generation reaches 40 %. What are the characteristics of heat exchange in fever? Why does the body temperature rise?

There are two variants possible:

1) heat loss reduction;

2) heat production intensification.

The investigation of pyrogens effects has shown that the body itself produces active fever. Temperature rise at the initial stage is associated with a decrease in heat elimination – this is *the main link of pathogenesis.*

Strengthening of heat production helps to raise the temperature quickly (warm up faster).

The chain of fever pathogenesis:

1) injection of exogenous pyrogens in the body;

2) interaction of exopyrogens with body phagocytes;

3) activation of phagocytes;

4) producing of interleukin-$_1$ by activated phagocytes;

5) effect of Interleukin-$_1$ on the thermoregulatory center (firstly on the termo-determining point);

6) increase of excitability of cold-sensitive neurons and decrease of excitability of heat-sensitive neurons;

7) induction of enhanced synthesis of prostaglandin E_2 in nerve cells of the hypothalamus and excitement of sympathoadrenal structures;

8) restriction of heat elimination (due to the spasm of superficial blood vessels) and increase of heat production;

9) increase of body temperature up to a new level of regulation.

The effect of physical exertion and ambient temperature on fever – it is estimated that: 1) physical exertion; 2) moderate warming; 3) moderate cooling during fever do not change the body temperature.

Increased heat generation even by more than 200 % does not change the body temperature. During fever, the thermoregulatory mechanisms are active; a feverish body keeps temperature high, saving temperature homeostasis.

The evidence of direct action of endopyrogens on the thermoregulatory centers:

1) anesthesia suppresses fever;

2) injection of stimulants – enhances it;

3) in patients with mental illnesses during the stage of excitation pyrogens cause a higher fever than during the state of depression;

4) after pyrogens injection there is an increase of bioelectrical activity of the thermoregulatory centers in the EEG;

5) malnourished, debilitated people, old people with low reactivity of the central nervous system have a weakened febrile reaction;

6) the use of antipyretic drugs (that have a specific inhibitory effect on the thermoregulatory centers) causes a decrease in body temperature due to the dilation of blood vessels and increased heat elimination.

The status of thermoregulation centers is reflected in the character of the temperature curve:

– permanent fever indicates a sustainable (optimal) excitation of the thermoregulatory center;

– remittent curve indicates an instable excitation of the thermoregulatory center;

– intermittent fever is a characteristic of septic conditions;

– hectic fever has an adverse course – it shows that the periods of excitation of the thermoregulatory center are followed by the periods of limited inhibition.

The character of the temperature curve reflects the state of reactivity of the respiratory and vasomotor centers. That is why these curves have a diagnostic and prognostic value.

Particularly unfavorable is the perverse character of fever – which indicates a rapid depletion of the thermoregulatory center.

The biological significance of fever is in creation of a higher temperature background for metabolic processes that leads to increased defense reactions:

1) activating of enzymes;

2) enhancing of phagocytosis.

It is known that biochemical processes run much faster at the temperature of 39°, than 36°. This is one of the body's adaptive responses.

TEST TASKS FOR THE LECTURE 9

Choose the correct answer

9.1. CELLS THAT FORM PYROGEN
1) megalocytes
2) basophils
3) reticulocytes
4) neutrophils
5) eosinophils

9.2. MECHANISM OF TEMPERATURE RISE IN FEVER
1) metabolic disturbance
2) damage to receptors metabolism
3) damage to receptors
4) disruption of thermoregulation
5) active restructuring of the thermoregulatory system

9.3. CHARACTERISTIC CLINICAL SIGN OF THE FIRST STAGE OF FEVER
1) fever
2) pain
3) sweat
4) chills
5) cyanosis

Write a detailed answer

An acute inflammation was reproduced on the rabbit's ear skin, after which a 1 % solution of trypan blue was administered intravenously. Which ear was more brightly colored in blue: healthy or inflamed? Please explain the answer.

Lecture 10. HYPERTHERMIA

Topics discussed in this lecture:

1. Forms, causes and pathogenesis of hyperthermia.
2. Difference between fever and hyperthermia.
3. Doctor's tactics in body temperature increase.
4. Features of overheating in children.

Hyperthermia – a pathological process characterized by an increase of body temperature, the level of which depends mainly on the environment.

It is a very dangerous condition, because it is accompanied by failure of thermoregulatory mechanisms. Hyperthermia occurs under the conditions when the body does not have time to eliminate an excessive amount of heat.

Unlike fever, hyperthermia is a condition characterized by violation of the thermal balance and increased heat content in the body.

The amount of heat elimination is regulated by physiological mechanisms, the most important of which is the *vasomotor response*. Due to decreasing of the vascular tone the blood flow in human skin may increase from 1 to 100 ml / min to 100 cm^3.

Up to 60 % of basal heat metabolism can be eliminated through hands, although their area is 6 % of the total surface.

Another important mechanism is sweating – *heavy work* of sweat glands promotes exudation of up to 1.5 liters of sweat per hour (evaporation of 1 g of water consumes 0.58 kcal, and 1.5 l–870 kcal / h) and that's enough to keep normal temperature under severe exertion and the increase in ambient temperature.

The third mechanism – *evaporation of water* from mucous membranes of the respiratory tract.

Classification of hyperthermia depending on the source of excessive heat formation:

1) hyperthermia of the exogenous origin (physical);

2) endogenous hyperthermia (toxic);

3) hyperthermia resulting from overstimulation of sympathoadrenal structures (pale hyperthermia).

Exogenous hyperthermia occurs with prolonged and significant increase of the ambient temperature (when working in hot shops, in tropical countries, etc.) with excessive heat entering from the environment (especially in high humidity conditions making perspiration difficult), in this case there is a risk of heat stroke.

This is physical hyperthermia in normal thermoregulation.

Overheating of the body is accompanied by increased sweating with a significant loss of body water and salt, which leads to thickening of blood, increasing of its viscosity, impairing of blood flow and oxygen deficiency.

The leading element of heat stroke pathogenesis is a disturbance of the water – electrolyte balance due to disturbances of sweating and the activity of the hypothalamic thermoregulatory center.

Heat stroke is often accompanied by the development of collapse. Excess potassium released from red blood cells produces a toxic effect on the myocardium and, therefore, contributes to circulatory disorders.

In case of heat stroke the regulation of breathing and kidney functions and various types of metabolism are also affected.

In heat shock hyperemia and edema of brain tissue membranes as well as multiple hemorrhages develp in the central nervous system.

As a rule, there is repletion of internal organs, small punctulated bleedings under the pleura, pericardium and epicardium, mucous membranes of the stomach and intestines, often pulmonary edema, degenerative changes in the myocardium.

A severe heat stroke develops suddenly. There is a change of consciousness from mild to a coma, tonic and clonic spasms, intermittent agitation, often delirium, hallucinations.

The breathing is shallow, rapid, abnormal. The pulse is up to 120–140 per minute, heart sounds are dull. The skin is dry, hot and covered with sticky sweat. The body temperature is 41–42 and higher.

The ECG shows signs of diffuse myocardial damage. There is thickening of blood with an increase of residual nitrogen, urea and decrease of chlorides. There is a risk of fatal outcome caused by respiratory paralysis. The mortality rate is up to 20–30 %.

Pathogenetic therapy – any simple cooling – the use of air conditioners, in hot shops – various boards.

Endogenic (toxic) **hyperthermia** results from a sharp increase of heat formation in the organism when the body is unable to eliminate excessive heat by perspiration or using other mechanisms.

Its reason is the accumulation of toxins (diphtheritic, pyogenic microbes, in an experiment – thyroxine and – dinitrophenolum) in the organism.

If normally 70 % of energy in oxidation of nutrients is usually used for ATP synthesis and 30 % is spent for primary heat formation, then in toxic hyperthermia nutrition energy is used only for heat production.

Stages of exogenous and endogenic hyperthermias and their clinical manifestations:

1. The adaptive stage is characterized by the fact that the body temperature isn't increased at the expense of sharp increase of thermolysis due to:

– diaphoresis;

– tachycardia;

– skin vasodilatations;

– rapid breathing.

A patient suffers from a headache, weakness, nausea, the pupils are dilated. After medical help hyperthermia symptoms disappear.

2. The exaltation stage is characterized by a greater feeling of fever and the increase of heat elimination, but it isn't enough and the body temperature increases to 39–40.

There is sharp adynamia, intensive headache with nausea and vomiting, somnolentia, uncertainty in movements, periodic short-term loss of consciousness.

The pulse and respiration are rapid, the skin is hyperemic and wet, perspiration is strengthened. When treated the body temperature decreases and all functions are normalized.

3. The stage of paralysis of the respiratory and vasomotor centers.

Pathogenetic therapy – as antipyretic substances do not help in exo – and endogenous hyperthermia, the temperature is reduced only by cooling of the body in any way. It is very important to facilitate perspiration.

Medical help: take the patient away from the area of overheating, put him in a place that is well ventilated and protected from the sun, strip to the waist, wet with cold water – put ice or a cold towel on his head, neck, limbs and liver area.

Inhalation of oxygen. Intravenous or subcutaneous saline, glucose, if necessary – camphor, caffeine, strophanthin, lobeline, drip enema. If necessary – chlorpromazine, diphenhydramine, anticonvulsants, if indicated – lumbar puncture.

Pale hyperthermia (hyperthermia results from pathological excitation of the thermoregulation centers, hyperthermic syndrome.

The causes are severe infections or the introduction of large doses of adrenergic substances, or substances that cause sharp stimulation of the sympathetic nervous system.

This leads to stimulation of the sympathetic centers, the spasm of skin blood vessels and a sharp decrease of heat elimination and the increase of body temperature to 40 or more.

The reasons of hyperthermic syndrome can be different: functional impairments or structural damages of the hypothalamic centers of thermoregulation, brain tumors, brain traumas, brain hemorrhages, infections, complications of anesthesia in combination with muscle relaxants.

Anesthesia and muscle relaxants aggravate the defect of muscle cells membranes and increase the release of blood cellular enzymes. This leads to disruption of metabolism in muscle cells, stimulation of actin and myosin, persistent tonic contraction of muscles, decomposition of ATP into ADP, increase of K^+ and Ca^{++} ions in blood – sympathoadrenal crisis and *sympathoadrenal* hyperthermia develops.

The body temperature may reach 42-43 and there is:

1) general muscular rigidity;

2) spasm of peripheral vessels.

3) high blood pressure;

4) tachycardia;

5) shortness of breath;

6) hypoxia;

7) feeling of fear.

There also fast metabolic acidosis, hyperkalemia, anuria, increased blood creatinphosphokinase, aldolase, myoglobin.

Pathogenetic therapy aims at inhibition of sympathoadrenal mechanisms, reducing of heat production and increasing of heat transfer.

It's necessary to use: analgin, acetylsalicylic acid, which selectively reduce sensitivity of the hypothalamic thermoregulation center and enhance heat transfer through increased sweating.

Neuro-vegetative blockade is carried out: aminazine, droperidol. Antihistamines: diphenhydramine, promethazine. Ganglionic substances: pentamine, hygronium. Physical cooling, craniocerebral hypothermia. Mortality in this hyperthermia – up to 70 %.

Differences between fever and hyperthermia:

1) different etiological factors;

2) different manifestations of the stage of temperature rise – fever is characterized by chills and moderate stimulation of functions (1° rise of body temperature increases the heart rate by 8–10 beats per minute and 2–3 respiratory movements), hyperthermia – by sudden sweating, feeling of fever, sharp acceleration of pulse and respiratory rate (by 10–15 breaths in 1° rise of the body temperature);

3) while cooling the body in fever the temperature does not change, in hyperthermia it is reduced;

4) antipyretics reduce temperature in fever and are not effective in hyperthermia.

In fever the processes of oxidative phospholyration are activated, ATP synthesis is intensified and defense reactions are accelerated. In hyperthermia there is blockade of ATP synthesis and their decay, a lot of heat is produced.

Doctor's tactics in case of fever: to diagnose what it is: fever or hyperthermia. In case of hyperthermia extra cooling is necessary, in case of fever it's not necessary to administer antipyretics at once.

If fever is subfebrile or moderate and not accompanied by respiration and circulation disturbances, it's not necessary to decrease it, because it has a protective value.

If temperature is very high (39 and continues to grow causing disturbances of vital systems – the central nervous system – severe headache, insomnia, delirium, loss of consciousness), it is necessary to reduce it using antipyretics.

It should be noted that that an infection is often a combination of fever and hyperthermia, and in this case it is necessary to use antipyretics.

At a high temperature, especially in purulent infections, you should ventilate a ward very well and relieve the patient's condition.

Overheating in children. Unlike adults, newborns and children under one year of age are prone to overheating, because of peculiarities of their heat exchange and thermoregulation, which gradually improve.

In newborns reactions of chemical thermoregulation are well developed, reactions of physical thermoregulation are poorly represented, fever is poorly expressed and temperature increases are often associated with overheating.

Overheating of the body in infants is caused by the increase of air temperature and excessive wrap, in elder children – a long stay in a hot, stuffy room, in the sun, prolonged physical stress.

Staying of 6–7-year old children in a room with the air temperature of 29–31 and the wall temperature of 27–28 for 6–8 hours causes the increase of body temperature to 37.1–37.6 °C.

Solar overheating occurs with the predominance of primary disorders of the central nervous system and the increased body temperature has an important, though not primary, meaning.

Infants overheating is manifested by lethargy, sudden weakness, sleep disturbance, decreased appetite, regurgitation, in some cases, indigestion.

On examination – skin hyperemia, sweating, rapid breathing and pulse, muffled heart tones and reduced arterial pressure.

Elder children develop headache, dizziness, weakness, drowsiness, fatigue, lethargy, possible vomiting, cramps, temporary loss of consciousness.

TEST TASKS FOR THE LECTURE 10

Choose the correct answer

10.1. THE MAIN PATHOGENETIC MECHANISM OF PALE HYPERTHERMIA

1) impaired heat transfer by sweating
2) action of exo- and endopyrogens
3) increased heat generation and increased heat dissipation
4) pathological excitation of thermoregulation centers

10.2. THE LEADING LINK IN THE PATHOGENESIS OF HEAT STROKE

1) violation of glucose supply to the neurons of the respiratory center
2) poisoning of the body with toxic metabolic products
3) increase in the blood content of catecholamines, glucocorticoids
4) disorder of water-electrolyte balance

10.3. PATHOGENETIC MECHANISM OF MALIGNANT HYPERTHERMIA

1) genetically determined defect of synaptic membranes
2) hyperproduction of catecholamines
3) formation of leukopyrogens
4) violation of one of the physiological mechanisms of heat transfer

Write a detailed answer

Patient S., 30 years old, was taken to a medical center in serious condition. The skin and mucous membranes are cyanotic. Pulse 146 beats/min., weak filling. Blood pressure is 90/60 mm Hg. Breathing is rapid and shallow. Body temperature 40.6 °C. According to the accompanying persons, the victim, liquidating the accident, worked for 40 minutes at an air temperature of about 70 ° with and high humidity.

1. Is it advisable to prescribe antipyretic drugs to this patient? Why?
2. What pathological process caused the temperature rise?
3. What is the stage (phase) of the pathological process in the patient?

Lecture 11. PATHOPHYSIOLOGY OF WATER-SALT EXCHANGE. ACID-ALKALI BALANCE

Topics discussed in this lecture:

1. Pathology of water-salt metabolism.
2. Edema, its types, causes and pathogenesis
3. Pathophysiology of acid-alkali balance, classification of its disorders.
4. Causes, characteristics and pathogenesis of acidosis and alkalosis.

Water is the main component providing the constancy of the internal environment of the body. In an adult about 2/3 of water is in the intracellular sector and 1/3 – in the extracellular one.

The extracellular sector includes *intravascular* (blood plasma), *interstitial* ("organized" fluid of connective tissue) and *intercellular* (secretion of digestive glands, spinal and other) fluids.

The exchange of water and salts between plasma and the extracellular medium occurs in capillaries. Osmotic pressure in conditions of normal water-salt metabolism does not significantly matter.

Filtration is carried out due to the difference in the hydrostatic (35 millimeters of mercury) and oncotic (25 millimeters of mercury) pressure in the arterial end of the capillary.

In the venous end of the capillary, the hydrostatic pressure is 13 millimeters of mercury and, therefore, liquid moves to the venous part.

Violations of water-electrolyte balance (dyshidria). Dyshidria is divided into two groups: dehydration (water loss) and *hyperhydration* (water retention).

Depending on the prevalence of disorders in the cellular or extracellular space, there is *intracellular* and *extracellular* dyshidria.

According to the concentration of electrolytes in plasma we distinguish hypertonic, isotonic and hypotonic dyshidria.

Hypertonic dehydration is associated with lack of water and excess

salts in diseases of the gastrointestinal tract, vomiting, overheating, non-sugar diabetes.

Dehydration of cells develops, catabolic processes and cellular exsicosis increase. There are neurological disorders, the body temperature rises.

Isotonic dehydration occurs with the simultaneous loss of water and electrolytes in pathologies of the gastrointestinal tract (diarrhea, vomiting) and extensive burns.

There are circulatory disorders with blood pressure decrease up to hypovolemic shock, neurological disorders, dry skin and mucous membranes, soft eyeballs.

Hypotonic dehydration develops due to sodium deficiency in plasma (loss through the kidneys, skin, digestive tract).

High osmotic pressure inside the cell promotes water moving into the cell, causing its hyperhydration.

This redistribution of water leads to circulatory disorders – tachycardia, hypotension, dryness of mucous membranes, decrease in tissue turgor.

Hypertonic hyperhydration occurs in increased sodium reabsorption followed by water retention in tissues, in the introduction of large amounts of electrolytes, in cardiovascular failure.

Excess sodium in the extracellular space is accompanied by the development of edema and appearance of fluid in cavities.

Isotonic hyperhydration occurs when plasma and the extracellular space are filled with isotonic fluid, while the intracellular sector remains normal – in heart failure, pregnancy toxicosis.

Edema in isotonic hyperhydration appears when the concentration of protein in blood plasma begins to decrease.

Diluted plasma due to low oncotic pressure is not retained in the vascular bed and passes into the interstitial space.

Hypotonic hyperhydration occurs when the extracellular space is filled with fluid with low osmotic pressure in case of a long salt-free diet, increased excretion of Na +, circulatory insufficiency, hyperproduction of antidiuretic hormone.

As a consequence of decreasing plasma osmolality, water passes into cells and cellular hyperhydration develops – "*water poisoning*" of the body with marked neurological disorders, vomiting, convulsions, violation of consciousness up to coma.

Edema is retention of fluid in the organism, mostly in the intercellular space

Increase of the hydrostatic pressure in vessels, reduction of the oncotic pressure of blood plasma, increase of the permeability of the vascular wall and lymph flow disorders play a significant role in the pathogenesis of edema.

Several mechanisms can be involved in the formation of edema.

Cardiac or *congestive edema* is associated with a difficulty of blood outflow. As a result of increased venous pressure (hydrostatic factor), fluid from vessels more actively passes into the interstitial space, which is promoted by increased permeability due to development of hypoxia.

This mechanism is associated with increased permeability of the tubules of renal glomeruli and limited reabsorption of protein in them, renin production and formation of angiotensin-I and -II are increased, aldosterone production is stimulated, sodium reabsorption is intensified, ADH is intensively secreted, and water reabsorption in the distal sections of renal tubules increases.

The consequence of these processes is an increase in the mass of the circulating blood, the filtration pressure in vessels becomes higher and water reverts to the interstitial sector.

Renal edema is often associated with a decrease in glomerular filtration (acute glomerulonephritis). In nephrotic syndrome the permeability of glomeruli for protein increases, the oncotic plasma pressure falls and fluid moves to the interstitial space.

Hungry (cachectic) edema develops in protein deficiency, especially in chronic diseases of the stomach and intestines.

Hypovolemia develops and, as a compensatory reaction, reabsorption of sodium and water increases which exacerbates edema.

Inflammatory edema is associated with increased vascular permeability, high osmotic and oncotic pressure in tissues.

Acid-alkali (base) balance (ABB) is a relative constancy of the hydrogen index of the internal environment of the organism, caused by combined action of buffer and some physiological systems.

When the reaction of the medium changes, there is a change of physical-chemical characteristics of colloids of cells and intercellular structures – the degree of their dispersion, hydrophilicity, adsorption capacity, etc.

Normally, pH is between 7.37 and 7.44, and the level below 6.8 and above 7.8 is incompatible with life.

pH is kept constant by means of a complex of *buffer systems*:

1. Carbonate buffer system.
2. Phosphate buffer system.
3. Buffer system of blood proteins, primarily HB.

The highest buffer capacity of blood falls on hemoglobin (up to 75 %). Buffer systems are the most fast-reacting, they need up to 30 seconds to restore pH.

A significant role in maintaining the acid-base balance is played by homeostatic metabolic processes occurring in tissues, especially the kidneys, liver and muscles.

Organic acids are oxidized to form either volatile acids, or are converted to non-acidic substances. Inorganic acids can be neutralized by salts of K^+, Na^+, ammonia. Alkalis are neutralized mainly by lactic acid.

Violation of ABB occurs either in prolonged continuous action of moderate damaging factors, or short-term but strong effects.

In addition, violation of ABB can occur in primary damage of one or another link in the homeostatic system ensuring its permanence (kidney disease, lungs).

Violations of ABB are divided into:

1) acidosis – violation of ABB, which either increases the number of organic and inorganic acids, or decreases the number of bases;

2) alkalosis.

Types of acidosis:

1. Metabolic – occurs in accumulation of intermediate acid exchange products, such as ketone bodies. The concentration of ketone bodies in pathology can increase by hundreds of times.

Some ketone bodies are excreted by the kidneys in the form of Na^+ and K^+ salts, which can lead to large losses of alkaline ions and development of uncompensated acidosis.

Hypoxia and H-hyperionia cause an increase in vascular permeability with a tendency to edema development.

With a sharp increase in permeability in the renal tubules, there is suppression of filtration, oliguria develops, inadequate removal of potassium, sodium, chlorine and other electrolytes, increase in their concentration in blood and intercellular fluid.

The increase of osmotic pressure caused by potassium and other low-molecular substances causes dehydration of cells with a profound disturbance of oxidation-reduction processes, progression of acidosis and severe general intoxication.

Acidosis in severe liver damage (cirrhosis, toxic dystrophy), in cardiac decompensation and other forms of oxygen starvation.

2. Non-gas excretory acidosis occurs in decreased release of non-volatile acids and is observed in kidney diseases.

3. Gas acidosis is characterized by accumulation of carbonic acid in blood with the insufficient function of external respiration or a significant amount of CO_2 in the inspired air, that is, in all cases of hypercapnia.

An increase in pCO_2 in blood, regardless of the cause, entails hemodynamic disorders in the form of arteriolar spasm.

An increase in the tone of renal arterioles leads to a decrease in blood supply in renal tubules, stimulation of the renin-angiotensin-aldosterone system, and an increase in systemic vascular tone.

This creates increased resistance to the work of the heart. In contrast to peripheral vessels, brain vessels under the influence of increased pCO_2 expand, which is accompanied by an increase in the formation of cerebrospinal fluid and increased intracranial pressure.

Mixed forms of acidosis are also possible.

Moderate compensated acidosis occurs without significant clinical symptoms and is recognized when determining the pH of blood and urine. When acidosis develops, one of the first symptoms is rapid breathing.

Uncompensated acidosis is characterized by violations of the cardiovascular system and gastrointestinal tract, due to the fact that acidosis reduces the intensity of impulse of α- and β-adrenoreceptors of the heart, vessels and intestines, reduces the functional and metabolic action of catecholamines.

Acidosis leads to an increase in catecholamines in blood, which, at first, increases the cardiac activity, pulse, arterial pressure and vinute volume of the heart.

Then the activity of adrenoreceptors decreases and, in spite of a large content of catecholamines, cardiac activity is inhibited, arterial pressure falls, heart rhythm is broken (extrasystoles, up to ventricular defibrillation).

Acidosis enhances parasympathetic influence, causing bronchospasm, increased secretion of bronchial glands, vomiting, diarrhea. There are violations of the central nervous system – dizziness, drowsiness, possible loss of consciousness.

In acidosis in cells there is an increase in the intake of H^+ in exchange for K^+ and the concentration of K^+ in blood can serve as a sign of a "biochemical trauma".

Alkalosis is divided into:

1. Non-gas alkalosis, which occurs when large doses of alkaline preparations are administered, when large amounts of bicarbonate are introduced, when chlorine is lost by the body – hypochloric alkalosis, in case of K^+ deficiency – hypokalemic alkalosis, vomiting, intestinal fistulas, pregnancy toxicosis, steroid hormone excess, in kidney disease.

Compensatory mechanisms, that develop in alkalosis, are mainly in reducing the excitability of the respiratory center due to increase in pH, as well as in mobilization of renal mechanisms.

The effectiveness of buffer systems of blood in alkalosis is less than in acidosis. A decrease in the minute volume of breathing leads to a compensatory increase in pCO_2 in blood, which causes formation of a large amount of carbonic acid, which is the source of H^+ ions.

2. Gas alkalosis, resulting from hyperventilation in altitude sickness, hysteria, brain damage (trauma, swelling), in hyperthermia.

Symptoms of alkalosis are weakening of the respiratory function, exacerbation of neuromuscular excitability, which can lead to tetany.

This is due to a decrease in the content of Ca^{++} in plasma, (similar to the insufficiency of parathyroid hormone). Simultaneously, the amount of CL in plasma increases, the amount of ammonia in urine decreases (inhibition of ammoniogenesis), and urine pH moves to the alkaline side (the result of enhanced elimination of bicarbonates).

Alkalosis increases excitability of β-adrenergic receptors in the heart, intestinal vessels, bronchi, reducing parasympathetic effects. This leads to tachycardia, constipation, increased blood pressure.

The pathological effects of gas alkalosis include an increase in the tone of brain and heart vessels and a decrease in the tone of peripheral vessels, which lead to hypotension up to collapse.

There are mixed forms of alkalosis. Combined acid-base balance disturbances can also occur. For example, in artificial ventilation during anesthesia, gas alkalosis (increased release of CO_2) and metabolic acidosis (disruption of oxyhemoglobin dissociation, including alkalosis) can occur. Such violations can also occur in altitude sickness. Thus, acid-alkaline homeostasis (one of the most important components of homeostasis) can be compensated for a long time, but with a decrease in protective mechanisms a violation of pH most often leads to irreversible changes.

TEST TASKS FOR THE LECTURE 11

Choose the correct answer

11.1. TYPES OF DYSHYDRIA
1) hypertonic
2) atonic
3) antitonic
4) isotonic
5) hypotonic

11.2. TYPES OF EDEMA
1) cardiac
2) renal
3) hepatic
4) inflammatory

11.3. TYPES OF BUFFER SYSTEMS
1) carbonate
2) sodium
3) phosphate
4) phosphoric
5) blood proteins

Lecture 12. HYPOXIA

Topics discussed in this lecture:

1. Classification and characteristics of certain types of hypoxia.
2. Adaptive and compensatory responses in hypoxia.
3. Diagnosis, therapy and prevention of hypoxia.

Hypoxia is a disruption of oxidative processes in tissues. It occurs in case of insufficient oxygen supply or violation of its utilization in the process of biological oxidation (oxygen deficiency).

Depending on the etiological factor, rate of rise and duration of the hypoxic condition, the degree of hypoxia, reactivity, etc. hypoxia manifestation can vary a lot.

Changes occurring in the body are a combination of:

1) direct effects of hypoxic factors;

2) secondary violations;

3) developing compensatory and adaptive reactions. These phenomena are closely related and sometimes don't differ.

Classification of basic types of hypoxia:

1) hypoxic;

2) respiratory;

3) blood;

4) circulatory;

5) tissue;

6) hyperbaric;

7) hyperoxic;

8) stress hypoxia;

9) mixed – a combination of different types of hypoxia.

Classification of hypoxia according to its severity:

1) hidden (revealed only on exertion);

2) compensated (tissue hypoxia doesn't occur at rest due to straining of oxygen delivery systems);

3) expressed – with decompensation phenomena (lack of oxygen in tissues at rest);

4) uncompensated – marked metabolic disturbances with symptoms of poisoning;

5) terminal – irreversible.

According to the rate of development and duration there is:

1) peracute form – within a few tens of seconds;

2) acute – a few minutes or tens of minutes (acute heart failure);

3) subacute – several hours;

4) chronic – weeks, months, years.

Hypoxic hypoxia is an exogenous type of hypoxia. It develops with decreasing barometric pressure of oxygen (altitude sickness) or reducing of partial pressure of oxygen in the inhaled air.

At the same time there is hypoxemia (decreased PO2 in arterial blood), haemoglobin (Hb) oxygenation and total oxygen content in blood stream.

Hypocapnia developing due to compensatory hyperventilation of the lungs produces a negative influence, too.

Hypocapnia leads to a poor blood supply of the brain and heart, alkalosis, electrolyte disturbance in the internal environment of the body and raising consumption of oxygen by tissues.

Respiratory (pulmonary) type of hypoxia occurs as a result of insufficient gas exchange in the lungs due to alveolar hypoventilation, violations of ventilation-perfusion relations, or difficulty of oxygen diffusion, violation of patency of the respiratory tract, or disorders of the central regulation of breathing.

The minute ventilation volume reduces, the partial pressure of oxygen in alveolar air and oxygen tension in blood decrease. Hypercapnia joins hypoxia.

Blood hypoxia (hemic type) occurs as a result of reduction of oxygen capacity of blood in anemias, polyplasmia and violation of Hb ability to bind, transport and give oxygen to tissues during carbon monoxide poisoning, formation of methemoglobin (MetHb) and some Hb abnormalities.

Hemic hypoxia is characterized by the combination of normal oxygen tension in arterial blood and its low content in severe cases up to 4–5 %.

In case of carboxyhemoglobin (COHb) and methemoglobin (МетHb) formation oxygenation of the remaining Hb and dissociation of oxyHb in tissues can be difficult.

Oxygen tension in tissues and venous blood as well as arteriovenous difference of oxygen are significantly reduced.

Circulatory hypoxia (cardiovascular type) occurs in disorders of blood circulation that lead to insufficient blood supply of organs and tissues with a massive blood loss, hypohydration, decreased cardiovascular activity.

Circulatory hypoxia of vascular origin develops in excessive increase of the vascular bed capacity due to reflex and centrogenic disorders of vasomotor regulation, deficiency of glucocorticoids, increase in blood viscosity and presence of other factors preventing normal blood flow through the capillary net.

Gas composition of blood is characterized by normal tension and content of oxygen in arterial blood, its reducing in venous blood and a significant arterio-venous difference of oxygen.

Tissue hypoxia (histotoxic) occurs due to the violation of tissue ability to absorb oxygen from blood or due to reduction of the efficiency of biological oxidation because of a sharp decrease in the conjugation of oxidation and phosphorylation in inhibition of biological oxidation by various inhibitors.

As well as due to disrupting of enzyme synthesis or damage of membrane structures of cells by poisoning with cyanides, heavy metals, barbiturates, germ toxins.

The tension, saturation and content of oxygen in arterial blood can stay normal up to a certain point but in venous blood these values greatly exceed.

A decrease in the arteriovenous difference of oxygen is characteristic for a violation of tissue respiration.

Hyperbaric hypoxia can occur in oxygen-treatment under high pressure.

Elimination of normal hypoxic activity of peripheral chemoreceptors leads to decreased excitability of the respiratory centre and

depression of pulmonary ventilation. This leads to increased arterial pCO_2 which causes dilation of brain blood vessels. Hypercapnia leads to an increased minute volume of breathing and hyperventilation.

As a result, CO_2 pressure falls in arterial blood, brain vessels constrict and pO_2 in brain tissue reduces.

The initial toxic effect of oxygen to cells is associated with inhibition of respiratory enzymes and accumulation of lipid peroxides that cause damage of cellular structures (especially SH enzyme groups), changes of metabolism in the tricarboxylic acid cycle and disruption of synthesis of high energy phosphate compounds and formation of free radicals.

Hyperoxic hypoxia (aviation, oxygen therapy) can exist in two forms of oxygen toxicity – pulmonary and convulsive.

The pathogenesis of the pulmonary form is associated with the disappearance of the basic function of inert gas, toxic effect of oxygen on vascular endothelium of the lungs (increase of permeability, surfactante leaching, alveoli decrease and atelectasis and pulmonary edema development).

Convulsive form is connected with sharp excitation of all parts of the CNS (especially the brain stem) and violation of tissue respiration.

Mixed type of hypoxia is observed very often, it is a combination of two or more major types of hypoxia. Often the hypoxic factor affects several parts of physiological systems of oxygen transport and utilization.

Carbon monoxide actively gets into communication with Fe^{2+} of Hb. Its high concentrations produce a direct toxic effect on cells by inhibiting the cytochromenzyme system.

Barbiturates inhibit oxidative processes in tissues and inhibit the respiratory centre causing hypoventilation.

Primarily metabolism changes occur in carbohydrate and energy metabolism. In all cases of hypoxia the primary shift is energy deficit.

Glycolysis enhances, this leads to a decrease of glycogen content,

but increase of pyruvate and lactate. Excess of lactic, pyruvic and other organic acids contributes to the development of metabolic acidosis.

There is a negative nitrogen balance. As a result of lipid metabolism disorders hyperketonemia develops.

Electrolyte exchange is disturbed, processes of active movement and distribution of ions in biological membranes are the first to be disturbed, the amount of extracellular potassium increases.

The sequence of changes in cell during hypoxia:

– increased permeability of cell membrane;
– disturbance of ion balance;
– swelling of mitochondria;
– stimulation of glycolysis;
– reduction of glycogen;
– inhibition of synthesis and increased protein breakdown;
– destruction of mitochondria;
– ergastoplasm, intracellular net machine;
– fat decomposition of cells;
– destruction of lysosome membranes;
– release of hydrolytic enzymes;
– autolysis and complete disintegration of cells.

Adaptive and compensatory reactions. Under the influence of factors, causing hypoxia, reactions aimed at preserving homeostasis are immediately involved.

There are reactions that are aimed at adaptation to relatively short-term acute hypoxia (occur immediately) and reactions proving adaptation to less intense but long-term or recurring hypoxia.

Respiratory system reactions to hypoxia are an increase of alveolar ventilation due to deepening and increasing of frequency of respiratory excursions and mobilization of reserve alveoli. The ventilation increase is accompanied by an increased pulmonary blood flow.

Compensatory hyperventilation can cause hypocapnia, which is compensated by exchange of ions between plasma and erythrocytes, increased excretion of bicarbonates and basic phosphates with urine.

Reactions of the circulatory system are expressed by an increased heart rate, increase of the circulating blood mass due to depletion of the blood pool, increase of venous flow, strike and minute heart volume, speed of blood flow and redistribution of blood in favor of the brain and heart.

During adaptation to prolonged hypoxia the formation of new capillaries can occur. In connection with heart hyperfunction and changes in neuro-endocrine regulation cardiac hypertrophy with compensatory-adaptive character may occur.

Reactions of the blood system are manifested by an increased blood oxygen capacity due to the increased wash-out of erythrocytes from the bone marrow and activation of erythropoiesis due to the increased formation of erythropoietic factors.

The properties of Hb to bind the almost normal amount of oxygen even with a significant reduction in the partial pressure of oxygen in alveolar air and blood in pulmonary capillaries mean a lot.

However, Hb is able to give more oxygen even with a moderate decrease of pO_2 in tissue fluid. Acidosis contributes to increased dissociation of oxyhemoglobin.

Tissue adaptive mechanisms are limitation of the functional activity of organs and tissues that are not directly involved in providing air transportation, increase of conjugation of oxidation and phosphorylation, increased anaerobic ATP synthesis due to activation of glycolysis.

There is an increase of synthesis of glucocorticoids which stabilize lysosome membranes, activate enzyme systems of the respiratory chain. The number of mitochondria per a mass unit of the cell increases, too.

The principles of diagnosis. The diagnosis is based on:

– the symptoms of brain damage and the dynamics of neurological disorders;

– data of hemodynamic study (A/E, ECG, cardiac output);

– assessment of gas exchange;

– detection of oxygen in the inspired air;

– the content of gases in alveoli;

– gas diffusion through the membrane of alveoli;

– assessment of oxygen transport with blood;

– detection of pO_2 in blood and tissues;

– detection of acid-base balance, buffer properties of blood;

– biochemical indicators (lactic and pyruvic acid, sugar and blood in urea).

Therapy and prevention. Due to the fact that in clinical practice usually there are mixed forms of hypoxia, treatment should be comprehensive and related to the cause of hypoxia in each case. Hyperbaric oxygenation is a versatile technique in all cases of hypoxia (respiratory, blood, circulatory). You need to break vicious circles of ischemia, congestive heart failure.

Under the pressure of three atmospheres a sufficient amount of oxygen (six volume %) dissolves in plasma even without participation of red blood cells. In some cases, it may be necessary to add 3–7 % of CO_2 for breathing centre stimulation, expanding of vessels of the brain and heart, prevention of hypocapnia.

In case of circulatory hypoxia, cardiac and hypertension medicines as well as blood transfusion are prescribed.

In case of hemic type it is necessary to:

– transfuse blood or erythromass, stimulate haematopoiesis, use artificial oxygen carriers – perftoran;

– remove products of metabolism (hemosortion, plasmapheresis);

– suppress osmotic swelling – solutions with osmotic substances;

– in ischemia – antioxidants, stabilizers of membranes, steroid hormones;

– inject substrates that replace the function of cytochromes – methylene blue, vitamin C;

– increase tissue energy supply – glucose.

TEST TASKS FOR THE LECTURE 12

Choose the correct answer

12.1. PATHOLOGICAL CHANGES IN THE METABOLISM OF FATS CAN OCCUR

1) at violation of the processes of digestion and absorption of fats
2) insufficient production of hormones that promote catabolism of carbohydrates: STH, thyroxine, adrenaline, glucocorticoids and others
3) in violation of fat oxidation in tissues
4) kidney pathology

12.2. CAUSES OF KETOSIS

1) deficiency of carbohydrates in the body
2) renal pathology
3) liver damage
4) deficiency of vit. E
5) chronic inflammatory processes

12.3. FORMS OF DYSPROTEINEMIA

1) hypoxia
2) hyperproteinemia
3) aproteinemia
4) hypovolemia
5) hypoproteinemia
6) liver cirrhosis

Write a detailed answer

Determine the type of hypoxia if the content of oxyhemoglobin in arterial blood is 86 %, in venous blood-32 %, the minute volume of the heart is 1.5 liters, and the oxygen capacity of the blood is 23 vol. %. Justify your conclusion.

Lecture 13. METABOLISM

Topics discussed in this lecture:

1. Causes and pathogenesis of protein metabolism disorders.
2. Causes and pathogenesis of carbohydrate metabolism disturbances.
3. Pathogenesis of diabetes mellitus.
4. Causes and pathogenesis of fat metabolism disorders.

Metabolic disorders are the basis of all functional and organic damages to organs and tissues leading to the onset of a disease.

One of the most common causes of general protein metabolism disorders is quantitative or qualitative protein deficiency of primary (exogenous) origin.

13.1. Pathophysiology of protein metabolism

Disturbances of cleavage and absorption of proteins. The main causes of inadequate protein breakdown are a quantitative decrease in the secretion of salt acid and enzymes, decrease in the activity of proteolytic enzymes (pepsin, trypsin, chymotrypsin) and the associated insufficient formation of amino acids, decrease in the time of their action (acceleration of peristalsis).

Insufficient digestion of protein in the upper sections of the gastrointestinal tract is accompanied by an increase in the transfer of products of its incomplete cleavage into the large intestine and intensification of the process of bacterial cleavage of amino acids.

Delay in the intake of amino-acids in organs and tissues. Since a number of amino acids are the starting material for the formation of biogenic amines, their retention in blood creates conditions for accumulation of corresponding proteinogenic amines in tissues and blood and manifestation of their pathogenic effects on various organs and systems. Increased blood levels of tyrosine contribute to accumulation of tyramine, which is involved in the pathogenesis of

malignant hypertension. An increase in the content of amino acids in blood is manifested by an increase in their excretion in urine and the formation of a specific form of metabolic disorders – aminoaciduria.

Violation of protein synthesis. Synthesis of protein structures in the body is the central link of protein metabolism. The absence of at least one of 20 essential amino acids in cells stops protein synthesis as a whole.

Disorders of protein biosynthesis can be *qualitative and quantitative*. Quantitative changes in biosynthesis of organ and blood proteins are of a particular interest. They lead to a shift in the ratios of individual fractions of proteins in blood serum – dysproteinemia.

There are two forms of dysproteinemia: *hyperproteinemia* (increase in the content of all or certain types of proteins) and *hypoproteinemia* (decrease in the content of all or individual proteins). Thus, a number of liver diseases (cirrhosis, hepatitis) and kidneys (nephritis, nephrosis) is accompanied by a pronounced decrease in albumin content.

Infectious diseases, accompanied by extensive inflammatory processes, lead to an increase in the content of gamma globulins. The development of disproteinemia is accompanied, as a rule, by serious shifts in body homeostasis (violation of oncotic pressure, water exchange).

A significant reduction in proteins synthesis, especially albumins and gamma globulins, leads to a sharp decrease of body resistance to infection, a decrease of immunological resistance. With damage to the liver and kidneys, in case of some acute and chronic inflammatory processes (rheumatism, infectious myocardium, pneumonia) the body begins to synthesize special proteins with altered or abnormal properties.

Pathology of interstitial protein metabolism (impaired metabolism of amino acids). The central place in the interchange of proteins is taken by *reamination* reaction, as the main source of formation of new amino acids.

Transamination violation can occur as a result of deficiency of vitamin B_6 in the body. This is explained by the fact that the phosphorylated form of vitamin B_6 (phosphopyroxoxal) is an active group of transaminase-specific transamination enzymes between amino and keto acids. The reason for a decreased activity of transamination can be the inhibition of transaminase activity due to a violation of the synthesis of these enzymes (with protein starvation), or a disturbance in the regulation of their activity by a number of hormones.

The processes of amino acid transamination are closely related to the processes of *oxidative deamination*, during which enzymatic cleavage of ammonia from amino acids is carried out. Deamination is determined as both the formation of final products of protein metabolism, and the entry of amino acids into energy metabolism. Weakening of deamination may occur due to a disturbance of oxidative processes in tissues (hypoxia, hypovitaminosis C, PP, B-2).

The sharpest violation of deamination occurs when the activity of aminoxidases decreases, either due to weakening of their synthesis (diffuse liver damage, protein deficiency), or as a result of their relative activity insufficiency (an increase in the content of free amino acids in blood).

Interstitial exchange of a number of amino acids is accomplished not only in the form of transamination and oxidative deamination, but also by *decarboxylation* (loss of CO_2 from the carboxyl group) with formation of the corresponding amines, called "biogenic amines" (in decarboxylation of histidine – Histamine, tyrosine-tyramine, 5-hydroxy-sitriptophan-serotonin).

Change in the rate of protein breakdown. A significant increase in the rate of breakdown of tissue and blood proteins is observed with an increase of body temperature, extensive inflammatory processes, severe trauma, hypoxia, malignant tumors, etc. This is due to either the action of bacterial toxins (in case of infection), or a significant increase in the activity of proteolytic enzymes of blood (in hypoxia), or the toxic effect of products of tissue decay (in trauma).

In most cases, acceleration of protein breakdown is accompanied by the development of a negative nitrogen balance in the body in connection with the predominance of processes of protein breakdown over their biosynthesis.

Pathology of the final stage of protein metabolism. The main final products of protein metabolism are ammonia and urea. The pathology of the final stage of protein metabolism can be manifested by a violation of the formation of final products, or excretion. The main mechanism of *ammonia binding* is the process of urea formation in the citrulline-arginine-ornithine cycle. Disorders of urea formation can occur as a result of a decrease in the activity of enzyme systems involved in this process (hepatitis, cirrhosis), total protein deficiency.

When urea formation is disturbed, ammonia accumulates in blood and tissues and the concentration of free amino acids increases, which is accompanied by the development of hyperaemia and pronounced ammonia intoxication (with impairment of the functions of the central nervous system).

Another final product of protein metabolism is *creatinine*. In case of fasting, vitamin E deficiency, febrile infectious diseases, thyrotoxicosis and a number of other diseases, creatinuria indicates a violation of creatine metabolism.

13.2. Pathophysiology of carbohydrate metabolism

Disturbance of carbohydrate metabolism can be caused by a violation of their digestion and absorption in the digestive tract. If the production of amylolytic enzymes is inadequate, di- and polysaccharides entering from food do not split up to monosaccharides and are not absorbed. Absorption of glucose is affected by the violation of its phosphorylation in the intestinal wall.

Disturbance of synthesis and cleavage of glycogen. Pathological increase in decomposition of glycogen occurs with strong excitation of the central nervous system, an increase in the activity

of hormones stimulating glycogenolysis (STH, adrenaline, glucagon, thyroxine). Increase in the breakdown of glycogen with simultaneous increase in muscle glucose consumption occurs with severe muscular load. Synthesis of glycogen can change toward decreasing or pathological amplification.

Reduction of glycogen synthesis occurs with severe damage to hepatic cells (hepatitis, poisoning with hepatic poisons), when their glycogen-forming function is disrupted, and in hypoxia, as in the conditions of hypoxia formation of ATP necessary for glycogen synthesis decreases.

Hyperglycemia – increased blood sugar levels. It can develop under physiological conditions, has an adaptive value – it ensures the delivery of energy material to tissues.

Depending on the etiological factor the following types of hyperglycemia are distinguished:

1) alimentary hyperglycemia, which develops after the intake of a large number of easily assimilated carbohydrates (sugar, sweets, flour products, etc.);

2) neurogenic (emotional) hyperglycemia – with emotional arousal, stress, pain, ether anesthesia;

3) hormonal hyperglycemia accompanies dysfunctions of the endocrine glands, hormones of which are involved in the regulation of carbohydrate metabolism.

Hyperglycemia in insulin deficiency is the most pronounced and persistent. It can be pancreatic (absolute) and extra-pancreatic (relative).

Pancreatic insulin deficiency develops when the insular pancreas apparatus is destroyed or damaged. The insular apparatus is overstrained and can be depleted by excessive and frequent consumption of digestible carbohydrates.

Extrapancreatic insufficiency of insulin. It can be caused by excessive connection of insulin with carrying blood proteins. Insulin, associated with protein, is active only in relation to fatty tissue. It

provides the transition of glucose to fat, inhibits lipolysis. The so-called obese diabetes develops.

With diabetes all types of metabolism are violated.

Violations of carbohydrate metabolism determine a characteristic symptom of diabetes – persistent expressed hyperglycemia. It is caused by the following features of carbohydrate metabolism in case of diabetes: decreased passage of glucose through cell membranes and its assimilation by tissues; slowing of glycogen synthesis and acceleration of its decomposition; increased gluconeogenesis – formation of glucose from lactate, pyruvate, amino acids and other products of non-carbohydrate metabolism; Inhibition of the transition of glucose to fat.

The importance of hyperglycemia in the pathogenesis of diabetes is twofold. It plays a certain adaptive role, since it inhibits the decomposition of glycogen and partly increases its synthesis. Glucose easily penetrates into tissues, and they do not experience a sharp lack of carbohydrates. Hyperglycemia also has a negative significance. With it, the intake of glucose into the cells of insulin-independent tissues is sharply increased (lens, liver cells, Langerhans islets β cells, neural tissue, erythrocytes, aortic wall).

In hyperglycemia, the concentration of gluco- and mucoproteins, which easily fall out in the connective tissue, promote the formation of hyaline, increases.

With hyperglycemia exceeding 8 mmol/l, glucose begins to pass into the final urine – glucosuria develops. This is a manifestation of decompensation of carbohydrate metabolism. In diabetes, the processes of phosphorylation and dephosphorylation of glucose in tubules cannot cope with excess glucose in the primary urine. The activity of hexokinase is reduced, so the renal threshold for glucose decreases compared to normal. Glycosuria develops.

In severe forms of diabetes mellitus, the sugar content in urine can reach 8–10 %. The osmotic pressure of urine increases, and therefore a lot of water passes into the final urine. During a day 5–10 liters and more of urine (polyuria) with a high relative density due to sugar

is excreted. As a result of polyuria, dehydration of the organism develops, and as a consequence – increased thirst (polydipsia). With a very high level of sugar in blood (30–50 mol/l and higher), the osmotic pressure of blood sharply increases. As a result, dehydration of the body occurs. Hyperosmolar coma may develop. The condition of such patients is extremely serious. They are unconscious. The signs of tissue dehydration are sharply expressed (eyeballs on palpation are soft).

As a result of dehydration, there is renal damage, their function is violated up to the development of renal failure.

Disturbances of *fat metabolism*. In insulin deficiency there is a decrease of glucose entrance to adipose tissue and the formation of fat from carbohydrates.

Resynthesis of triglycerides from fatty acids is reduced, ketone bodies are formed – acetone, acetoacetic and β-hydroxybutyric acid. They are similar in structure and are capable of interconversion. Normally, serum contains 0.1–0.6 mol/l ketone bodies. The accumulation of ketone bodies in diabetes mellitus occurs in connection with an increased transfer of fatty acids from the depot to the liver and accelerated oxidation of them to ketone bodies; delay in resynthesis of fatty acids due to the lack of NADP; violation of oxidation of fatty acids in Krebs cycle.

In diabetes, the concentration of ketone bodies increases by many times, they have a toxic effect. Hyperketonemia is decompensation of metabolic disorders in diabetes mellitus. Ketone bodies in high concentration inactivate insulin, aggravating the phenomena of insulin deficiency. A vicious circle is being created.

The highest one is the concentration of acetone. It damages cells, dissolving their structural lipids. Ketone bodies cause cell poisoning, inhibition of enzymes. The activity of the central nervous system is sharply depressed. With diabetes, cholesterol metabolism is impaired. The excess of acetoacetic acid goes to the formation of cholesterol – hypercholesterolemia develops.

Violations of *protein metabolism*. Synthesis of protein in diabetes mellitus is reduced, as it sharply decreases the stimulating effect of insulin on the enzyme systems of this synthesis. The level of energy metabolism that provides protein synthesis in the liver decreases; passing of amino acids through cell membranes is disturbed. With insulin deficiency, the brake from the key enzymes of gluconeogenesis is removed and intensive formation of glucose from amino acids and fat takes place – amino acids are consumed for gluconeogenesis.

Thus, in diabetes mellitus, protein breakdown predominates over its synthesis. As a result, plastic processes are suppressed, wound healing worsens, antibody production decreases, and the body's resistance to infections decreases. Children grow and develop slowly. There are also qualitative changes in protein synthesis. In blood there are altered, unusual proteins – paraproteins. They are associated with damage to the vessel wall (angiopathy), including retinal vessels (retinopathy).

13.3. Pathophysiology of fat metabolism

Pathological changes in the metabolism of fats can occur at various stages: in disturbed processes of digestion and absorption of fats; disturbed transport of fat and its transfer to tissues; disturbed oxidation of fats in tissues; violated intermediate fat metabolism; violated fat metabolism in adipose tissue (excessive or insufficient formation and deposition).

Violation of the process of digestion and absorption of fats is observed:

1) with lack of pancreatic lipase;

2) with deficiency of bile acids;

3) with increased peristalsis of the small intestine and lesions of small intestine epithelium by infectious and toxic agents;

4) with an excess of calcium and magnesium in food, when water-insoluble salts of bile acids – soaps are formed;

5) with avitaminosis A and B, lack of choline, as well as in case

of violated phosphorylation process (inhibition of fat absorption).

As a consequence of malabsorption of fat, steatorrhoea develops (feces contain many higher fatty acids and unsplit fat). Together with fat calcium is lost.

Violation of the intermediate fat metabolism leads to ketosis, which manifests itself in an increase in the level of ketone bodies in blood (ketonemia) and the release of them in increased amounts with urine (ketonuria).

Causes of ketosis:

1) deficiency of carbohydrates in the body;

2) stress;

3) when the liver is damaged by toxic infectious factors its ability to synthesize and store glycogen is disrupted, there is an increased entering of NEFA to the liver and the development of ketosis;

4) deficiency of vitamin E, which slows down oxidation of higher fatty acids;

5) suppression of oxidation of ketone bodies in Krebs cycle;

6) disruption of resynthesis of ketone bodies into higher fatty acids with insufficient hydrogen sources.

Pronounced ketosis leads to intoxication of the body (CNS), the electrolyte balance is disturbed due to the loss of sodium with urine (sodium forms salts with acetoacetic and β-hydroxybutyric acids). Acidosis develops; a decrease in sodium content in blood can cause secondary aldosteronism. All this characterizes the diabetic coma.

Disturbance of fat metabolism in adipose tissue. Obesity is the body's tendency to excessive weight gain under the influence of certain conditions. In this case, body weight increases due to abnormal accumulation of fat in the depot.

According to etiology obesity manifests in three types: alimentary, hormonal, cerebral. The essential role of heredity in the pathogenesis of obesity is proved.

Obesity develops as a result of the following three main pathogenetic factors:

1) increased intake of food (carbohydrates, fats) with inadequate energy intake of fat;

2) Insufficient use (mobilization) of fat depots as a source of energy;

3) excessive formation of fat from carbohydrates.

The *effects of obesity*:

1) violation of glucose tolerance;

2) hyperlipemia;

3) hyperinsulinemia;

4) increased excretion of glucocorticoids with urine;

5) after physical exertion, during sleep, after administration of arginine, there are fewer fluctuations in the concentration of chondrotropic hormone (CTH) in plasma;

6) decreased sensitivity of increased adipocytes and musculature to insulin;

7) increased content of non-esterified fatty acids (NEFA) in blood – increased intake of them by muscles;

8) hypertrophied lipocytes react more strongly to norepinephrine and other Patients with obesity often develop cardiovascular diseases, hypertension, cholelithiasis (in obesity bile is lithogenic, i.e. contains few detergents dissolving cholesterol esters).

Obese people do not tolerate anesthesia and surgical interventions. Thromboembolism often occurs as a postoperative complication. One of the most terrible complications of obesity is diabetes. With obesity, the possibility of cirrhosis development increases. Women suffering from obesity are more likely to develop endometrial cancer, Their fatty tissue has a greater ability to metabolize androstenedione into estrone. With obesity, dyspnea is observed, because massive subcutaneous fat deposits limit movements of the chest, the accumulation of fat in the abdominal cavity prevents the descent of the diaphragm. Oxygen need is increased, but gas exchange is difficult, relative pulmonary insufficiency increases, frequent surface breathing develops.

Excessive feeding of a child during the first year of life contrib-

utes to the development of hyperplastic (multicellular) obesity (abnormal increase in the number of fat cells). This obesity has a poor prognosis with regard to weight reduction. It is constantly combined with hypertrophy and is observed with obesity of a high degree.

Obesity, which develops in older children, is hypertrophic (increased volume of fat cells). It is usually the result of overeating. With normal (corresponding to energy expenditure) function of the food center, the reason for obesity may be insufficient use of fat from fat stores as an energy source.

This can occur with a decrease in the sympathetic tone and an increase in the tone of the parasympathetic nervous system, with the inhibitory effect of the cerebral cortex on the centers of the sympathetic part of the diencephalic region. The phenomena of interstitial neuritis are found in the nerve branches of adipose tissue.

TEST TASKS FOR THE LECTURE 13

Choose the correct answer

13.1. PROTEIN DEFICIENCY MAY BE DUE TO

1) stress

2) impaired breakdown and absorption of proteins in the GI tract,

3) liver damage

4) slowing of amino acids in organs and tissues

5) infectious diseases

13.2. CAUSES OF EXTRAPANCREATIC INSULIN INSUFFICIENCY

1) liver pathology

2) increased insulinase activity due to excess somatotropic hormone and glucocorticoids

3) chronic inflammatory processes

4) chronic kidney disease

ANSWER STANDARDS

Answers to tests

1.1	3	**7.5**	1
1.2	5	**7.6**	2
1.3	4	**8.1**	4
2.1	3	**8.2**	1
2.2	2	**8.3**	2
2.3	5	**8.4**	4
3.1	3	**8.5**	1
3.2	2	**8.6**	1
3.3	2	**9.1**	4
4.1	2	**9.2**	4
4.2	2	**9.3**	4
4.3	1	**10.1**	4
5.1	3	**10.2**	4
5.2	2	**10.3**	1
5.3	4	**11.1**	1, 2
6.1	2	**11.2**	1, 4
6.2	3	**11.3**	1, 2
6.3	4	**12.1**	1, 3
7.1	5	**12.2**	1, 3
7.2	4	**12.3**	2, 5
7.3	2	**13.1**	2, 4
7.4	4	**13.2**	2

Answers to situational tasks

Situational task No. 1 (Lecture 2)

The mechanism of origin of VDD symptomsis based on circulatory disorders caused by the appearance of gas bubbles in the blood and tissues, which passes from a dissolved to a gaseous state when the external pressure decreases.

Situational task No. 2 (Lecture 4)

1. The patient has impaired adrenal function, as the examination revealed bilateral hypertrophy of these glands and an increased level of ACTH (adrenocorticotropic hormone).

2. The disease that corresponds to the described symptoms is called Cushing's disease – syndrome) hyperfunction of the adrenal cortex associated with hypersecretion of ACTH.

Situational task No. 3 (Lecture 7)

1. The child has developed serum sickness.

2. Serum sickness refers to immediate hypersensitivity (type III allergic reactions according to Gell & Cooms).

3. The immune complex type of reactions is associated with the deposition of immune complexes formed in the vascular bed in the vascular wall and paravasally.

4. Complement, which is fixed on immune complexes deposited in the vascular wall and activated by the classical pathway.

Situational task No. 4 (Lecture 9)

An inflamed rabbit ear will be more brightly colored in blue than a healthyone, since inflammation increases vascular permeability, which contributes to a more intense spread of the dye in the focus of inflammation.

Situational task No. 5 (Lecture 10)

It is not advisable, since hyperthermia is caused by a "breakdown" of thermoregulation mechanisms, hyperthermia is not associated with the production of pyrogenic substances.

An increase in temperature is associated with a "breakdown" of thermoregulation mechanisms. Stage I (stage of decompensation).

Situational task No. 6 (Lecture 12)

Hypoxia is mixed: respiratory and circulatory. A decrease in the content of oxyhemoglobin in arterial blood indicates a violation оксигенацииof its oxygenation in the lungs, i.e., the presence of respiratory hypoxia. However, a significant decrease in MOS indicates a hemodynamic disorder and is characteristic of circulatory hypoxia.

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Education edition

A COURSE OF LECTURES ON PATHOPHYSIOLOGY FOR FOREIGN MEDICAL STUDENTS

In two parts

Part 1

Manual

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Signed for use 10.07.2026.
Circulation 50 copies.

Publication Activity Center
FSBEI HE Academician Ye.A. Vagner PSMU MOH Russia
27 Petropavlovskaya St., Perm, 614990

Minimum system requirements:
PC, Intel(R) Celeron(R) processor or higher, frequency 2.80 GHz;
Super VGA monitor with resolution. 1280×1024 display 256 or more colors;
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CD drive; keyboard, mouse