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This manual includes 29 lesson-manuals for practical classes on pathological physiology. The methods of carrying out experiments in the practicals, questions and modern bibliography on general and specific courses of pathological physiology are given in this manual. It is intended for students of medical institutes of higher education.

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PART: INTRODUCTION. PATHOPHYSIOLOGY AS FUNDAMENTAL AND INTEGRATIVE SCIENCE AND EDUCATIONAL SUBJECT

Theme: Modeling of pathologic processes.

Objective of class: To study the objectives of pathophysiology, its logical structure and peculiarities of experimental method in research of mechanisms of pathological processes and disease development.

The **subject** of pathophysiology is a disease; its **method** is a pathophysiological experiment. Many sciences (physiology, pharmacology) use the experiment, but pathophysiology has a special experiment with modeling of a disease on an animal. Pathophysiology studies mechanisms of the development of a disease and applies the obtained data to clinical practice.

Structure of pathophysiological experiment comprises of three phases:

1) studying the parameters of vital functions in initial conditions;

2) modeling of pathological process and studying it in dynamics with the help of modern methods of scientific analysis;

3) search for pathogenic therapy.

An experiment permits such effects on animal organs (trauma, burn, transplantation, tumour, radiation) which are impermissible in clinical practice. Only experiments on animals give an opportunity to test new drugs. All experiments are divided into acute (modeling of bleeding) and chronic ones (reproduction of tumor) depending on the research objectives.

Objective of experiment: Studying phases of pathophysiological experiment.

Experiment 1. Reproduction of histamine hypotonia and its experimental therapy.

Method: After a rabbit is fixed, record the parameters of its arterial pressure (AP), the electrocardiogram (ECG) and the pneumogram (PG) with the help of a thermal recorder. Then inject 0.1% solution of histamine intravenously at the rate of 5 mg/kg. Then register the same parameters within 15 minutes. In 15 minutes upon the development of hypotonia carry out intravenous infusion therapy with 6% solution of Polyglucinum. Just after medical measures are finished and in 15 minutes again register the same parameters of vital activity of the animal.

Record the experimental results, tabulate the numerical material and analyse it. Draw a conclusion from the data about the pathophysiological experiment phases, their importance for the study of pathological processes and the determination of a pathogenic therapy method.

Multiple Choice Questions

Choose the right answer

001. THE SUBJECT OF PATHOPHYSIOLOGY IS

1) disease
2) symptoms of a disease
3) causes of a disease

002. THE BASIC METHOD OF PATHOPHYSIOLOGY IS

1) experiment
2) tests
3) mathematical analysis

003. BASIC TASK OF PATHOPHYSIOLOGY IS

1) gaining knowledge of mechanisms of disease development and recovery
2) testing of new medicines
3) disease prevention

004. PATHOGENIC THERAPY IS

1) elimination of basic and leading link of pathogenesis
2) elimination of basic symptoms of a disease
3) elimination of basic
4) causes of a disease

PART: GENERAL PATHOPHYSIOLOGY. (GENERAL NOSOLOGY. DOCTRINE OF DISEASE.)

Theme: General nosology. Pathogenic effect of environmental factors.

Objective of class: To study the fundamental notions of common nosology.

Health is defined by the WHO as a condition of complete physical, intellectual and social well-being, not only an absence of ailments or physical defects. Ascertaining of health is based on average statistical indicator of healthy people, i.e. the norm. The norm is an optimal condition of vital activity of the body in particular conditions of its existence. In practical medicine it is an average statistic quantity from given units in a majority of healthy people with indication of possible limit fluctuations.

Disease is a dynamic condition of the body as a response to lesion, characterized by dialectic unity of pathologic and protective adaptive change, causing decreased social and biological adaptation of the person.

Significant criteria of a disease are complaints of the patient (malaise, pain, different functional disorders and so on); results of objective patient examination that reveal one or other abnormality and establish characteristic symptoms of a disease; decreased working ability and adaptability.

Pathologic process is a combination of general and local pathologic and defensive adaptive reactions developing in the body under the influence of a pathogenic factor evident from morphologic, metabolic and functional disorders.

Etiology is a study about causes and conditions of occurrence and development

of diseases. Diseases occur when the balance between the body and the surrounding environment is disturbed due to particular conditions, i.e. adaptation of the body becomes insufficient.

The cause of the disease is that agent which causes the disease and gives it specific features.

Contemporary notions of causality in pathology are based on the basis of dialectics:

1) all events in nature have their causes;

2) the cause interacts with the body; e.g. changing the body the cause changes itself;

3) the cause is material, it exists in itself outside and independently from us;

4) the cause gives the processes a new quality and unique features.

Following these assumptions the researcher looks for the cause and when he finds it, he can determine the way to eliminate the disease and prevent its recurrence. A cause of a disease acts on the body under particular extremely important conditions. Some conditions can be unfavorable (risk factors), and others counteract them and create favorable factors.

Pathogenesis is a branch of pathologic physiology studying the mechanism of disease development. Studying more general patterns of occurrence, development, course and outcome of diseases composes the content of general doctrine about pathogenesis. A cascade of changes in the body for every disease is established, cause-and-effect relations between various structures, metabolic and functional changes are detected. This is called 'vicious circle'.

Knowledge of cause-and-effect relations in pathogenesis of diseases allows a purposeful interference in the mechanisms of disease course.

Objective of experiment: To study the role of the cause and conditions of development of pathological processes on the model of acute oxygen insufficiency.

Experiment 1. Development of hypoxia against initial hypercapnia.

Method: In two bottles of identical capacity place one mouse, close them air tightly. Observe the behaviour and general condition of animals, note the time. Then carbonic gas is pumped into one of bottles. You continue to watch the animal till convulsions develop and animals die of asphyxia. The results of the experiments have to be written down into the protocol.

Experiment 2. Development of hypoxia against initial hypercapnia

Method. The experiment is made in the same way after pumping pure oxygen under the cowl.

The results of the experiments have to be written down into the protocol. On the base of obtained findings make a conclusion about the role of the cause and accompanying conditions.

Experiment 3. Body changes in hypoxia depending on environment temperature.

Method. In three bottles of identical capacity place one mouse. Close them air tightly simultaneously, note the time then place one bottle in the water which has been warmed up to 38-40 degrees, the second - in cold (+5 degrees), leave the third one at room temperature. Water temperature throughout the experiment is maintained at one level. Observe the behaviour of mice, change of indicators of vital activity of

the body. Explain the obtained results.

Multiple Choice Questions

Choose the right answer

001. THE CORRECT STATEMENT IS

1) pathological process
   is the basis of any disease
2) notions of a pathological
process and a disease are identical

002. SPECIFIC FEATURES OF THE DISEASE DEPEND ON

1) causes of the disease
2) conditions contributing
to the development of the disease
3) reactivity of the body

003. THE CORRECT DEFINITION OF AETIOLOGY IS

1) aetiology is the doctrine
   about a disease
2) aetiology is the doctrine
   about the causes and conditions
   of development of diseases
   and pathological processes

004. THE STATEMENT "DISEASE IS A COMBINATION OF SEVERAL PATHOLOGICAL PROCESSES"

1) is correct
2) is not correct

PART: REACTIVITY AND RESISTANCE OF THE BODY. THEIR ROLE IN PATHOLOGY.

Theme: The influence of exogenous and endogenous factors on the reactivity and resistance of the body.

<u>Objective of class:</u> To study the role of reactivity and resistance mechanisms in pathology. To study the mechanisms of immunity and its role in pathology.

Reactivity of the body (Latin "reactio" – opposition) is its ability to react to the endogenous and exogenous influence by changing its vital activity.

Types of reactivity.

Species (biological) reactivity is the reactivity typical of particular species of animals.

Group reactivity is the reactivity of separate groups of people (or animals) sharing a common feature which determines the reaction specifics of all the representatives of this group to external exposure. Such features are: age, sex, constitution type, race, blood group, higher nervous activity type, group of people with the same illness, etc.

Individual reactivity. Every human being or animal possesses a range of reactions typical of a certain group or species. Therefore, they respond to external agents changing their vital activity in their own, particular way.

Specific reactivity is the ability of an organism to respond to the influence of an antigen by producing antibodies or with a complex of cell reactions that are specific to this antigen, i.e. it is the reactivity of the immune system (immune reactivity).

Nonspecific reactivity. All changes in the body occurring in response to the influence of external agents and not associated with the immune reaction are the signs of nonspecific reactivity.

Physiological reactivity means a change of the bodily vital activities, definite forms of reaction to the influence of external agents that do not disturb its homeostasis; it is the reactivity of a healthy person (or an animal) to non-pathogenic stimulants (e.g. adaptation to moderate physical strain, processes of thermoregulation, secretion of hormones and peptic enzymes, natural emigration of leucocytes, etc.).

Pathologic reactivity manifests itself when an organism is exposed to nosogenic factors causing lesions of the body and disturbing its homeostasis.

Types of reactivity.

The following types of reactivity are singled out: normal reactivity – normergy, increased – hyperergy (hyper – more, ergon – act), decreased – hypoergy, perverted – disergy. The lack of reaction to any influence is called anergy.

Reactivity should be estimated in relation to a particular intervention. Quite often reactivity to one agent is coupled with low reactivity to another (for example, reactivity to hypoxia and acceleration, overheating and over-cooling, to physical overstrain and starvation, reactivity to different infective agents, etc.). During prenatal development an embryo does not respond to enteric fever and jail fever infection but responds to diphtheria, staphylococcus and streptococcus.

Resistance is the body insusceptibility to pathogenic effects.

Primary resistance is hereditary. It is based on the morphofunctional specifics of the body owing to which an organism is resistant to the action of extreme factors (unicellular organisms and worms are resistant to radiation, cold-blooded animals – to hypothermia, etc.).

Hereditary resistance (immunity in particular) may be absolute and relative.

Secondary resistance is acquired (for example, immunity develops after some infectious diseases, after the administration of vaccines and sera).

Passive resistance of the body is provided by its barrier systems (skin, mucous membranes, hematoencephalic barrier, etc.), the present bactericidal agents

(hydrochloric acid in the stomach, lysozyme in the saliva) and hereditary immunity.

Active resistance is provided by the activation of its protective-adapting and compensatory mechanisms, such as production of leukocytes, phagocytosis, production of antibodies, neutralization and excretion of toxins, secretion of stress hormones, changes of blood circulation and breathing, fever, synthesis of acute phase proteins by the liver, increase of leuco- and erythropoiesis, etc.

Reactivity and resistance are interrelated but not always unidirectional. For example, a newborn animal has low reactivity and high resistance to hypoxia, while in a mature animal the opposite is true. In surgery anesthesia is used to reduce the patient's reactivity and at the same time to boost their resistance to trauma.

Specific reactivity is the ability of an organism to respond to the influence of an antigen by producing antibodies or with a complex of cell reactions, that are specific to this antigen, i.e. it is the reactivity of the immune system (immune reactivity).

All these concepts are united by the following attributes:

-unresponsiveness of humans and animals to infectious diseases (immunity),

-reactions of biological incompatibility of tissues (heterogeneous, isogeneic, individual, reactions of interaction of embryonic tissues with the tissues of an adult organism or with each other),

-reactions of hypersensitivity (allergy)

-the phenomena of acquired tolerance to poisons of various origins

Its types are as follows: active specific immunity, allergy, autoimmune diseases, immunodeficiency and immunosuppressive conditions, immunoproliferative diseases.

All these phenomena are united by the following attributes:

1. All specified phenomena and reactions arise in the body under the impact of antigenes or haptens (substances of a non-albuminous nature having antigenic properties),

2. These reactions, in the broad sense of the word, refer to reactions of biological protection and are directed at preservation and maintenance of individual antigenic structure of an organism.

3. Processes of interaction of antigenes with antibodies have a determining effect in the mechanism of most specific reactions.

Objective of experiment: To study the manifestations of reactivity and resistance mechanisms and possibility of changing the organism reactivity and resistance under the influence of exogenous and endogenous factors.

Experiment 1. Change of the body resistance to hypoxia under the influence of doses of physical exertion.

Method: after 10-20 min of running in apparatus TC-1 the rats are placed into the glass cowl of Komovski apparatus. At the same time control rats are placed there too. With the pump the atmospheric pressure is lowered. The results of the experiment have to be written into the protocol. You have to note the time of the appearance of convulsions, general status of the animal.

On the basis of the obtained data you have to make a conclusion about the change in reactivity under the influence of physical loading doses.

Experiment 2. The influence of reactivity of all kinds on the resistance of the organism to hypoxia.

Method: A frog and a mouse must be placed in a jar. The jar must be hermetically closed. After that you must note the time of death of the animal caused by asphyxia. The results of the experiment have to be recorded.

Experiment 3. **Dependence of the reactivity of the organism on the function of the nervous system.**

Method: you have to place three mice in three hermetically closed jars. The first one is narcotised by an injection of 0.2-0.3 ml of 1% solution of Hexenalum, the second one is given a subcutaneous injection of caffeine (0.3-0.4 ml 1% solution) and the third one is a control (intact) mouse. You must mark the time of asphyxia onset.

You have to record the results of the experiment and explain the obtained results.

Experiment 4. The influence of disturbance of acidic-alkaline balance on the reactivity of the organism.

Method: inject 0.5 ml of 1:10000 solution of adrenalin into the abdominal vein with simultaneous registration of the cardiac rhythm after determination and registration of the basic cardiac rhythm of the frog. When the cardiac rhythm is normal, you have to inject 5 ml of 0.5% solution of lactic acid into the abdominal vein. Reaction to adrenalin before and after the change of acid-base balance in the organism must be recorded.

In any case you have to draw a conclusion about the change of the reactivity of the organism in disorder of the acid-base balance in the body.

Multiple Choice Questions

Choose the right answer

001. REACTIVITY IS

1) ability of tissues to answer with protective and adaptive reactions to pathogenic influences
2) ability of the whole organism to answer with changes of vital activity to various influences of the environment

002. THE CORRECT DEFINITION OF RESISTANCE IS

1) stability of cells to the action of pathogenic factors of the environment
2) ability of the organism to resist the action of pathogenic factors of the environment

003. CHARACTERISTIC OF MECHANISMS OF ACTIVE RESISTANCE OF THE ORGANISM IS

1) emigration of leukocytes and phagocytes
2) barrier functions of the skin and mucous membranes

004. A STRONG BALANCED MOBILE BODY TYPE ACCORDING TO I.P.PAVLOV AND HIPPOCRATES IS

1) choleric person
2) phlegmatic person
3) sanguine person
4) melancholic person

005. SPECIFIC REACTIVITY OF AN ORGANISM IS

1) reactivity of immune system
2) phagocytic activity
3) hormonal reaction of an organism to pathologic stimuli

006. MANIFESTATION OF SPECIFIC REACTIVITY IS (***choose the right answers)***

1) allergy
2) immunodeficiency state
3) autoimmune disease
4) active specific immunity

007. A GENERAL FORM OF SPECIFIC REACTIVITY IS

1) formation of immunity to previous disease
2) elevation of systemic arterial pressure
3) increased pulmonary ventilation

008. A LOCAL FORM OF SPECIFIC REACTIVITY IS

1) degranulation of sensitized mast cells upon contact with an allergen
2) reddening
3) edema

PART: STANDARD PATHOLOGICAL PROCESSES.

Theme: Cell damage.

<u>Objective of class:</u> To study the etiology and mechanisms of cell damage.

Damaged cells differ from normal ones in that after the influence of damaging factors a change in their structure and function occurs.

Damage of tissue may cause formation of many etiological factors of endogenous and exogenous origin. The following cell components are affected by the influence of cell damaging agents:

1) Cell membrane
2) Mitochondria
3) Structural proteins
4) Enzymatic proteins
5) Nucleus

There are two types of influence which are caused by harmful factors:

1) primary
2) secondary

Direct primary damage of cells is of specific character. In a healthy the primary effect of damaging factors on target cells is accompanied by a change in other cells. These changes indirectly disturb the functioning of cells called secondary target signs. **Specific damage** plays a role of initial mechanism in the development of a cascade of general nonspecific reactions. Upon damage of plasmolemmas any factor a chain of consequences which includes a number of nonspecific cellular responses:

1. insufficiency of sodium pump, potash and function of ion channels;
2. loss of physiological transmembrane ion gradients;
3. sodium and water into the cell, swelling cells develop intracellular edema;
4. calcium into the cell;
5. activation of membrane phospholipases;
6. release and transformation of arachidonic acid;
7. disorder of local microcirculation.

Cascade of these reactions ends in general response to the adverse impact on cells as a whole. Depending on the strength and duration of exposure we distinguish stages of the response: adaptation to damage, paranecrosis, necrobiosis, cell death.

Urgent adaptation is most often manifested in hyperfunction of intact cells of micro circulation at the expense of regulatory mechanisms, mobilising their reserves. Long-term adaptation under different conditions can appear as hyper-, hypo- and dysfunction and, accordingly, is seen as hypertrophy, hypotrophy and atrophy with dystrophy.

Acute damage to cells can be divided into:

1. reversible (the process stops upon development of intracellular edema)
2. irreversible (the process ends in violent death of cells).

Upon a weak damaging impact a reversible damage to cells develops, which corresponds to the stage of paranecrosis. Deep, partly irreversible stage of damage to cells preceding their death is referred to as necrobiosis. Posthumous irreversible

change consisting in gradual enzymatic destruction of cells (autolysis) and denaturation of proteins is called necrosis.

Cell death can be:

1. Programmed. This type of cell death is via **apoptosis** and autophagocytosis.
2. From injury.

This type of cell death is:

a) through **necrobiosis** originating from hypoxia or free radicals,

b) or via **autophagocytosis** with autoimmune processes.

Objective of experiment: To study disturbances of cells function during their acute damage.

Experiment 1. Studying specific movement function change of cilia of the ciliary epithelium upon alteration of the frog oral mucous membrane.

Method: A frog is made motionless by destroying the spinal cord. The upper jaw is cut off and the animal is fixed to the sectional table. You must put a silk thread 1 cm long on the mucous membrane of the esophagus entry and observe its movement to the esophagus for 3-5 min. Then the mucosa of the jaw must be treated with 1% solution of hydrochloric acid and a silk thread is placed there again for some minutes. You have to be sure that after mucous alteration the movement of the silk thread is stopped because the movement of the cilia is depressed.

Experiment 2: Studying the reaction of mast cells to damage.

Method: You must give a rat an intramuscular injection of cortisone in a dose of 5mg/100 g of mass. It leads to an increase in the number of mast cells in the peritoneal fluid. One day later inject a mixture of 0.7% solution of sodium salt and 1.5% solution of sodium citrate heated to a temperature of 37° into the rat intraabdominally in order to wash the mast cells from the serous membrane. The animal is given anaesthesia after 3 min. The abdominal cavity is opened; the fluid is taken and carried on two object-plates with the help of Pasteur's pipette. Add one drop of 1% solution of hydrochloric acid to a drop of the peritoneal fluid (experiment) and add a drop of physiological solution to the other (control). After 30 sec. you have to prepare smears from these drops, dry them and fix them in a mixture of spirit and ether (1:1), for 15 min and stain them by Romanovsky's staining. After the staining the smears are washed in running water, dried and examined under the immersion system. You must count 100 mast cells and calculate the percentage of degranulation. Determine and explain the difference between the experiment and control samples.

Multiple Choice Questions

Choose the right answer

001. MECHANISMS OF CELL DAMAGE CONSIST IN

1) increased coupling of oxidative phosphorylated process, increased activity of enzymes of DNA reparation system
2) increase of free radical

oxidation of lipids, release
of lysosomal enzymes into the
hyaloplasm

002. CAUSE OF HYPERHYDRATION OF A CELL IN DAMAGE IS

1) decreased activity of Na +/K +- ATPase ,
increased intracellular osmotic pressure
2) decreased activity of glycogensynthetase
3) increased activity of phosphofructokinase
4) decreased activity of phospholipase C

003. NONENZYME FACTOR FOR ANTIOXIDANT PROTECTION OF CELLS IS

1) bivalent ions of iron
2) glucuronidase
3) vitamin E

004. INCREASED FREE IONIZED CALCIUM CONCENTRATION IN A CELL CAUSES

1) activation of phospholipase C,
activation of lipid peroxidation,
increased release of K+ from a cell,
hyperhydration of a cell
2) inactivation of phospholipase C,
hyperpolarization of a cytoplasmic
membrane, increased content of free
calmodulin

PART: STANDARD PATHOLOGICAL PROCESSES.

Theme: Pathophysiology of organ and tissue blood circulation and microcirculation.

Objective of class: To study the types and mechanisms of peripheral circulation and microcirculation disturbances.

Arterial and venous hyperemia, ischemia and stasis are standard types of peripheral blood circulation disturbances.

Arterial hyperemia or active hyperemia is characterized by dilatation of arterioles and capillaries, which are affected either by sympathetic neurogenic mechanism or via the vasoactive substances. The affected tissue is pink or red in appearance (erythema).The examples of active hyperemia are seen in the following conditions:

- Inflammation e.g. congested vessels in the walls of alveoli in pneumonia;

- Blushing i.e. flushing of the skin of the face in response to emotions;
- Menopause flush;
- Muscular exercise;
- High-grade fever.

There are the following kinds of active hyperemia:

- after ischemia that takes place after removing a tourniquet from the extremity;
- after paralysis of nerves which takes place after incision or paralysis of vasoconstrictive nerves and after paralysis of their centres;
- after the increase of the nervous tonus, which develops after irritation of vasodilatators and their centres;
- myoparalysis, which is caused by the affected neuromuscular apparatus of vessels;
- hyperemia caused by cupping.

Venous hyperemia (venous congestion)

The dilatation of veins and capillaries due to impaired venous drainage results in passive hyperemia or venous congestion. Congestion may be acute or chronic, the latter being more common and is called chronic venous congestion (CVC). The affected tissue or organ is bluish in colour due to the accumulation of venous blood (cyanosis). The obstruction of the venous outflow may be local or systemic. Accordingly, venous congestion is of two types:

- Local venous congestion results from obstruction of the venous outflow from an organ or a part of the body e.g. portal venous obstruction in cirrhosis of the liver, the outside pressure on the vascular wall as occurs in a tight bandage, plaster, tumours, pregnancy, hernia, etc. or intraluminal occlusion by thrombosis.

Systemic (general) venous congestion is engorgement of systemic veins e.g. in the left-sided and the right-sided heart failure and diseases of the lungs which interfere with pulmonary blood flow like pulmonary fibrosis, emphysema, etc. For example, in the left-side heart failure (such as due to mechanical overload in aortic stenosis) or due to the weakened left ventricular wall (as in myocardial infarction) pulmonary congestion results, whereas in the right-sided heart failure (such as due to pulmonary stenosis or pulmonary hypertension) systemic venous congestion results.

Ischemia is a disorder of peripheral haemocirculation, which is caused by decreased or completely ceased inflow of the arterial blood. Ischemia is characterized by a decrease of metabolism in the tissues, pains, paleness and decreased metabolism. There are three kinds of ischemia:

1. Compression, caused by the pressure of tissue on the artery.
2. Obturation, caused by artery plugged up by fibrin.
3. Angiospastic ischemia develops due to irritation of angionervous apparatus and its reflectory spasm.

Stasis is slowing-down and full stopping of the blood flow in the capillaries, small arteries and veins. There is capillary stasis caused by pathological failure of capillaries or blood transport in them. After a complete stopping of the blood flowing from the arteries into the capillary ischemic stasis is observed. Venous stasis takes place there after slowing down of the blood flow.

Objective of experiment: To learn the kinds and mechanisms of failure of the peripheral blood circulation.

Experiment 1. Reproducing neuroparalytic arterial hyperemia.

Method: A frog is anaesthetized with 0.4-0.5 ml of 1% solution of Hexenalum injected into the lymphatic sac. The frog must be fixed on the preparation board with its abdomen down. On one extremity in the middle part of the thigh uncover the sciatic nerve, which is carefully ligated. The membrane of the same extremity must be stretched under the side window of a board and moistened with warm physiological solution. You have to observe the initial status of circulation under slight magnification with a microscope and then you have to cut quickly the sciatic nerve continuing your observation.

The results have to be recorded and sketched. On the basis of obtained data draw a conclusion about the cause of arterial hyperemia development after paralysis of nerves and the nature of disturbance of blood circulation in it.

Experiment 2. Reproducing neurotonic arterial hyperemia and studying the failure of blood circulation in it.

Method: A frog is anaesthetized with 0.4-0.5 ml of 1% solution of Hexenalum injected into the lymphatic sac. The frog must be fixed on the preparation board with its abdomen down. The lower jaw must be close to the central aperture, and one of the posterior extremities - near the side aperture. The lower jaw must be fixed with a pin. Pull out the tongue, stretch it, fixing with pins at an angle. Study the preparation of the tongue under slight magnification, note the diameter of the arterial blood vessels, the number of functional capillaries and general picture of blood circulation. Mechanically irritating the branch of uvular nerve estimate the status of microcirculation again.

On the basis of obtained data you have to draw a conclusion about the cause of development of neurotonic arterial hyperemia and the nature of disturbance of blood circulation in it.

Experiment 3. Reproducing myoparalytic arterial hyperemia and studying the failure of blood circulation in its development.

Method: The experiment is made on the former preparation after normalization of blood circulation. Two drops of 1:10000 solution of adrenalin are dropped on the tongue of the frog. Then the failure of circulation is registered. Wash adrenalin with physiological solution and after circulation is restored, the mucous membrane is smeared very carefully with turpentine. You have to study repeatedly the reaction of blood in stable hyperemia and make a sketch of it.

On the basis of obtained data you have to draw a conclusion about the cause of development of myoparalytic arterial hyperemia and the nature of disturbance of blood circulation in it.

Experiment 4. Reproducing venous hyperemia and studying its external characteristics.

Method: A plug with a groove on the side is put into the ear of a rabbit. The veins will be constrained, but the central artery will remain free. You must see the changes of colour of the ear, the status of the blood vessel net and the temperature of the ear. The results must be protocolled and sketched.

On the basis of obtained data you have to draw a conclusion about the cause of development of venous hyperemia and its external characteristics.

Experiment 5. Reproducing compressive ischemia and studying its external characteristics.

Method: In the same rabbit after observation of the circulation in the ear and its external characteristics, you have to fix a plug with two grooves. These grooves must coincide with marginal veins, and the artery must be compressed. You have to observe the change of the ear colour, disturbance of circulation and temperature. Write down and sketch the results of the experiment. On the basis of obtained data you should draw a conclusion about development of ischemia and its external signs.

Multiple Choice Questions

Choose the right answer

001. SIGNS OF ARTERIAL HYPEREMIA ARE

1) cyanosis of the organ
2) reddening of the organ or tissue
3) marked edema of the organ

002. CAUSE OF RED COLORATION OF THE ORGAN IN BLOOD CIRCULATION DISORDER IS

1) increased concentration of oxyhemoglobin in blood
2) decreased concentration of oxyhemoglobin in blood
3) reduction of volumetric blood circulation
4) increased concentration of reduced hemoglobin in blood

003. CONSEQUENCES OF VENOUS HYPEREMIA ARE

1) growth of the connective tissue
2) increase of the organ's function
3) haemorrhage

004. NON-TYPICAL CHANGES IN ISCHEMIA ARE

1) necrosis
2) acidosis
3) decreased function
4) increased function
5) accumulation of Ca^{2+} in the cellular hyaloplasm
6) increase of Na^{+} concentration in the cell

PART: STANDARD PATHOLOGICAL PROCESSES.
Theme: Inflammation.

Objective of class: To study the etiological factors, stages and mechanisms of the development of acute and chronic inflammation.

Inflammation is a local response of living mammalian tissues to injury due to any agent.

It is a typical pathological process.

Stages of inflammation

- Alteration
- Exudation
- Proliferation

All stages are characterized by vascular and cellular events.

Initial alteration is the result of an injuring influence of the most powerful inflammatory agent.

Initial alteration is not a component of inflammation, because inflammation is reaction to the damage caused by the inflammatory agent, on initial alteration

Secondary alteration begins under the influence of enzymes from lysosome and free radicals of oxygen from phagocytes, of C5-C9 complex from plasma and tissue liquid. It is the same substances which being formed in various body tissues in physiological concentration, are responsible for regulation of functions at cellular and tissue level in normal conditions of the body. In an inflammation, these substances liberated (owing to activation of cells and plasma) in abundance, acquire a new quality, mediators of inflammation.

Thus, secondary alteration does not depend directly on the inflammatory agent, for its development there is no necessity for the further presence of the inflammatory agent.

At the same time initial and secondary phenomena of alteration are hardly separable from each other. Alteration in the microvasculature (arterioles, capillaries and venules) is the earliest response to tissue injury. These alterations include: haemodynamic changes and changes in vascular permeability.

Haemodynamic changes: transient vasoconstriction of arterioles (from 3-5 seconds to 5 minutes), vasodilatation (mainly the arterioles); progressive vasodilatation elevates the local hydrostatic pressure resulting in transudation of fluid into the extracellular space, vasodilatation (mainly the veins), slowing down or stasis of microcirculation occurs next.

Increased permeability of microvasculature results in increased concentration of red cells, and thus, raised blood viscosity.

The appearance of **inflammatory oedema** due to increased vascular permeability of microvascular bed is explained on the basis of Starling's hypothesis. Forces that cause an outward movement of fluid from microcirculation are increasing intravascular hydrostatic pressure and oncotic and osmotic pressure of interstitial fluid.

Stasis or slowing down is followed by leucocytic margination or peripheral orientation of leucocytes (mainly neutrophils) along the vascular endothelium. The leucocytes stick to the vascular endothelium briefly. Adherence of leucocytes to the endothelium at the site of inflammation may result in activation of leucocytes. The activated leucocytes release proteolytic enzymes and toxic oxygen species which may

cause endothelial injury and increased vascular permeability. After sticking of neutrophils to endothelium, the former move along the endothelial surface till a suitable site between the endothelial cells is found where the neutrophils throw out cytoplasmic pseudopods. The neutrophils lodged between the endothelial cells and basement membrane cross the basement membrane by damaging it locally with secreted collagenases and escape out into the extravascular space; neutrophils are the dominant cells in acute inflammatory exudate in the first 24 hours, and monocyte-macrophages appear in the next 24-48 hours. The chemotactic factor-mediated transmigration of leucocytes after crossing several barriers (endothelium, basement membrane, perivas cular myofibroblasts and matrix) to reach the interstitial tissues is called chemotaxis. The agents acting as potent chemotactic substances for different leucocytes are called chemokines.There are specific receptors for each of the chemoattractants listed above. In addition, chemotactic agents also induce leucocyte activation that includes: production of arachidonic acid metabolites, degranulation and secretion of lysosomal enzymes, generation of oxygen metabolites, increased intracellular calcium, and an increase in leucocyte surface adhesion molecules.

Phagocytosis is defined as the process of engulfment of solid particulate material by the cells (cell-eating).

The process of phagocytosis is similar for both polymorphs and macrophages and involves the following 4 steps:

Attachment stage (opsonisation).

Engulfment stage

Secretion (degranulation) stage

Killing or degradation stage.

Inflammatory proliferation is duplication of local cellular elements in the center of inflammation. Proliferation develops from the very beginning of inflammation with the phenomena of alteration and exudation, but becomes prevailing later in the process.

When inflammation overwhelms the host, systemic inflammatory response syndrome is diagnosed (leukocytosis, fever, accumulation of protein of acute phase). When it is due to infection, the term sepsis is applied, with bacteremia being applied specifically to bacterial sepsis and viremia specifically to viral sepsis. Vasodilation and organ dysfunction are serious problems associated with widespread infection that may lead to septic shock and death.

Objective of experiment: To learn pathological changes in an inflammation locus.

Experiment 1. The study of pus proteolytic activity.

Method: Dilute the pus in 6 test-tubes. Technique of pus dilution: Fill 6 test-tubes with 1 ml of the physiological solution. Then add 1 ml of pus into the test-tube № 1, in dilution 1:10, then stir the contents of the test-tube №1, take 1 ml of the mixture from it and transfer it into the test-tube № 2. Similarly take 1 ml of the mixture from it, transfer it into the test-tube № 3 etc. Remove 1 ml of the mixture from the last test-tube to make the conditions of the experiment identical.

Add 2 ml of 0.25% casein solution into each test-tube and place them into a thermostat. Then take the stand with the test-tubes out of the thermostat and add 5-6

drops of acetic acid carefully (on the wall of the test-tubes). Mark the presence or absence of opacification of the contents of different test-tubes (opacification is observed if protein is split incompletely).

Record and tabulate the results. Draw a conclusion from the data about the presence or absence of pus proteolytic activity.

Experiment 2. The study of circulation change in an inflammation locus.

Method: Make a preparation of the intestinal mesentery of a frog, anaesthetized with Hexenalum. Study the circulation character in its vessels. Then make a burn with an incandesent spirit-lamp needle near the locus of the vascular network in the visual field.

Record and tabulate the results. Draw a conclusion from the data about **t**he study of circulation change in an inflammation locus.

Multiple Choice Questions

Choose the right answer

001. INFLAMMATION IS AN ADAPTIVE REACTION OF THE ORGANISM BECAUSE ***(choose the right answers)***

1) it isolates the site of damage preventing the spread of phlogogenic factor and products of organism alteration
2) it inactivates the phlogogenic agent and products of tissue alteration
3) it mobilizes specific and nonspecific factors of organism protection
4) it contributes to regeneration or replacement of damaged tissue structures

002. SIGNS WHICH INDICATE THE PRESENCE OF INFLAMMATION IN THE ORGANISM ARE ***(choose the right answers)***

1) leukocytosis
2) fever
3) increased erythrocyte sedimentation rate (ESR)
4) increased gamma-globulin concentration in blood serum
5) accumulation of C-reactive protein in blood

003. FACTORS WHICH CONTRIBUTE TO EDEMA DEVELOPMENT IN THE INFLAMMATORY FOCUS ARE ***(choose the right answers)***

1) increased oncotic pressure of the intercellular fluid
2) increased permeability of the vascular wall
3) increased pressure in the venous part of capillaries and venules
4) increased osmotic pressure of intercellular fluid

004. MEDIATORS OF INFLAMMATION OF THE CELLULAR ORIGIN ARE

1) cyclic adenosine monophosphate, cyclic guanosine monophosphate, serotonin, lymphoquins, histamine, lysosomal enzymes, lysosomal cationic proteins, prostaglandins
2) factors of blood coagulation, kinins, complement

05. MEDIATORS OF INFLAMMATION OF THE HUMORAL ORIGIN ARE

1) cyclic adenosine monophosphate, cyclic guanosine monophosphate, serotonin, lymphoquins, histamine, lysosomal enzymes, lysosomal cationic proteins, prostaglandins
2) factors of blood coagulation, kinins, complement

PART: STANDARD PATHOLOGICAL PROCESSES.

Theme: Fever.

Objective of class: To study the types of pyrogens and their role in fever pathogenesis and antipyretic mechanisms.

Fever is one of the components of acute phase response.

Fever is a typical pathological process, which appears in case of influence of pyrogens on the thermoregulatory centre and is characterized by an active temporary reorganization of thermoregulation directed at temperature increase inside the body independently from environmental temperature.

Fever development is caused by a shift of work point of temperature homeostasis to a higher level under the influence of many pyrogenic substances. These are exogenous and endogenous, primary and secondary, infectious and non-infectious pyrogens, which lead to the appearance of infectious and non-infectious fever accordingly.

Most often, they are bacteria and their endotoxins, viruses, yeasts, spirochets, protozoa, immune reactions, several hormones, medications, and synthetic polynucleotides. These substances are commonly called **primary** (**exogenic and endogenic) pyrogens**.

Cells stimulated by exogenic pyrogens form and produce cytokines called **secondary endogenic pyrogens (interleukin-1, 6, 8, TNF or cachexin, FNO β or lymphotoxin, interferons (INF-β, INF-γ, INF-α).** They are synthesized in the centre of infectious, aseptic or immunoallergic inflammation by irritated granulocytes, monocytes of blood and lymph, tissue macrophages, natural lymphocyte killers, B lymphocytes, microglial and macroglial cells, mesaglial elements, endotheliocytes, APUD-cells and mast cells as a result of interaction of exopyrogens with specific receptors of the mentioned above elements, and also as a result of pino- and phagocytosis of exopyrogens or damaged structures of the body, immune complexes and others.

Endopyrogens circulating in the blood exert a specific influence over thermosensitive neurons of the organs. As a result of metabolism transformation of cold-sensitive neurons, irritability increases, and of heat-sensitive neurons – decreases, and the temperature of the internal medium is conceived as deficient. In connection with this the mechanisms directed at preservation of heat in the body are included.

First phase of Fever, phase of increase (stadium incrementi). Increase of the internal medium temperature takes place because of considerable limitation of heat loss and accumulation of heat in the organism. Additional increase of thermal energy arises as a result of activation of mechanisms of contractile and then non-contractile thermogenesis.

Second phase of Fever, climax phase (stadium acme). Climax means that the body temperature culminates. At culmination of fever, such a temperature is achieved to which the thermoregulatory center is reset. The center is washed by blood that has the temperature originally adjusted. Because of this, activation of sympathetic compartments stops. However, the parasympathetic compartment of the thermoregulatory center is activated.

Third phase of Fever, climax phase, descent stage (stadium decrementi). Normal sensitivity of the center of temperature regulation is restored increasing the heat loss, and the third stage is characterized by a decrease of the body temperature. The decrease of fever may be lytical or critical.

Objective of experiment: To study the change of functioning of the main life supporting systems in fever.

Experiment 1. Study the change of respiration and cardiac activity during fever development.

Method: Measure aural and rectal temperature with a thermometer in two rabbits. Make records of the pneumogram (PG) and electrocardiogram (ECG) with the help of the standard two-channel electrocardiograph. Count the cardiac and respiratory movements in conditions of fixation of the animal on its stomach.

Inject Pyrogenalum into the experimental rabbit's marginal vein of the ear at the rate 10 μg/kg of the animal weight. In 20, 30, 40 and 60 minutes remeasure rectal, aural temperature and remake records of the pneumogram and electrocardiogram both in the experimental animal and in the control one (without Pyrogenalum injection).

The experimental rabbit has a temperature increase in the experiment dynamics.

Record the results. Draw a conclusion from the data about disturbance of activity of the main life supporting systems of an organism during fever development.

Multiple Choice Questions

Choose the right answer

001. MEDIATORS OF THE ACUTE PHASE RESPONSE WITH PROPERTIES OF ENDOGENOUS PYROGENS ARE ***(choose the right answers)***

1) interleukin-1
2) interleukin-6

3) tumor necrosis factor-α

002. CHANGES CAUSED BY SECONDARY PYROGEN IN NEURONS OF HYPOTHALAMIC TEMPERATURE-CONTROLLING CENTRES ARE

1) accumulation of lipopolysaccharides
2) decreased prostaglandin E-group formation
3) decreased cyclic adenosine monophosphate formation
4) increased excitability of heat neurons
5) increased excitability of cold neurons

003. CORRELATION OF HEAT PRODUCTION AND EMISSION OF HEAT AT THE FIRST STAGE OF FEVER DEVELOPMENT IS

1) production of heat increases, emission of heat decreases
2) production of heat does not change, emission of heat decreases
3) production of heat increases, emission of heat also increases, but to a lesser extent
4) production of heat and emission of heat change equally
5) production of heat decreases, emission of heat does not change

004. CORRECT STATEMENT IS

1) increased temperature of the body indicates of the development of fever
2) fever is characterized by the rise of body temperature, signs of organism intoxication
3) fever is a reaction of warm-blooded animals to the action of pyrogenic factors

005. SECONDARY PYROGENS CAN BE PRODUCED BY ***(choose the right answers)***

1) monocytes
2) tissue macrophages
3) erythrocytes
4) lymphocytes

5) granulocytes

PART: STANDARD PATHOLOGICAL PROCESSES.

Theme: Standard disturbances of metabolism. Disturbance of carbohydrate metabolism.

Objective of class: To study the etiological factors and mechanisms of standard disorders of carbohydrate metabolism.

For the unremitting of the process of glycolysis and Crab's cycle glucose should be delivered continuously to the tissues. It happens because of a constant level of glucose (3,3-5,5 mmol/lit) in the blood, which in physiological conditions never decreases to a critical level. Glucose level in the blood can be identified by the speed of endogenic glucose production on the one hand, and by the speed of glucose utilization on the other.

Several types of regulation of carbohydrate metabolism can be distinguished:

- **substrate,**
- **nervous,**
- **hormonal,**
- **renal.**

The increase of concentration of glucose in the blood stimulates secretion of insulin by stimulating β-cells of Langerhans's isles, which are glucose sensors. The effect of counterinsular hormones on carbohydrate metabolism decreases and glucose concentration decreases to a normal level. Gastrine, secretine, cholecystokinine can stimulate releasing of insulin. The level of insulin in plasma can be identified by the speed of metabolism in the liver and in kidney due to insulin activating enzyme system and protease enzyme system.

Carbohydrate metabolism disorders of any of its three main stages:

1. **Cleavage and absorption of carbohydrates in the digestive tract.**

2. Synthesis and disintegration of glycogen in the liver.

3. Utilisation of carbohydrates by the cells.

Disturbance of one stage of carbohydrate metabolism or of the regulating mechanism cause disfunction of carbohydrate metabolism and it appears with the change of glucose concentration in blood (hypo- or hyperglycemia).

Physiological Hypoglycemia:

- It is observed at heavy and prolonged physical loading;
- in breast-feeding women;
- develops at once after alimentary hyperglycemia as a result of release of insulin in blood.

Pathological Hypoglycemia (with hyperinsulinism):

- the cause can be overdose of insulin in treatment;
- another cause can be adenoma of ß- cells of pancreas;
- Zolinger-Allison syndrome (adenoma or carcinoma of pancreas which develops from α- cells of pancreas responsible for allocation of glycogen).

Pathological Hypoglycemia (without hyperinsulinism):

• insufficiency of adrenal glands (deficiency of glucocorticoids);

• galactosemia and in some types of glycogenosis; starvation or unbalanced diet (alimentary Hypoglycemia);

• insufficiency of mechanisms of regulation of carbohydrate metabolism in newborns.

Physiological Hyperglycemies are quickly convertible conditions.

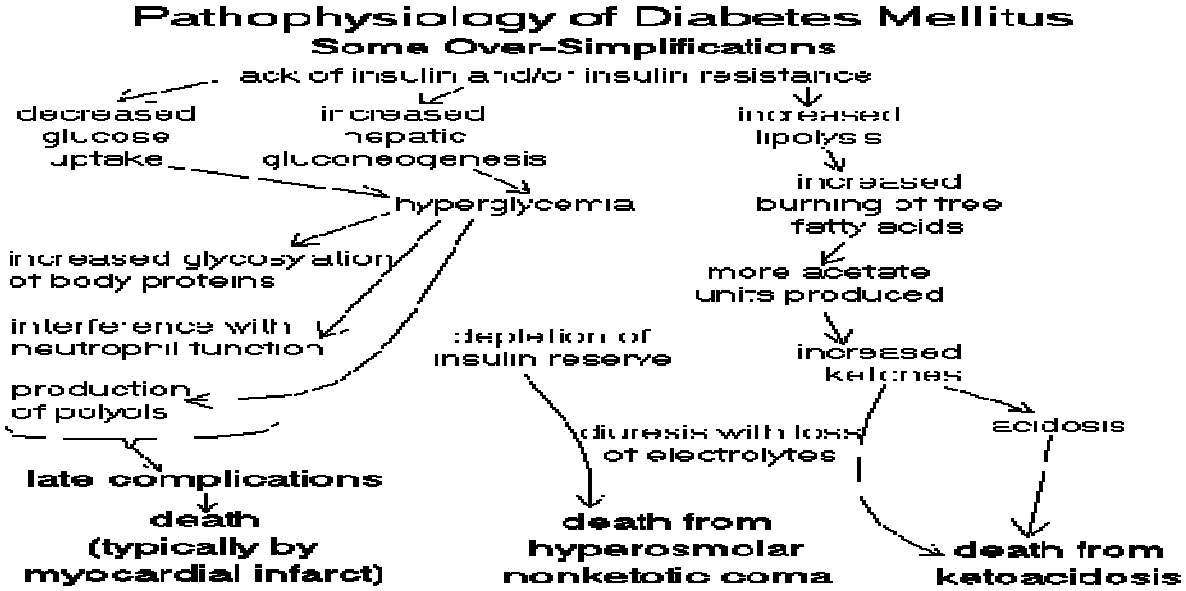
Normalization of the level of glucose in blood occurs without any external influence.

Pathological Hyperglycemia.

Its development can be caused:

by neuroendocrinal disorders, which disturb optimum balance between levels of hormones (insulin and countreinsulins) in blood, organic lesion of central nervous system, disorder of brain circulation; inflammatory or degenerative lesions of liver, convulsive conditions, some kinds of narcotic substances stimulate the sympathetic nervous system and promote development of hyperglycemia.

Most frequently pathological hyperglycemia is noted after insufficiency of insulin (diabetes).



Etiologic classification of Diabetes Mellitus (DM)

• Type 1 DM – Beta-cell destruction that usually leads to absolute insulin deficiency

– Immune-mediated

– Idiopathic

• Type 2 DM – predominantly insulin-resistant with relative insulin deficiency to a predominantly secretory deficiency with insulin resistance

• Gestational DM

• Other specific types

Although the 2 major types of diabetes have different pathogenic mechanisms and metabolic characteristics, the long-term complications are the major causes of morbidity and death from diabetes.

These complications include:

– coronary heart disease which can lead to heart attacks;
– retinopathy which can lead to blindness;
– nephropathy which can lead to kidney failure and the need for dialysis;
– neuropathy which can lead to, among other complications, foot gangrene requiring amputation.

Objective of experiment: To study mechanisms of development and pathogenetic meaning of hypo- and hyperglycaemia.

Experiment 1. Insulin hypoglycaemia in a mouse.

Method: Inject 0.25-0.5 units of insulin solution in 0.1 ml of isotonic solution subcutaneously into three starving mice of a dry mass of 20 g. Inject 1ml of 10% solution of glucose immediately intraabdominally into one of the mice. Mark all the mice and keep them under a glass funnel. After 30-60 min in the mice, which were injected with insulin without glucose, symptoms of hypoglycaemia coma will develop: unusual pose, tachycardia, bradycardia, fits. These phenomena are easily subsided after injecting 10% solution of glucose intraabdorninally or subcutaneously. Otherwise the mice, which were not given glucose, will die. On the basis of experiment 1 we can draw a conclusion about the role of carbohydrate metabolism disorders in vital activities of the body.

Multiple Choice Questions

Choose the right answer

001. POSSIBLE CAUSES OF HYPOINSULINISM ARE ***(choose the right answers)***

1) decrease of sensitivity of tissues to insulin
2) chronic excess of somatotropic hormone
3) chronic excess of adrenaline
4) prolonged excessive intake of carbohydrates with food

002. THE MAIN PATHOGENETIC LINK OF HYPOGLYCEMIC COMA IS

1) carbohydrate and energetic "starvation" of neurons of the brain
2) carbohydrate starvation of myocardium
3) hypoosmia of blood
4) non- compensated ketoacidosis

003. FACTORS WHICH CONTRIBUTE TO THE DEVELOPMENT OF DIABETIC ANGIOPATHY ARE ***(choose the right answers)***

1) excessive glycosilation of proteins
2) hyperlipidoproteinemia
3) dislipoproteinemia
4) deposit of sorbitol in the vascular walls

004. THE MAIN PATHOGENETIC FACTOR FOR TYPE 2 DIABETES IS

1) deficiency, low affinity of receptors of effector cells - "targets" to insulin
2) hyperglycemia
3) hyperketonemia

PART: STANDARD PATHOLOGICAL PROCESSES.

Theme: Standard disturbances of metabolism. Disturbance of lipid metabolism.

Objective of class: To study the etiological factors and general mechanisms of lipid metabolism disorders.

Pathologic changes in lipid metabolism can occur in case of the following impairments:

- impairment of the process of fat digestion and absorption;
- impairment of the transport of lipids and their transfer to tissues;
- impairment of lipid oxidation in tissues;
- impairment of intermediate lipid metabolism;
- impairment of lipid metabolism in fatty tissue (excessive or deficient lipid formation and deposition).

Lipids are classified into 2 general types:

– fats and waxes (can be hydrolyzed with ester linkages)
– cholesterol and steroids (cannot be hydrolyzed)

The main objective of studying lipid metabolism is to reveal as early as possible **hyperlipidemia** as a risk factor of cardiovascular disease (one of the leading causes of death). Hyperlipemia is characterized by an increase of lipids in blood serum of over 2 mmoles/l. One can distinguish alimentary, transport and retention hyperlipidemia.

Lipoproteins present a class of complex substances for example, free fatty acids, neutral fats, phospholipids and cholesterols can be present in the structure of lipoproteins.

The process of lipoprotein content increase, one or several classes, due to disorder of lipoprotein formation, transport and utilization in the blood plasma is called **hyperlipoproteinemia** (HLP).

HLP may be primary, i.e. caused by genetic anomalies and environmental factors, or secondary, resulting from such diseases as diabetes, liver and kidney conditions, hormone disorders, etc.

Hypo- or alipoproteinemia, i.e. lipid deficiency in the blood develops during a prolonged period of adipose transport damage.

Atherosclerosis development is closely associated with cholesterol transport to the arterial wall as part of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) and cholesterol release from the arterial wall with the help of

high-density lipoprotein (HDL). The primary process in case of atherosclerosis development is considered to be focal changes in the structure and function of endothelial cells of vascular wall. Local and systemic disorders of cholesterol and lipoprotein metabolism, dislipoproteinemias occur at the early stage of atherosclerosis development. In most cases the content of atherogenic particles increases in the blood plasma, the main component is cholesterol, apoprotein - B as a protein, and LDL concentration decreases in 30 % of cases. Cholesterol, triglycerides and saturated fatty acids have atherogenic properties. Atherogenic lipoprotein concentration increase can be caused by a decrease in their release from the blood to the liver, by an increase in their synthesis, by lipoprotein metabolism disorder in plasma including the formation of abnormal modified lipoproteins.

Obesity is a factor predisposing to the development of cardiovascular disease (atherosclerosis), gallstone formation, fatty infiltration of the liver, diabetes mellitus. Obesity is a tendency of the organism to increase the body weight excessively under the influence of certain conditions. In this case body weight increases due to abnormal fat accumulation.

Leptinic system plays a major role in body weight regulation. Leptin is a small protein produced only by adipocytes of fatty tissue; interacting with receptors of hypothalamus it leads to a sensation of satiety and individuals refuse to eat. Leptin level increases with the proliferation of fatty tissue. Obesity is considered to be associated with the decrease of tissue sensitivity to leptin. According to its etiology three types of obesity are distinguished: alimentary, normal and cerebral. Heredity plays an important role in the pathogenesis of obesity. Obesity develops as a result of three basic pathogenic factors:

- fat and carbohydrate overconsumption beyond the body's energy requirement;
- insufficient fat utilization as a source of energy;
- excessive formation of lipids from carbohydrates.

Objective of experiment: To study mechanisms of development and pathogenetic meaning of disorder of lipid metabolism – Hyperlipidemia, Obesity and Atherosclerosis.

Experiment 1. Alimentary hyperlipidemia of rats.

Method: It is necessary to feed an experimental rat with fatty food (bacon) plentifully for 3-4 hours before the beginning of experiment. From an experimental and control rat take blood with anticoagulant sodium citrate. After centrifugation of blood estimate appearance of plasma. If plasma of blood is transparent, the level of triglycerides does not exceed 2.2 mm/litre.

Expressed opalescence of plasma develops when concentration of triglycerides is 3-6 mm/l, milky color of plasma develops when concentration of triglycerides in plasma is more than 6 mm/l. Presence of chylomicrons in plasma can be revealed with the test of standing (at standing plasma during 16 hours at temperature +4°C there is "cream" on the surface of plasma).

Record the results. Draw a conclusion from the data about the change in the appearance of plasma. In any case you have to draw a conclusion about the occurrence of

Hyperlipidemia.

Multiple Choice Questions

Choose the right answer

001. DEVELOPMENT OF OBESITY WITHOUT CHANGES OF ADYPOCYTES NUMBERS

1) is possible
2) is not possible

002. DEFICIENCY OF LIPIDS IN AN ORGANISM DEVELOPS IN ***(choose the right answers)***

1) disturbance of lipids absorption in intestine
2) lipiduria
3) acne

003. ALIMENTARY HYPERLIPEMIA IS

1) increased level of chylomicrons in blood following fattening meals
2) increased cholesterol level in blood
3) increased blood lipids of low-density

004. TRANSPORT HYPERLIPEMIA DEVELOPS IN

1) reinforced mobilization of lipids from the depot
2) absorption of lipids in the intestine
3) amplification of lipids synthesis in the liver

PART: STANDARD PATHOLOGICAL PROCESSES.

Theme: Standard disturbances of metabolism. Disorders of water metabolism. Disturbance of ion exchange and acid-base balance.

Objective of class: To study the standard forms of water-salt metabolism disturbances and mechanisms of their development.

Water is present in the body in various sectors.

The intracellular sector contains about 55 % of total water in the human body which is found in free, combined and bound water forms.

The extracellular compartment makes up about 45 % of all water of total content of water in the body, which represents plasma, transcellular, interstitial and crystallised forms of water.

The water balance is a balance between the intake (2,5 l/day) and excretion

(2,5 l/day) of water. The water balance depends on the following three processes:

1) intake of water with food and drinking,

2) endogenous water formation which is formed during metabolic reaction,

3) excretion of water from the body.

Water balance is classified as positive, negative, neutral.

a) positive water balance in which the entry of water is more than excretion of water b) negative water balance in which excretion of water is more than the intake of water

c) neutral - in which the intake of water equals excretion of water.

Typical forms of water balance disorders are called **dyshydration**.

Dyshydration is classified according to three criteria:

The first criterion – water content in the body.

According to this there are:

1) Hypohydration (dehydration) – total water content in the body is reduced.

2) Hyperhydration - total water content in the body is increased.

The second criterion – osmolarity of extracellular fluid.

Depending on the osmolarity:

1) hypoosmotic - when osmolarity of blood plasma is less than 280 mOsm /kg),

2) hyperosmotic - when osmolarity of blood plasma is more than 300 mOsm /kg

3) isoosmotic form - when osmolarity of blood plasma is between 2800 - 300 mOsm /kg

The third criterion – compartment of the body in which disorder in the water exchange is present. According to this criterion we include :

1) cellular,

2) extracellular

3) mixed forms of water balance disorders or dyshydrations.

To characterize disturbances of water balance we can use the following terms:

1. Hypovolemia – decrease of volume of extracellular water.

2. Hypervolemia - increase of volume of extracellular fluid (in interstitial and intravascular compartmens); as a rule, hypervolemia is accompanied by development of oedema.

Oedema is excess accumulation of a fluid in interstitial space and in cavities of the body due to disturbance of fluid metabolism in capillary-tissue system.

Objective of experiment: To familiarize students with pathogenetic factors of the development of standard forms of water balance disturbance.

Experiment 1. Studying the role of hydrostatic pressure in the development of filtration rate.

Method: In a vertical glass tube set (imitation of hydrostatic pressure), the lower part of which is closed with a colloidal bag (imitation of the biological membrane), pour distilled water up to the mark 20-40 tag. Collect strained liquid. Note the amount of liquid that has strained from the marks 20 and 40 for 1 minute.

Record the results. Based on the data make a conclusion about the role of hydrostatic pressure in the development of oedema.

Experiment 2. Studying the role of osmotic pressure in the development of dyshydration in a frog.

Method: Introduce 0.2 ml of 20% NaCl solution in the dorsal lymph sac of experimental frog, and the same dose of saline solution to the control animal. Weigh both frogs and place them in the jar with water. After 20 min re-weigh them.

Record the results. Based on the data make a conclusion about the role of osmotic pressure in the development of dyshydria.

Experiment 3. Studying the role of pH in water bound by collagen hydrolysate.

Method: Take pieces of gelatin of the same weight and size, place them in three test tubes filled with 0.1 N solution of HCl, 0.1 N solution of NaOH and saline solution accordingly. After 20 min remove all three pieces simultaneously, dry them with filter paper and weigh.

Record the results. Based on the data make a conclusion about the role of pH in oedema formation.

Multiple Choice Questions

Choose the right answer

001. HYPOTHALAMUS PARTICIPATES IN REGULATION OF WATER-ELECTROLYTE EXCHANGE DUE TO ***(choose the right answers)***

1) synthesis of vasopressin
2) presence of the central osmoreceptors in 3-rd ventricle region
3) the ability to regulate intake of liquid through the thirst centre
4) sympathetic regulation of renin secretion by juxtaglomerular apparatus of kidneys
5) abilitiy to regulate a salt appetite

002. MANIFESTATIONS OF GENERAL DEHYDRATION SYNDROME ARE ***(choose the right answers)***

1) thirst
2) weakness
3) dry skin and dry mucosa
4) decreased arterial pressure
5) increase of blood viscosity
6) decrease of daily diuresis
7) decrease of body weight

003. LESION OF MEMBRANOGENIC FACTOR IS ASSOCIATED WITH

1) edema in starvation

2) Quincke's edema
3) edema in nephrotic syndrome
4) edema in hepatic insufficiency

004. EFFECTIVE HYDROSTATIC PRESSURE IN THE VENOUS END OF A CAPILLARY IN STAGNANT HEART INSUFFICIENCY

1) increases
2) decreases
3) does not change

PART: STANDARD PATHOLOGICAL PROCESSES.

Theme: Disturbance of tissue growth.

Objective of class: To study the initial factors and molecular mechanisms of carcinogenesis and interrelation of a tumor and the body.

Tumor process is pathological proliferation of cells due to a hereditary fixed capacity for unlimited, uncontrollable growth which differs from other types of pathological tissue overgrowth (hyperplasia, hypertrophy, regeneration after injury).

The **causative factor** leading to not lethal (for life of cells) DNA damage, is called carcinogen. Carcinogenic factors in nature are divided into three groups: chemical (polycyclic aromatic hydrocarbons), physical (ionizing radiation, ultraviolet radiation), biological (oncoviruses). Hereditary predisposition plays an essential role in the development of tumours.

The main targets of genetic DNA breakdowns in cell are as follows:

1) two classes of regulatory genes - initiating cell division, protooncogens and inhibitory cell division – suppressor genes (antioncogens);

2) the genes that control apoptosis;

3) the genes that regulate DNA repair.

Protooncogens in a normal cell accelerate cell division, participating in the transport of mitogenic signals from cell growth factor receptors to nucleus. The number of protooncogens is several dozen. Protooncogens Ras-coding proteins, MAP-kinase (ERK1, ERK2), transcription activating proteins (c-Jun, c-Fos, v-Jun, v-Fos), cell cycle "driving" proteins (cyclin-dependent serine/thyreonine-protein-kinase (Cdk) and cyclin themselves (G1-, S1-, G2- cyclin).

Due to mutations, protooncogens become dominant and turn into oncogens, encoding synthesis of oncoprotein. Oncoprotein activates intracellular signaling pathways dividing cells without external mitogenic stimulus. Oncoproteins trigger the genetic neoplastic programme, and neoplastic signs become manifest. The activation of oncogenes is not enough for tumor development, as suppressor genes (Rb, p-53, APC) impede uncontrolled cell growth arresting cellular mitosis at checkpoints. At the first checkpoint DNA damage is repaired as G1/S control mechanism blocks replication of DNA. Disturbance of reparation induces apoptosis.

At the second checkpoint G2/M monitoring mechanism blocks mitosis until replication is completed. Due to that the stability of genome is provided. In case of

mutation supressor genes become recessive allele, and the activity of proteins decreases rapidly; a cell with genetic breakdowns starts uncontrolled reproduction and creates a clone of similar descendants.

Three stages of pathogenesis of tumors.

1.**Initiation** of tumor growth.

At this stage normal cells acquire the capacity for unrestrained and uncontrolled division, but remain under the control of tissue and regulation of intercellular growth. Alleged mechanisms: a) oncoproteins bind to receptors for growth factors and form complexes generating signals for cell division, b) oncoproteins increase the sensitivity of receptors for growth factors (lower sensitivity to inhibitors of growth). Oncoprotein acts as growth factors.

2**. Promotion** occurs with participation of additional cocancerogene factors. Central to the pathogenesis of this stage is implementation of the newly acquired capacity for unrestrained and uncontrolled reproduction with formation of the primary tumor site. Alleged mechanisms: amplification of oncogenes, protooncogenes activation, additional genetic and chromosomal aberrations, inclusion of promoter.

3. Further growth and **progression of a tumor**. Progression means increasing signs of malignancy independently of each other. Prospective mechanisms are the same as in the 2-nd stage.

Objective of experiment: The study of tumor transplantation and properties of tumor tissue.

Experiment 1. Familiarization with a method of reproduction of tumor by transplanting malignant tumor tissue.

Method: Anaesthetize a mouse with Rocker`s sarcoma with ether, fix it to the dissecting table and shear the fur over the tumor. Smear the skin with iodine, make a cut, and extract a piece of the tumor. Cut the piece, in sterile conditions wash it with physiological solution in a Petri dish, and then carefully grind with scissors. Take the tissular suspension in a small amount of physiological solution in the syringe and inject 0.3-0.5 ml under the skin of intact mice aseptically. A few days after transplantation under the skin there appears an infiltration, and after 2-3 weeks, the tumor becomes large; general intoxication develops and the animal dies.

Experiment 2. Familiarization with a tumor subnoculation method by cell suspension.

Method: Anaesthetize a mouse with ascitic form Erlich`s carcinoma, as in experiment 1. The work is carried out in sterile conditions. Using a syringe aspirate 0,2 ml of abdominal ascetic fluid (from the abdomen cavity) diluted in 1 ml of physiological solution. Inject 0,2 ml of diluted ascetic fluid in aseptic conditions intraperitoneally. In about 10 days ascetic fluid accumulates, and after 3 weeks general intoxication develops and the animal dies.

Multiple Choice Questions

Choose the right answer

001. MANIFESTATIONS OF ATYPICAL GROWTH OF MALIGNANT TUMOURS ARE ***(choose the right answers)***

1) metastasis
2) without any recurrence
3) invasive growth
4) increase of proliferative pool of tumoral cells
5) retardation or the block of maturing of cells
6) weakening of contact retardation of cells

002. "A TUMORAL PROGRESSION" IS

1) qualitative and quantitative difference of basic biological properties of tumoral tissue from normal autologous one, and from pathologically changed tissues
2) qualitative and quantitative genetic peculiarities that are transmitted from to cell independently from each other and determine the extent of malignisation

003. ONCOPROTEINS ARE

1) proteins stimulating tumoral progression
2) proteins blocking cellular respiration
3) proteins oppressing glycolysis
4) proteins causing tumoral transformation of a normal cell

004. PATHOLOGICAL HYPERTROPHY OF TISSUE IS

1) increase of mass and volume of structural elements after formation of organs and tissues.
2) increase of mass and volume of structural elements of tissues and organs after excessive

physical exertion
3) increase of mass and volume of structural elements of tissues and organs inadequate to their function.

PART: STANDARD PATHOLOGICAL PROCESSES.

Theme: Extreme conditions.

Objective of class: To study the initial factors and mechanisms of urgent condition development: shock, coma, collapse.

Shock is a special conflicting condition of the organism homeostasis involving the loss of hemorheological and metabolic balance with a natural tendency to self-deterioration. Shock is a continuous pathologic systemic manifestation, which arises at the moment when the power and the time of action of primary lesions exceeds the 'shock threshold' when a haemorrhage becomes a hemorrhagic shock, sepsis becomes a septic shock, a musculoskeletal trauma becomes a traumatic shock and so on. A generalized reaction develops. Shock results from 'incongruous perfusion of tissues' which immediately affects 'incongruous cell metabolism', no matter what primary mechanism induced the shock.

Shocks of any aetiology have a number of pathogenic characteristics in common

- Decreased volume of circulating blood (VCB) in combination with increased vessel resistance owing to catecholamines.
- Hypoxia, lacticemia.
- Rheodynamic disturbances.
- Cell hypoxia, deficient energy genesis which is followed by accumulation of waste products and acidosis.
- Emergence of necrosis loci.
- Damage of a cell nucleus, impairment of DNA-chains and irreversible disorganization of cells.

The vitality of cells is impaired and they die **forming necrotic zones**. In the post-shock period these phenomena determine insufficiency of organs that is their disability to perform their specific functions.

Syncope which is a temporary loss of consciousness as a result of insufficient blood flow to the brain (cardiac rate disturbance, stimulation of the carotid sinus, pulmonary embolism). The action of the vagus nerve prevails (in case of shock sympathetic innervation prevails).

Fainting is considered a symptom and consists in incomplete transient loss of consciousness accompanied by decreased tone of muscular vessels of lower extremities and bradycardia. In case of shock a person may have tachycardia, cold sweat, loss of consciousness or may go pale.

Coma is a partial or complete loss of consciousness when vegetative functions are normal and the correlating functions are depressed in case of primary brain

lesions such as hypoxia, acidosis; it can occur at the final stage of shock.

Collapse occurs either in case of a sudden decrease of the content of vessels (haematogenic collapse) or in case of sudden dilation of vessels (vasomotor collapse). Collapse is a sign of a haemodynamic disturbance between the lumen of vessels and the volume of blood in them. In case of shock circulation becomes centralized, it can be treated with vasodilators while collapse is treated with vasoconstrictors.

Objective of experiment: Reproduction of experimental anaphylactic shock.

Experiment 1. Reproduction of anaphylactic shock in a mouse.

Method: Sensibilisation of the mouse must be made 2-3 weeks before the experiment by injecting horse serum (0.1 ml for 3 days). After registration of the pneumogramme of the mouse inject a dose of horse serum intraabdominally in the amount of 0.5-0.7 ml. Notice the development of anaphylactic shock, register the respiratory volume and indicate the activities of the animal. Enter your result into your protocol and discuss it. On the basis of the obtaned findings draw your conclusions about the causes and mechanisms of the anaphylactic shock development.

Multiple Choice Questions

Choose the right answer

001. EXTREME CONDITIONS ARE

1) uraemic coma, diabetic coma, traumatic shock, collapse
2) immunodeficiency conditions, hyperhydration, hypervolemia

002. MANIFESTATIONS OF TORPID PHASE OF SHOCK ARE

1) tachycardia, arterial hypertension, motor and speech excitement, hyperreflexia
2) weakening of effects of symphato-adrenal and hypophysis-adrenal systems, decrease of heart function, deposition of blood in peripheral blood stream , arterial hypoxemia, oliguria

003. CHANGES OF NERVOUS AND ENDOCRINE SYSTEMS IN ERECTILE STAGE OF SHOCK ARE

1) decrease of activity of sympatho-adrenal system, decrease of activity of hypothalamo-pituitary system, sleepiness of the patient
2) activation of sympatho-adrenal system, activation of

hypothalamo-pituitary system, excitement of the patient

004. CHANGES OF NERVOUS AND ENDOCRINE SYSTEMS IN TORPID STAGE OF SHOCK ARE

1) decrease of activity of sympatho-adrenal system, decrease of activity of hypothalamo-pituitary system, hyporeflexia, retardation of the patient
2) activation of sympatho-adrenal system, activation of hypothalamo-pituitary system, excitement of the patient, hyperreflexia

005. CAUSES OF COMA ARE THE FOLLOWING

1) autointoxication with products of metabolism and disintegration of substances, deficiency of necessary substrates of metabolism, exogenic intoxication, endocrinopathy
2) extracellular hyperhydration, normoosmolar hypervolemia, hypolipidemia

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of nervous system.

Objective of class: To study the etiology and main mechanisms of nervous system function disturbances, neurodystrophy and its influence on pathological process development.

Disturbances of the nervous system function can be caused by the same factors which cause damages of other organs and systems. However pathogenesis of nervous system diseases has a number of features:

1. Destruction of neurons leads to irreversible consequences so long as nervous cells of adult are not capable of division.

2. The zone of inhibition around the injured nervous cells which has protective value («protective inhibition» by I.P. Pavlov) increases and aggravates the functional defect.

3. Functional recovery occurs not due to regeneration of neurons (which do not restore) but due to normalization of reversible damaged cells and reduction of intact neurons inhibition.

The severity of consequences of a disease is determined by measure of compensation of lost neurons activity by uninjured neurons. Thus two main

interrelated mechanisms of compensation are called into action:

1) ability of neurons to reorganize their synaptic contacts to target cell;
2) ability of nervous system to training and formation of new skills.

Presence of paracrine, unimpulsive and neuropeptide activity of nerve endings in tissues underlies a phenomenon of nervous trophism (Magendie F., 1824, Orbeli L.O., 1935, Speranskij A.D., 1937) and explains neurodystrophy as a nonspecific component of any pathological process development.

Theoretical base of experimental models of neuropathological syndromes development such as: convulsive, painful, emotional behavioural is the theory of generator, determinant and systemic mechanisms developed by academician G.N.Kryzhanovsky.

Objective of experiment: To become familiarised with forms of disturbances of reflex activity.

Experiment 1. Disturbance of a reflex in case of switching out of the afferent tract after cutting-off the sciatic nerve of a frog.

Method: Inject 5% solution of Hexenalum subcutaneuosly into an intact frog in proportion of 0.2-0.3 ml per 100 g of weight. When deep narcosis in one of the lower extremities is achieved, prepare the sciatic nerve and ligate it. The other extremity is a control one. Accomplish painful irritation of both extremities. Note how the control extremity reacts to irritation with a motor reaction. There is no reaction in the extremity with ligated nerve because afferent tracts of the reflex are switched out.

Write down the results of the experiment. On the basis of the obtained data draw a conclusion about the causes of reflex activity disturbance.

Experiment 2. Disturbance of some kinds of sensitivity in case of partial lesion of the spinal cord.

Method: After studying pain, tactile and temperature sensitivity in the intact frog (with the help of electric irritation of the skin sector, Turk's reflex and plunging the posterior extremities into the vessel with warm water) inject 0.5 ml of 1% Hexenalum solution into the lymphatic sack, make laminectomy on the level of scapulae and carefully dissect the left or the right half of the spinal cord. Thirty minutes later, when the influence of narcotic substance decreases, verify sensitivity of both extremities again.

Write down the results of the experiment. On the basis of the obtained data draw a conclusion about the causes and mechanisms of sensitivity disturbance.

Experiment 3. Disturbance of the reflex activity in case of spinal shock.

Method: Determine the time of Turk's reflex in the intact frog. Simultaneously dissect the spinal cord on the level of 3-4 thoracic vertebrae and immediately note the time of reflex again. During the following 30 minutes note the time of reflex every 5 minutes.

Write down the results of the experiment. On the basis of the obtained data draw a conclusion about the causes and mechanisms of disturbance of the reflex activity of the spinal cord.

Experiment 4. Disturbance of the reflectory activity in condition of switching out the receptor apparatus of the reflex arch.

Method: Determine the time of Turk's reflex in a frog. Inject subcutaneously into the upper third of the leg 1ml of 0.5% solution of Novocainum. Note the time of Turk's reflex again.

Write down the results of the experiment. On the basis of the obtained data draw a conclusion about the causes of the reflex activity disturbance.

Experiment 5. Disturbance of the motor activity in condition of camphor epilepsy.

Method: Take two mice. One is intact, the other is under narcosis. Inject intramuscularly 0.3-0.4 ml of warm camphor oil to both mice. Watch the behaviour of both mice. Write down the results of the experiment.

On the basis of the obtained data draw a conclusion about the causes and mechanisms of disturbance of the motor activity in condition of epilepsy.

Multiple Choice Questions

Choose the right answer

001. CHANGES IN THE NERVE INTEGRITY DISORDER:

1) the peripheral part of the nerve regenerates, but the proximal part degenerates
2) the proximal part of the nerve regenerates, but the distal part degenerates

002. A MARKED DENERVATION SYNDROME DEVELOPS AS A RESULT OF

1) dissociation of the nervous system from organs and tissues
2) dissociation of the cerebral cortex from the subcortical centres
3) partial decortication

003. TYPICAL MANIFESTATIONS OF THE CENTRAL PARALYSIS ARE

1) preservation of voluntary movements, absence of tendon reflexes, atrophy of muscles
2) increase of a muscle, strengthening of tendon reflexes, loss of voluntary movements, development of pathological reflexes

004. CHARACTERISTIC MANIFESTATIONS OF PERIPHERAL PARALYSIS ARE

1) strengthening of spinal reflexes, development of pathological reflexes, hypertonus of muscles
2) hypertrophy, muscular hypotonia, hypo-, areflexia

005. «PAINFUL IMPULSATION» IS PROVIDED BY PERIPHERAL NERVES FIBRES

1) fibres A- alpha, fibres A-beta, fibres A- gamma
2) fibres A-delta, fibres of group C

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of endocrine system.

Objective of class: To study the causes and mechanisms of the development of basic types of endocrine disturbances, stress– reaction, distress and stress-limiting systems.

The endocrine and nervous systems co-ordinate the functions of the other organ systems as regulators of the function of the whole body.

The endocrine system exerts its influence through blood-borne substances (hormones) produced in glands without secretory ducts (endocrine glands).

The endocrine glands comprise the **hypothalamo-hypophyseal axis**, which regulates the function of the thyroid, parathyroid, adrenal, and reproductive glands. Other important hormones are the growth factors, cytokines and gastrointestinal hormones.

Hormones are messenger or signal molecules. Classical endocrine hormones are secreted into the blood and transported to their distant target cells, which are equipped with receptors that recognise each hormone. The hormones co-ordinate the activities of different cells in order to maintain homeostasis and to secure growth and reproduction. Hormone molecules form a large signal family together with neurotransmitters, autocrine and paracrine acting substances.

Paracrine and autocrine signal molecules are secreted and diffused into the interstitial fluid surrounding the cells and their actions are restricted either to nearby cells (paracrine) or to the cell of origin (autocrine).

Neurotransmitters (acetylcholine, adenosine, amines, amino acids, ATP, peptides) exert a type of paracrine action, since they are released in the synaptic region.

All reactions in the cell linking stimulation and secretion together are termed stimulation-secretion couplings. Stimulation-secretion coupling involves depolarization of the cell membrane or opening of Ca^{2+} -channels, so that Ca^{2+} can diffuse into the cell and combine with its Ca^{2+}-binding proteins. A rise in intracellular concentration [Ca^{2+}] is necessary for exocytosis.

Elimination of hormones takes place by metabolic processes such as the inactivation of peptide hormones by proteolytic enzymes, or the transformation of hormones in the liver. Hormones are also eliminated by excretion in the urine or bile. In the liver hormones are coupled to glucuronic acid or sulphate, but these hormones are in part reabsorbed in the entero-hepatic circuit.

Protein binding protects small hormone molecules (such as the thyroid hormone) from elimination. Protein binding also eases the transportation of the lipid-soluble steroids, and maintains equilibrium with a small free pool of hormones, so the concentration of free hormones is maintained.

Hormones can be divided into three chemical categories:

Peptides and proteins include neuropeptides, pituitary and gastrointestinal hormones.

Steroids consist of adrenal and gonadal steroids and vitamin D, which is converted to a hormone. Steroids are lipid soluble (lipophilic).

Monoamines (modified amino acids) comprise catecholamines, histamine, serotonin, and melatonin. Catecholamines (dopamine, noradrenaline and adrenaline) are derived from tyrosine - and serotonin/melatonin from tryptophan - by a series of enzymatic conversions. Monoamines and amino acid hormones are water soluble just like peptides. Thyroid hormones are iodinated derivatives of tyrosine, and thyroid hormones are lipophilic.

The water-soluble hormones are packed in the Golgi complex in secretory granules that migrate to the cell surface.

Exocytosis of the granule contents to the interstitial fluid (ISF) and diffusion through fenestrae to the capillary blood is a common method. The secretory cells are first stimulated by chemical or electrical signals.

Transcription of the hormone gene results in a specific mRNA determining the synthesis of a single hormone. However, a single gene may dictate the synthesis of different peptides in different cells. As the signal protein is cut off, the prohormone is formed and transported to the Golgi apparatus and stored in granules. The hormone specific amino acid sequence is contained in the prohormone.

An endocrine feedback system is a system whereby the first hormone controls the secretion and liberation of the second. The second hormone acts by feedback to modulate the secretion of the first.

A negative feedback system contains at least one step of inhibition. The total effect is to minimise any external change introduced to the system. Almost all hormone systems maintain homeostasis by negative feedback.

A positive feedback system exaggerates any primary change initiated. - This is an auto-accelerating phenomenon and a rarity.

The most important example in humans is the steep rise of estradiol in blood in the middle of the menstrual cycle. High estradiol, when maintained for longer than 35 hours, stimulates by positive feedback, the luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion from the adenohypophysis, which further stimulate oestradiol secretion etc.

By contrast, moderate plasma estradiol levels, which are present during the other parts of the cycle, provide negative instead of positive feedback. Long feedback systems act on the hypothalamo-pituitary system from remote target organs.

Short feedback systems use a short distance feedback, such as the influence of the hypophysis back to the hypothalamus. Auto-feedback refers to the action of a liberated hormone that was secreted on the cell from where it came thereby modulating its own secretion.

The causes of the endocrine disturbances are:

1) psychic trauma;

2) necrotic changes of the gland;

3) tumours;

4) inflammatory processes;

5) bacterial and viral infections;

6) exogenous and endogenous intoxications;

7) local disorders of blood circulation of the gland;

8) alimentary disorders (deficiency of iodine, cobalt, magnesium, lithium in food and drinking water);

9) ionizing radiation;

10) congenital chromosomal and genetic disorders.

Inheritable factors, congenital anomalies of sex development (dysfunction of gonads, true and false hermaphroditism), disturbances of the embryonic stage of development play an important role in arising of endocrine disturbances. Deficient (hypofunction) or increased (hyperfunction) activity of the endocrine glands is of major significance in the pathogenesis of most endocrine disturbances. Dysfunction of endocrine glands is also an independent form of endocrinopathies. It is characterized by various changes of production of hormones and physiologically active precursors, their biosynthesis in the same endocrine organ or synthesis of atypical hormonal products and their passing to blood. According to the extent of lesion of endocrine system there are the following mechanisms of endocrine diseases:

1) disturbance of the central regulation of endocrine functions;

2) disturbance of the biosynthesis and secretion of hormones;

3) disturbance of the transport, metabolism and realization of biologic action of hormones.

Besides independent forms of endocrine diseases, it is necessary to take into account the fact that disturbance of hormonal balance in the body creates a favorable background for arising and development of non-endocrine diseases. So, relative or absolute deficiency of corticosteroids promotes the development of rheumatism and bronchial asthma. Arterial hypertension may be a consequence of an increased secretion of glucocorticoids, aldosterone, catecholamines.

Objective of experiment: To study the role of hypothalamo-pituitary-adrenal axis, hypophysis, thyroid gland and adrenal glands disturbances in metabolism regulation and processes of human vital activity in experiment.

Experiment 1. Operation of adrenal glands excision in white rats.

Method: The operation is carried out in sterile conditions. The rat is fixed on the table in position with the abdomen downwards. Cut the fur on the back in the area of

inferior thoracic and lumbar vertebrae. The skin is treated with iodine solution. The rat is given ether narcosis. The operative field is covered with gauze pads. Make a 2 cm long incision down the medium vertebral line. Then dissect the aponeurosis on each side (retreat 0.5 cm from the vertebral edge), pull its edges externally. Separate muscles in the blunt way. Find adrenal glands near the superior pole of kidneys, bring the ligature under adrenals and extirpate them. 2-3 days later use the rat for experiment № 4.

Explain the character of changes in hypothalamo-pituitary-adrenal axis in unilateral and bilateral adrenalectomy in a rat. Describe mechanisms of urgent and long-term compensation in modeling of unilateral adrenalectomy.

Experiment 2. Adrenaline influence on resistance of white rats with extirpated adrenal glands to physical load.

Method: The experiment is carried out with two rats, whose adrenal glands were extirpated 2-3 days earlier. 15-20 min before the experiment inject to one of the rats 0.1% adrenaline solution intraperitoneally in proportion of 0.5 ml per 100 g of weight. The second rat is control. Before and after the injection of the drug study the behavior of the animals, take their body temperature, count the rate of respirations per minute. Then simultaneously put both rats into a vessel with water (temperature 35-37°C). Study the duration of swimming of each rat and their mobility. Determine the difference in behavior of the animals, in the change of their respiration. Compare the results and draw conclusions.

Experiment 3. Manifestation of experimental hyper –and hypothyroidism in white rats.

Method: Take three rats with the same body mass 7 days before the experiment. The first rat is a control one, hyperthyroidism is induced in the second one (by giving thyroidin in a dose of 0,1 g per 100g of body mass with food for 5 days), hypothyroidism is induced in the third rat (giving methylthiouracil in a dose of 30mg per100g of body mass).

Determine the rats' body mass, motor activity, respiratory rate, take an electrocardiogram in class. Compare the obtained data for every rat. On the base of the obtained data draw conclusions

Experiment 4. **Change of sensitivity to hypoxia in rats with experimental hyper– and hypothyroidism.**

Three rats (control, with hyper– and hypothyroidism) are put into glass containers of equal volume which are closed air tightly simultaneously. Note the time and high-grade hypoxia according to behavior changes in animals, respiratory types, appearance of cramps and time of death.

Enter the obtained results into your protocol, compare indices (figures) for each rat, explain their difference, and prove your conclusion.

Multiple Choice Questions

Choose the right answer

001. ENDOCRINE GLANDS REGULATED BY TRANSHYPOPHYSIS MECHANISM ARE

1) thyroid gland, cortex of
adrenal glands
2) adrenal medulla

002. EXCESSIVE PRODUCTION ACTH (ADRENOCORTICOTROPIC HORMONE) LEADS TO STRENGTHENING OF SECRETION OF

1) androgenic corticosteroids, corticosterone, cortisone, aldosterone
2) noradrenaline, adrenaline

003. THE MOST TYPICAL CONSEQUENCES OF PROLONGED PATHOLOGICAL STRESS ARE

1) anemias, hypertrophy of adenohypophysis, allergic reactions
2) hypodystrophia and dystrophia of a cortical layer of adrenal glands, suppression of humoral and cellular parts of immunity, erosion of a mucous membrane of the stomach and intestine, arterial hypertension

004. CHANGES TYPICAL OF THE 1ST STAGE OF THE COMMON ADAPTABLE SYNDROME ARE

1) increased size of thymus and lymph nodes, depletion of the function of adrenal glands cortex
2) activation of adrenal glands cortex, decreased size of thymus and lymph nodes

005. THE CORRECT SEQUENCE OF STAGES OF STRESS – REACTIONS IS

1) stage of resistence - stage of depletion, alarm reaction
2) alarm reaction - stage of resistence - stage of depletion
3) stage of resistence - alarm reaction - stage of depletion
4) alarm reaction - stage of depletion - stage of resistence
5) stage of depletion - alarm reaction - stage of resistence

006. HYPERFUNCTION OF THYROID GLAND

1) can have an autoimmune etiology
2) cannot have an autoimmune etiology

007. CHARACTERISTIC CHANGES FOR ADDISON'S DISEASE ARE

1) decrease of volume blood circulation and dehydration, decrease of arterial blood pressure, fatigue and muscular weakness, hypoglycemia
2) edema, tachycardia, accumulation of Na^+, loss of K^+ in organism

008. ENLARGMENT OF THYROID GLAND

1) indicates its hyperfunction
2) does not indicate its hyperfunction

009. CONDITION WHICH IS NOT ACCOMPANIED BY HYPERGLYCEMIA IS

1) acromegaly
2) inculinoma
3) Itsenko-Cushing syndrome

010. HYPERTHYREOIDISM IS CHARACTERISED BY THE FOLLOWING FEATURES:

1) decrease of concentration of Ca^{2+} in plasma of blood, increase of phosphates in plasma of blood, tetany
2) decrease of concentration of Ca^{2+} in plasma of blood, softening of bone tissue (osteomalacia)

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of immune system.

<u>Objective of class:</u> To study the principles of classification, general mechanisms of the development and specific features of allergic reactions.

Pathophysiology of the immune system includes immunodeficiency state, allergy, autoimmune and immunoproliferative diseases.

Immunodeficiency is a defect manifested by frequent, prolonged, and often life-threatening infections (also caused by otherwise harmless infectious agents) and certain tumors.

AIDS (acquired immunodeficiency syndrome) is caused by HIV-1 or HIV-2 (HIV = human immunodeficiency virus).

The term hypersensitivity or allergy is used to describe immune responses which are damaging rather than helpful to the host. Nearly 40 years ago Gell and Coombs proposed a classification scheme which defined 4 types of hypersensitivity reactions. The first 3 are mediated by antibody, the fourth by T cells.

Summary of Hypersensitivity classification

TYPE	DESCRIPTIVE NAME	INITIATION TIME	MECHANISM	EXAMPLES
I	IgE-mediated hypersensitivity	2-30 mins	Ag induces cross-linking of IgE bound to mast cells with release of vasoactive mediators	Systemic anaphylaxis, Local anaphylaxis, Hay fever, Asthma, Eczema
II	Antibody-mediated cytotoxic hypersensitivity	5-8hrs	Ab directed against cell-surface antigens mediates cell destruction via ADCC or complement	Blood transfusion reactions, Haemolytic disease of the newborn, Autoimmune Haemolytic anaemia
III	Immune-complex mediated hypersensitivity	2-8hrs	Ag-Ab complexes deposited at various sites induces mast cell degranulation via FcgammaRIII, PMN degranulation damages tissue	Arthus reaction (Localised); Systemic reactions disseminated rash, arthritis, glomerulonephritis
IV	Cell-mediated hypersensitivity	24-72hrs	Memory TH1 cells release cytokines that recruit and activate macrophages	Contact dermatitis, Tubercular lesions

Three stages are distinguished in any form of allergy: immunological, pathochemical, pathophysiological. An antigen causes sensibilisation of the organism when it enters the organism. Sensibilisation is the term, which explains the time duration from the injection of an antigen up to the formation of an antibody or sensibilated lymphocytes to this antigen. The pathochemical stage initiates after secondary introduction of an antigen. In the pathochemical stage formation of biologically active mediators takes place. The stimulus to their occurrence is the interactions of an allergen with antibodies or with sensibilated lymphocytes. Releasing bioactive substances and interactions with the body marks the pathophysiological stage. False allergic reactions are characterized by allergic signs, but have no immunological stage or sensibilisation in their development.

Objective of experiment: Reproduction of the experimental anaphylactic reaction and local allergic reaction, their study.

Experiment № 1. Arthus phenomenon (demonstration).

Method: 20-30 days before starting the practical lesson 1 ml of normal horse serum is administered to the experimental rat. Injections are carried out in sterile conditions under the skin five times at a 5-6-day interval.

After the 3-rd and the 4-th sensitizing an infiltrate is formed in the place of serum introduction. Afterwards acute hyperergic inflammation with necrosis develops.

Experiment № 2. Anaphylactic reaction of the frog's heart and vessels.

Method: For this experiment sensitized frogs are taken. Sensitization is formed by introduction of normal horse serum (0.3 ml) into lymphatic sack of the frog 3-5 times at a 3-4-day interval (frogs must be big and strong, taken in summer or autumn and they are kept at temperature 20-22^{0}C).

A. Anaphylactic reaction of the frog's mesentery.

A sensitized frog is administered 10% solution of uretan for immobilization (1,5-2 ml is introduced into lymphatic sack of the frog) and fixed on the cork board. The back of the frog must be up and its right side must be close to the hole of the cork board. Then mesentery is taken from the abdominal cavity and stretched under the hole of the cork board and fixed with needles. The main characteristics of initial blood circulation such as capillary filling, blood vessels lumen, blood circulation rate and etc. are noted. Later on, 5 drops of antigene are placed on the mesentery. After that, blood corpuscles going out the blood vessels of the mesentery into the surrounding tissues can be observed in 3-5 minutes already. Some of the small vessels become empty and blood corpuscles are absent, but nevertheless contours of these vascular walls are clearly visible. In 1-2 minutes the blood flow slows down appears and stasis develops in the larger vessels of the mesentery (in some cases stasis develops within the first 2-3 minutes after antigen placement on the mesentery).

B. Anaphylactic reaction of the frog's heart.

A sensitized frog is fixed on the cork board with its belly up. Chest muscles of the frog are opened. The sternum is taken and raised, then its lower part is ablated, the heart is opened and the pericardium is taken off. The apex of the heart is taken with the serphin connected with the lever for recording heartbeat on cymograph.

Changes of heartbeat are observed after placing 6 drops of normal horse serum on the heart of the sensitized frog: the heart rhythm becomes irregular, the amplitude of heartbeat reinforces at first and then reduces right up to a temporary stop. Almost in all cases, after washing the heart with physiological solution cardiac activity is gradually restored to normal.

In 15 minutes 6 drops of previous antigen are applied on the heart again. But now there is no reaction of the heart or it is less manifest.

Enter the result of the experiment into your protocol. Come to the conclusion about the mechanism of development of local allergic reactions.

Multiple Choice Questions

Choose the right answer

001. LOW -MOLECULAR SUBSTANCES, FOR EXAMPLE, IODINE, SALTS OF GOLD, PLATINUM AND COBALT ACTING AS A HAPTEN

1) can cause the condition of sensitization
2) cannot cause the condition of sensitization

002. CONDITION WHICH REFERS TO ALLERGIC REACTIONS OF THE III^{D} TYPE OF IMMUNE DAMAGE IS

1) local reactions like Arthus phenomenon
2) serum disease
3) autoimmune hemolytic anemia
4) acute glomerulonephritis

5) exogenous allergic alveolitis

003. NON-TYPICAL CONDITION FOR AN ALLERGIC REACTION OF THE I^{ST} TYPE OF IMMUNE DAMAGE IS

1) the leading part of immunoglobulin E in pathogenesis
2) reaction develops 15-20 minutes after a repeated contact with an allergen
3) reaction develops 24-48 hours after a repeated contact with an allergen
4) histamine, kinins, leukotrienes, prostaglandins, thromboxane A_2 play the basic role in the mechanism of development of the disease

004. CLASS OF IMMUNOGLOBULIN IN ALLERGIC REACTIONS OF THE II^{ND} TYPE OF IMMUNE DAMAGE IS

1) Ig G
2) Ig A
3) Ig E

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of blood circulation system.

Objective of class: To study the etiology and mechanisms of the heart function disorders, hypotension and hypertensions, pathogenesis of essential hypertension.

Hypervolemia, or fluid overload, is the medical condition where there is too much fluid in the blood.

The opposite condition is hypovolemia, which is too little fluid volume in the blood.

In physiology and medicine, hypovolemia (also hypovolaemia) is a state of decreased blood volume; more specifically, decrease in the volume of blood plasma. It is thus the intravascular component of volume contraction (or loss of blood volume due to things such as hemorrhaging or dehydration), but, as it also is the most essential one, hypovolemia and volume contraction are sometimes used synonymously.

Hematocrit is a portion of general blood volume which is composed of erythrocytes. Hematocrit shows the ratio of erythrocytes to blood plasma, but not the total amount of erythrocytes. An increased hematocrit is seen in erythremia, symptomatic erythrocytosis (congenital heart disease, respiratory failure, hemoglobinopathy, liver growth accompanied by intensive erythropoietin formation, polycystic kidney); hemoconcentration in burn disease, peritonitis, dehydration (in marked diarrhea, intractable vomiting, profound sweating, and diabetes). A decreased hematocrit is seen in anemia, excessive hydration, second term of pregnancy.

Cardiac insufficiency is a typical form of pathology where the heart cannot pump enough blood to satisfy the nutritive needs of the body. Cardiac insufficiency is shown by decreased cardiac output and hypoxia of circulatory type.

Principles of classification of cardiac insufficiency types:

- According to its course: 1) acute, 2) chronic.
- According to the value of cardiac output (CO): 1) with decreased CO; 2) with increased CO (thyrotoxicosis, beriberi)).
- According to predominant involvement of a heart chamber: 1) left heart; 2) right heart; 3) total.
- According to pathogenetic principle: 1) myocardial; 2) overloading (preload is by blood volume, afterload is by resistance to blood flow); 3) mixed.
- According to primary nature of mechanism of development:

1) Primary (cardiogenic) cardiac insufficiency develops as a result of predominant reduction of contractile heart function in the value of venous blood inflow to the heart similar to normal (coronary heart disease (CHD), myocarditis, myocardiopathy).

2) Secondary (noncardiogenic) cardiac insufficiency arises due to primary predominant reduction of venous blood inflow to the heart in the value of contractile heart function similar to normal (hemorrhage, collapse, exudative pericarditis).

Reduction of contractile heart function is a result of cardiac insufficiency of various etiology. This fact gives the basis for conclusion: **in spite of distinction of causes and the known origin of initial links of cardiac insufficiency pathogenesis, its final mechanisms on cellular and molecular levels are identical.** The main following 4 mechanisms are distinguished:

1) Disturbance of energy supply of myocardium cells;
2) Damage of membranous apparatus and enzymatic systems of cardiac hystiocytes;
3) Ionic and fluid imbalance in cardiac hystiocytes;
4) Disorder of neurohumoral regulation of heart function.

Development of **compensatory hyperfunctioning** is a most common manifestation of protective and adaptive reactions in heart pathology.

For an estimation of disturbances of **Blood Pressure (BP**) the classification by WHO- JNC7 of 1999 is recommended (WHO - World Health Organization JNC7 – Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).

Classification of blood pressure disturbances (WH-JNC, 1999).

Blood pressure classification	SBP mmHg	DBP mmHg
Normal blood pressure		
Optimal	< 120	< 80
Normal	120-130	80-85
High normal pressure	130-139	85-89

Arterial hypertension		
Prehypertention	140-149	90 -94
Stage 1 HTN (“soft”)	140-159	90 -99
Stage 2 HTN (“medium”)	160-179	100-109
Stage 3 HTN (“severe”)	> 180	> 110
Isolated systolic hypertension	> 140	< 90

Types of haemodynamic changes in arterial hypertension

(by V.P.Kulikov , 2006).

For an estimation of pathogenetic mechanisms of **hypertension (HTN)** of importance is measurement of parameters of central haemodynamics. The major parameter of central haemodynamics is **SV – stroke volume of heart**. SV is 60-75 ml at rest. A derivate from SV is **MBV – Minute Blood Volume.** The norm is on average 3.5-5 l/min, and however deviations do not exceed ±10 % from **Must to be Minute Blood Volume (MMBV).**

MBV = SV x PR ; Where SV is the systolic volume, PR is the pulse rate

SV can be calculated by the formula of Starr:

SV = 100 + 0.5 PP – 0.6 DP- 0.6A , where **PP** is **Pulse pressure –** difference between systolic and diastolic pressure (mmHg); **DP** is **Diastolic pressure** (mmHg)**, A** is **age** (in years).

For each person there is a **Must to be Minute Blood Volume (MMBV)**, which can be calculated, if we know weight of the body, height and sex. In practice, more usefull is **CI (Cardiac Index)**, which can be easily calculated by the formula:

CI=MBV/S, where **MBV - Minute Blood Volume, S** is the **Surface area of the body** which is found by the formula:

S = root ((WxH)/3600) (m^2) where **W** is **weight of the body in kg, H** is **height of the body in cm.**

The **Cardiac index (CI)** of a healthy person is on the average **= 2.0-2.5 l / (min x m^2).**

Another major parameter necessary for an estimation of mechanisms of d**isturbance of** ABP is peripheral vascular resistance (CPVR). CPVR, common peripheral vascular resistance (dynes x sec x cm) characterizes the total vascular resistance created by resistive vessels, basically arterioles; consequently it serves for studying arterial tone, its changes in various pathological and physiological conditions. The normal CPVR is from 900 to 2500 dynes x sec x cm.

CPVR is calculated by the formula:

CPVR = (BP_a x 79.92)/MBV, where **79.92- the factor of transformation mmHg in dynes per cm^2,**

BP_a is an average BP which is calculated by the formula of Hickman:

BP_a= DP+ (SP - DP)/3, where SD is systolic pressure.

From another point of view it is more correct to use various height-weight parameters for estimation of **SPVR (Specific Peripheral Vessels Resistance).**

In the norm, SPVR varies within 35 to 45.

And it is calculated by the formula**: SPVR = BP_a/CI where BP_a - average arterial pressure in mmHg, CI is cardiac index in L / (min x m^2).**

Depending on the value of CI and SPVR we distinguish typical disturbances of the haemodynamics of arterial hypertension.

Types of haemodynamics in essential hypertension
(by L.I. Levina, A.M. Kulikova, 2007)

Type of haemodynamics	Cardiac index	
	male	Female
Hypokinetic	3.0 and less	2.5 and less
Eukinetic	3.1-3.9	2.6-3.5
Hyperkinetic	4.0 and more	3.6 and more

Normally, the types of disturbances of haemodynamics in arterial hypertension allow the doctor to be informed about the contribution made by both cardiac components (SV, MBV, CI) and vascular components (CPVR, SPVR) in the mechanism of increased blood pressure.

At early stages of development of arterial hypertension and for revealing of disregulation of cardiovascular system the estimation of reaction of BP to physical loading can be used.

There are three types of reactions of BP to physical loading:

Normokinetic – increase of BP is adequate to physical loading, CPVR is reduced, PP is increased. BP rises due to increasing SP while DP is reduced. Increase of SP is always proportional to physical loading; it also has its limits (not more than 160 mmHg at loading at the rate of 1 W per kg of body weight).

Hyperkinetic - inadequate increase of BP at physical loading is accompanied by normal or reduced CPVR, PP increased. BP will increase, BP increases due to SP increas, SP always increased disproportionately to physical loading and its level is higher than normal. DP cannot change or increases a little bit.

Hypokinetic – BP increased inadequately to physical loading. Also SV is reduced, CPVR is increased, PP is reduced. Increase of BP occurs due to an expressed increase of DP.

Objective of experiment: To study mechanisms of myocardium function disturbances and their electrocardiogram (ECG) signs. To study pathogenetic mechanisms of arterial hypertension.

Experiment 1. Reproduction of disturbances of heartbeat automatism.

Method. A frog immobilized by damaging the spinal cord is fixed in a supine position. Open the thorax and pericardium carefully, to count heart rate before and after application of a test-tube bottom with cold and hot water to the area of the sinus node (venae cavae orifice of the right atrium).

Write down the obtained results and explain the mechanisms of disturbances of heartbeat automatism**.**

Experiment 2. Reproduction of disturbances of myocardial conduction.

Method. A frog immobilized by damaging the spinal cord is fixed in a supine position. Open the thorax and pericardium carefully, to apply the first ligature of Stannius between the sinus and right atrium. Register the rhythm of atrial and ventricular contraction and the presence of complete loss of atrial and ventricular contraction.

Write down the obtained results and explain the mechanisms of disturbances of myocardial conduction**.**

Experiment 3. Reproduction of total atrioventricular heart block.

Method. A frog immobilized by damaging the spinal cord is fixed in a supine position. Open the thorax and pericardium carefully, to apply the second ligature of Stannius between the atriums and ventricle. Register the rhythm of atrial and ventricular contraction.

Write down the obtained results and explain the mechanisms of disturbances of myocardial conduction**.**

Experiment 4. Influence of cardiac tamponade on its work.

Method. A frog immobilized by damaging the spinal cord is fixed in a supine position. Open the thorax and pericardium carefully, to count beats per minute. Inject physiological solution to the pericardium under pressure. Compare the heartbeat count before and after introduction of fluid into the pericardium.

Write down the obtained result. Make a conclusion about the influence of cardiac tamponade on myocardial conduction**.**

Experiment 5. Experimental myocardial infarction.

Method: A frog immobilized by damaging the spinal cord is fixed in a supine position. Open the thorax and pericardium carefully. Connect electrodes to the limbs of the frog and register the initial ECG, after that on the left ventricle of the heart place some crystals of acidic silver nitrate which causes necrosis of the myocardium and then register the ECG readings. In acute stage of myocardial infarction (alteration and necrosis) in the ECG picture one can find dislocation of segment S-T from the isoline, because of difference in biopotential between the necrosed part and healthy tissue.

Experiment 6. Experimental reproduction of extrasystoles by inducing hyperkalemia condition.

Method: A rat lying under general anaesthesia with ether is fixed on a dissecting table in a supine position. Connect the limbs to the electrodes and register the bioelectric impulse of the heart. After the initial registration of ECG inject intra abdominally 1ml of 10% solution of potassium chloride per 100 grams of mass. After the absorption of potassium chloride from the abdominal cavity K^+ level in blood increases, which leads to a change in biopotential of the heart. In the ECG one can find extrasystoles. Due to the inhibition of the action of K^+ on the conduction system of the heart different types of block may develop. Paste the ECG readings of the rat into your protocol. Come to a conclusion about the cause of developing extrasystoles.

Experiment 7. Experimental reproducing of ischemia of the rat myocardium by injecting a big dose of adrenaline.

Method: Big dose of adrenaline acts on the metabolism of myocytes, increases oxygen need to the myocardium by causing a spasm of coronary vessels, which leads to ischemia of the myocardium. Weigh the rat, give general anaesthesia with ether, fix it in

a supine position. Connect the electrodes to the limbs and register the ECG readings in the initial state. Inject 0.1 ml 0.1% solution of adrenaline subcutaneously. Register the ECG changes each 10 min for 30-40 min, notice the processing of ischemia of myocardium developing (dislocation of S-T segment from the isoline, inversion of T wave, development of deep Q). Paste the ECG into your protocol. Draw a conclusion.

Experiment 8. Calculating Cardiac Index (CI) and Specific Peripheral Vessels Resistance (SPVR) of a patient.

Patient V. (50 years) was admitted to the department of internal diseases. From the anamnesis it is known he has had arterial hypertension for the last 10 years. In examination: weight - 82 kg, height – 168 cm, BP – 170/100 mmHg, PR - 92 per min.

Estimate the type of haemodynamics, peripheral vascular resistance (CPVR) and Specific Peripheral Vessels Resistance (SPVR).

Experiment 9. Calculating Cardiac Index (CI) and Specific Peripheral Vessels Resistance (SPVR) of a student.

Method: Measure the weight, height, BP and PR of a student in condition of physical and emotional rest.

Estimate the type of haemodynamics, peripheral vascular resistance (CPVR) and Specific Peripheral Vessels Resistance (SPVR).

Multiple Choice Questions

Choose the right answer

001. SIMPLE HYPOVOLEMIA IS OBSERVED IN CASE OF

1) after an acute blood loss in 30-40 min
2) overheating of the body

002. POLYCYTEMIC HYPERVOLEMIA IS OBSERVED IN CASE OF ***(choose the right answers)***

1) after an acute blood loss on the 4 th or 5 th day
2) erythremia (Vakes's disease),
3) chronic mountain disease

003. COMPARATIVE SURFACE OF A MUSCULAR FIBRE IN A HYPERTROPHIED MYOCARDIUM

1) decreases
2) increases

004. THE LEFT HEART INSUFFICIENCY IS CHARACTERIZED BY THE FOLLOWING CHANGES

1) system arterial pressure, pulse pressure
2) central venous pressure, pressure in capillaries of pulmonary artery

005. NON-TYPICAL FACTOR IN THE MECHANISM OF ISCHEMIC DAMAGE OF THE MYOCARDIUM IS

1) activation of phospholipases
2) activation of lipid peroxidation
3) activation of glycogenesis
4) increase of concentration of calcium ions in cytoplasm of cardiomiocytes
5) damage of mitochondrions

006. BIOCHEMICAL PARAMETERS OF BLOOD IN AN ACUTE HEART ATTACK ARE

1) decrease of activity of lactate dehydrogenase, decrease of content of lactic acid
2) increase of activity of creatinphosphokinase, increase of content of prothrombine, increase of activity of aspartate aminotransferase, lactate dehydrogenase

007. PATHOGENETIC FACTORS OF DEVELOPMENT OF HEART ARRHYTHMIAS ARE ***(choose the right answers)***

1) deficiency of ATP in the cells of the myocardium
2) loss of potassium ions by cardiomyocytes
3) accumulation of Ca^{2+} ions in sarcoplasm and mitochondrions
4) endocellular acidosis in cardyomiocytes

008. NEUROHUMORAL SYSTEMS WHOSE ACTIVATION LEADS TO RISE OF BLOOD PRESSURE IN ARTERIAL HYPERTENSION ARE

1) activation of renin-angiotensine system in the kidneys and tissues
2) activation of prostaglandin-kinine system in the kidneys
3) increase of production of Na-uretic factor

009. LOCAL AUTOREGULATION OF VASCULAR TONE IS MAINTAINED BY ***(choose the right answers)***

1) endothelin 1

2) thromboxane A_2
3) prostacyclin
4) endothelin relaxing (NO)

010. PULMONARY HYPERTENSION IS CHARACTERIZED BY

1) elevation of systolic, diastolic and intermediate
2) pressure in pulmonary artery
3) elevation of systolic pressure in pulmonary artery
4) elevation of diastolic pressure in pulmonary artery
5) elevation of intermediate pressure in pulmonary artery

011. MAIN LINK OF ACUTE VASCULAR INSUFFICIENCY IS

1) reduction of volume of blood circulation
2) spasm of vessels
3) elevation of venous pressure

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of blood system

Objective of class: To study basic principles of classification and mechanisms of the development of dyserythropoietic, hemolytic and hemodilution anemia, leucocytosis, leucopenia and leucaemia, physical and chemical properties of blood disorders, thrombosis and embolism.

Disturbance of **red blood cells system** includes polycythemia and anaemia.

Anaemia is defined as haemoglobin concentration in blood below the lower limit of the normal range for the age and sex of the individual.

CLASSIFICATION OF ANAEMIA

Several types of classifications of anaemia have been proposed.Two of the widely accepted classifications are based on pathophysiology and morphology.

PATHOPHYSIOLOGIC CLASSIFICATION

Depending upon the pathophysiologic mechanism, anaemias are classified into 3 groups:

1. Anaemia due to increased blood loss:
- acute posthaemorrhagic anaemia;
- chronic posthaemorrhagic anaemia.
2. Anaemia due to impaired red cell production:
- cytoplasmic maturation defects;
- deficient heme synthesis (iron deficiency anaemia);
- deficient globin synthesis (thalassaemic syndromes);
- nuclear maturation defect (Vitamin B_{12} and/or folic acid deficiency);
- direct stem cell proliferation and differentiation (aplastic anaemia, pure red cell aplasia);
- anaemia of chronic disorder;

- bone marrow infiltration;
- congenital anaemia.

3. Anaemia due to increased red cell destruction (haemolytic anaemia):
- extrinsic (extracorpuscular) red cell abnormalities;
- intrinsic (intracorpuscular) red cell abnormalities.

Smear for microscopic examination is characterized by normoblast model of blood formation, regenerative displacement with the appearance of polychromatophilic erythrocytes, reticulocytes and normocytes: oxyphiles, polychromatophiles and basophiles.

Smear for microscopic examination of patients with chronic posthemorrhagic anaemia is characterized by normoblast model of blood formation, hypochromia with signs of degenerative displacement: anisocytosis, poikilocytosis.

The smear for microscopic examination of patients with vitamin B_{12} and/or folic acid deficiency (megaloblastic anaemia) is characterised with megalobastic model of blood formation, hyperchromatism, has signs of degeneration, anisocytosis, poikilocytosis; Golly bodies and Cabot rings are seen in the cells.

The smear for microscopic examination of patients with hemolytic anaemia is characterised by normoblast model of blood formation, hypo-, iso-, hyperchromatism. The sign of regenerative displacement is the present of normocytes oxyphiles, polychromatophils and basophils and reticulocytes.

Disturbance of **white blood cells system** includes leukocytosis and leukocytopenia, leukemoid reaction, hemoblastosis and leukemia.

Leukocytosis is an increase in the total number of leukocytes (or their individual forms) beyond normal values due to physiological and pathological processes.

Leukocytosis is not an independent disease which has a temporary nature and disappears along with the factor which caused it. So this is a reaction of the blood to the corresponding etiological factors. Depending on the nature of these factors leukocytosis is classified into physiological and pathologic.

Mechanism of leukocytosis:

1) increased regeneration of leukocytes in bone marrow;

2) redistribution in the blood.

Leukocytosis can be physiological: for example, after meals, fright, different stress situations etc. This phenomenon is observed in the newborn babies during their first days of life, in females during and after pregnancy. It is generally a short-term reaction without any symptoms of illness. The mechanism of its occurrence is redistribution. The redistribution occurs from the existing pool of leukocytes in the vessels of the microcirculatory blood system, where most leukocytes are neutrophils. In this case it is neutrophilic leukocytosis without regenerative shift. This type of leukocytosis is not accompanied by a notable increase in blood leukocytes.

In the pathological forms, most common causes for leukocytosis are infections and septic conditions, necroses of tissue (myocardial infarction, kidney); systemic diseases of connective tissue are accompanied by leukocytosis. Reactive leukocytosis appears when there is a metastatic lesion of bone marrow.

Pathological leukocytosis can be of neoplastic or reactive origin. Neoplastic leukocytosis characterizes monoclonal leucosis (single cellular origin). Regenerative

leukocytosis is caused due to the increased effect of cytokines which stimulate proliferation, differentiation of leukocytes and their outflow from the bone marrow.

In pathological processes regenerative and degenerate shifts in the leukocytal composition of the blood occur. The regenerative shift is characterized by an increased content of young forms of leukocytes (myeloblasts, promyelocytes, myelocytes, metamyelocytes, lymphoblasts, myelolymphoblasts, monocytes and promonocytes) in the peripheral blood. Signs of degenerative shift are changes in the cytoplasm and in the nucleus of leukocytes, appearance of Knyaskova-Deli bodies, vacuolization with toxic grains, pycnosis. Pathology of white blood includes reactive states in the leucone, such as leukocytosis, leukopenia, leukemoid reaction and separate the blood system diseases, particularly leukemia.

Leukemoid reaction is a particular type of reactive state in the WBC, which is characterized by the presence of leukocytosis over a 40x (ten power nine) per litre with hypergenerative shift with the appearance of blast cells, combined with degenerative changes in the cytoplasm and nuclei of leukocytal cells in the peripheral blood.

Leukocytopenia means a decrease in the number of leukocytes in peripheral blood below 4.0 x109/l. Most often, leukopenia occurs when the blood has a reduced number of neutrophils. Reduction of neutrophils below 1500 cells/l allows us to say that it is neutropenia.

According to the pathogenetic principle we distinguish 4 types of *neutropenia*:

A) Neutropenia due to reduced production of neutrophils in the bone marrow. It develops due to a decreased proliferative activity of bone marrow or caused by difficulties in maturation of blast cells. Decreased proliferative activity is often associated with the myelotoxic effect on the precursor cells of myelopoiesis by cytostatics, radiation, and can lead to the development of immune agranulocytosis.

B) Neutropenia due to a slowdown in outflow of neutrophils from bone marrow into the blood stream. This neutropenia is associated with the reduction in the mobility of neutrophils. The so-called «lazy leukocyte syndrome» develops with defects in cytoskeleton and in the membrane of neutrophils. Due to this syndrome the bone marrow always contains more neutrophils. Mobility of neutrophils is impaired by the products of virulent micro-organisms, viruses, drugs (SFA). Limited mobility of neutrophils is also caused by a decreased number of receptors on their surface and reduction of glycogen, which is the main energy substrate of neutrophils (in diabetes).

C) Neutropenia due to reduction in the circulation time of neutrophils in blood stream. Most often, destruction of neutrophils occurs due to damage by the immune complexes.

The second cause which shortens the life of granulocytes after morphological and functional disability is B_{12} and folic acid deficient anemia and Chediak-Higashi disease. A peculiarity of this neutropenia is an active reaction of the bone marrow which is manifested by an enhanced production of promyelocytic and myelocytic cells.

D) Neutropenia associated with redistribution of neutrophils within the vascular channel. This is false neutropenia, benign and asymptomatic. The circulatory

pool of cells decreases in this case. This type of neutropenia is observed in athletes, after massive inflammatory processes, hyperthermia.

J) Acute agranulocytosis is registered if the total number of leukocytes decreases within the range 1.0-3.0 x10 /l, while the absolute amount is 750 cells/ml.

Leukemia is a tumor which originates from stem cells due to the primary damage of bone marrow.

In contrast to leukocytosis, leukemoid reaction and other types of reactive proliferation of the blood tissue, leukemia is uncontrolled cell proliferation, with a defect in differentiation and maturation. Leucotic cells, which have lost the ability to mature, can go through more cycles of division in comparison with normal cells, which provides for the enormous cell production typical of leukemia.

Leukemia is a tumor of hematopoietic system developing in the bone marrow. The target of neoplastic transformations during leukemia are bipotent and unipotent precursor cells, and, rarely, hematopoietic cells. Leukemia affects mainly the mechanisms of myelopoiesis or lymphopoesis, and is often characterized by: leukocytosis, and presence of immature, atypical cells in the peripheral blood. Proliferation of atypical cells in the bone marrow suppresses the normal hematopoietic tissue.

Leukemia is mainly classified into acute and chronic. Acute leukemia characterizes tumors with a complete halt-stop delay in differentiation and proliferation of hematopoietic blast cells; substrate for tumors comprises cells of II, III and IV classes according to modern pattern of hematopoeisis. The group of chronic leukemia is composed of tumors with a partial delay in maturation of cells and accumulation of cells with a certain degree of maturity. Blood smears of patients with acute leukemia are characterized by leukemic hiatus, i.e. the presence of blast cells and hypersegmented leukocytes. The content of intermediate forms of leukocytes gets dramatically reduced, which is characterized by the presence of leukemic hiatus. Normocytes are often found.

Blood smears of patients with chronic myeloid leukemia are characterized by the absence of leukemic hiatus, by the presence of basophilic-eosinophilic association. And also we can see myeloblasts, promyelocytes, myelocytes, metamyelocytes and segmented leukocytes. Blood smears of patients with chronic lympholeukemia are characterized by large numbers of mature lymphocytes, prolymphocytes and in blast crisis – lymphoblasts. Peculiarity is to detect in blood smears, cells of leukolysis (Botkin-Gumprecht shadows).

Basic laboratory tests allowing an evaluation of physical- chemical properties of blood are: osmotic resistance of erythrocytes, packed cell volume, protein composition of blood, and estimating the activity of coagulation and anticoagulation systems.

Erythrocyte resistance is their ability to withstand devastating effects: osmotic, mechanic, chemical, physical.

In hypertonic solutions erythrocytes lose water and shrink, but in hypotonic ones they absorb water and swell. In notable swelling hemolysis occurs. Isotonic solution for erythrocytes is 0.85% solution of sodium chloride. In 0.48 -0.44% solutions of sodium chloride less resistant erythrocytes (minimal osmotic resistance, upper threshold of resistance) are broken down. In concentration of 0.32-0.28% density all erythrocytes are hemolyzed

(maximal osmotic resistance, lower bound of resistance).

Decrease of osmotic resistance of erythrocytes (increase of minimal and maximal indexes of resistance) is observed in hemolytic disease in newborns and hereditary microspherocytosis, also (to a lesser degree) in toxicosis, bronchopneumonia, hemoblastosis, cirrhosis and etc. Decrease of osmotic resistance of erythrocytes takes place in some cases of polycythemia, and iron-deficiency anemia, as well as in haemoglobinosis S and after profuse bleeding.

The system of hemostasis is a set of biological and biochemical mechanisms, which, on the one hand, take part in maintaining the integrity of blood vessels and preservation of circulating blood fluidity, on the other hand – provide rapid congestion of damaged vessels and controlling bleeding.

Hemostasis is possible due to three interacting morphofunctionall components: vascular walls, blood cells (platelets) and plasma enzyme systems - coagulative, fibrinolytic (plasmatic), kallikrein- kinin and the system of complement.

Disorders of haemostasis include the following groups:

1. Conditions preceding thrombosis. Thrombotic syndrome development.
2. Haemorrhagic diathesis.
3. Disseminated intravascular coagulation (DIC).

Thrombosis is a process of a life-time formation of solid masses in the lumen of vessels, which consist of the blood elements impeding blood flow to some extent. These blood clots may be parietal or congestive.

Thrombosis may be caused by diseases which damage vascular walls. Firstly, these are inflammatory diseases (rheumatism, typhus, brucellosis, and syphilis), also atherosclerosis, ischemic heart disease, hypertonic disease, allergic processes.

Rudolph Virchow defined a “thrombotic triad”, according to which thrombosis may be caused by:

1. Damage of integrity of vascular walls
2. Abnormalities of activity of coagulative and anticoagulative systems
3. Deceleration of blood flow.

Thrombotic syndrome or thrombophilia is a condition which is characterized by excessive (inadequate) blood coagulation and thrombus formation, resulting in tissue and organ ischemia.

Haemorrhagic diseases and syndromes are pathologic conditions which are characterized by profuse bleeding as a result of incompetence of one or some haemostatic elements. Haemorrhagic diseases include the following groups: vasculitis, thrombocytopenia, thrombocytopathy, coagulopathy, DIC.

Phases of acute **DIC syndrome** are:

1. hypercoagulation and hyperaggregation;
2. coagulopathy and thrombocytopathy consumption with activation of fibrinolytic system;
3. generalization of fibrinolysis;
4. reconstruction.

Objective of experiment: To study the quantitative and qualitative changes in red blood cells and white blood cells system in pathology. To familiarise students with mechanisms of osmotic resistance of erythrocytes, types and mechanisms of

thrombosis and some other kinds of disorders of blood coagulation.

Experiment 1. Calculation of the number of erythrocytes in posthaemorrhagic anaemia.

Method: Posthaemorrhagic anaemia was induced in a rabbit by repeated blood-letting. The blood for count of erythrocytes was obtained from the marginal vein of the ear of the rabbit after a puncture with needle. The blood was collected in red blender to the mark of 0.5 and diluted with physiological solution to the mark of 101. The blender was shaken up for 2 min. 1/3 of contents was removed and was placed in the chamber of Goriaev. Erythrocytes count was done in 5 line large squares along diagonal. You have to use the formula:

$$Er = \frac{ax\,4000\,x200}{80}$$

where:

- **a** is the number of erythrocytes in five lines of large squares;
- **4000** is the volume of the small square in mm^3
- **200** is the degree of blood dilution;
- **80** is the quantity of the counted small squares.

You have to make a conclusion about the change of content of erythrocytes in posthaemorrhagic anaemia.

Experiment 2. Calculation of the number of reticulocytes in posthaemorrhagic anaemia.

Method: Students investigate the prepared smears of the blood, coloured with brilliant-cresyl-blue. The smear is examined under the microscope, with the immersion objective and ocular 7. The reticulocytes differ from erythrocytes by the presence of blue coloured net in their protoplasm. You have to count 1000 erythrocytes and note how many reticulocytes are among them.

You have to draw a conclusion about the content of reticulocytes in posthaemorrhagic anaemia.

Experiment 3. The study of morphology of blood in posthaemorrhagic anaemia.

Method: Prepare the smear of blood of a rabbit with experimental posthaemorrhagic anaemia. The smear is stained by Romanovski-Giemsa method for 20 min. The smear is dried and studied under the microscope. You have to note the colour, the form and the sizes of erythrocytes, signs of regeneration. You have to make a sketch of the smear.

Draw a conclusion about the character of failure in erythrocytes in posthaemorrhagic anaemia

Experiment 4. The study of morphology of blood in haemolytic anaemia.

Method: In the experiment haemolytic anemia is induced in a rabbit modelled with intradermal injections of 1% solution of phenylhydrosin for 10 days. Prepare a blood smear of the rabbit with experimental haemolytic anaemia.

Experiment 5. The study of blood smears of a patient with Vitamin B_{12} deficiency anaemia.

Method: Study the prepared smear of a patient with vitamin B_{12} deficiency anaemia. Sketch the cells typical of this kind of anaemia.

Experiment 6. Calculation of the leucocyte number in posthaemorrhagic anaemia.

Method: Calculate the number of leucocytes in 1mm^3 of blood of a dog, which has acute posthaemorrhagic anaemia. Collect in a mixer leucocytes to the mark 0.5 and 3% solution of acetic acid, stained with methylene blue to mark 2. After mixing the blood in a mixer for 3-4 min drop 2-3 drops from the mixer to fill the chamber of Goryaev. Calculate under slight magnification the number of leucocytes in 100 large squares, which are not divided into smaller ones. Determine the number of leucocytes in 1 mm^3 using the following formula:

$$L = \frac{ax4000\,x20}{1600}$$

where :

- **a** is the calculated number of leucocytes in 100 large squares;
- **4000** is the number of the small squares, their volume in 1 mm^3;
- **20** is the degree of dilution of the blood;
- **1600** is the number of calculated small squares.

The results need to be recorded. You have to draw a conclusion about the character of quantitative failure in leucocytes in posthaemorrhagic anaemia.

Experiment 7. Calculation of leucocyte formula of a patient with chronic leucaemia.

Method: calculate leucocyte formula of a prepared smear. Sketch the cells typical of this kind of leucosis. Record the results. Draw a conclusion about quanitative and qualitative disorders in leucocytes in chronic lymphocytic leucaemia.

Experiment 8. Calculation of leucocyte formula of a patient with chronic lymphocytic leucaemia.

Method: see experiment №7

Experiment 9. Calculation of leucocyte formula of a patient with inflammatory and infectious diseases.

Method: see experiment №7.

Experiment 10. Calculation of leucocyte formula of a patient with acute leukaemia.

Method: see experiment №7.

Experiment 11. Determination of the osmotic resistance in acute posthaemorrhagic anaemia.

Method: Scheme of carrying out the reaction and obtaining the concentration of hypotonic solution of sodium chloride.

Chemical	Test-tube number								
	1	2	3	4	5	6	7	8	9
1% sodium chloride, ml	4.0	3.5	3.0	2.5	2.0	1.5	1.0	0.5	0.0
Distilled water, ml	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Obtained concentration, %	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.0

It is necessary to add 2-3 drops of the blood into every test-tube. You have to determine the beginning and the end of hemolysis in one hour. You have to explain the mechanism of disorder of osmotic resistance in acute posthaemorrhagic anaemia.

Experiment: 12. Formation of a white thrombus.

Method: After giving anaesthesia to a frog and fixing it on a dissection table in ventral position open the abdominal cavity laterally. Catch the bowel and mesenterium carefully with the help of forceps and pull it over the opening in the board. Under the microscope one can find bifurcations of the mesenterial vein. (The vein can be differentiated from the artery by the direction and velocity of blood flow. In the artery blood flows from the main trunk to a branch and in a vein, inversely). Notice the character of the blood flow and then with the help of a moistened dissection needle, which is left with its apex to the branch of a blood vessel, place a crystal of sodium carbonate and note for a few minutes the formation of a white thrombus.

Draw and mark the result into your protocol. On the basis of the results which you have obtained come to a conclusion about the development of white thrombus.

Experiment: 13. Formation of a red thrombus.

Method: The method of fixation and dissection is the same as in the previous exp. In the same preparation of a mesentery find a vessel with normal blood flow. With the help of a dissection needle puncture the blood vessel and notice the changes which will follow (formation of a red thrombus). Note down the results in your protocol. On the basis of the experiment come to a conclusion about the formation of a red thrombus.

Experiment 14. Determination of coagulation time by the method of Bürker in posthaemorrhagic anaemia.

Method: A small drop of distilled water is placed on a slide and is mixed with a drop of blood (2-3 times larger), which is taken from the vein of the experimental rabbit. You have to register the time of taking the blood. Every 30 seconds you have to put down a glass stick into the drop and notice the time of formation of filaments of fibrin. Appearance of filaments of fibrin marks the beginning of blood coagulation. The end of coagulation is the moment when the whole drop of the blood is stuck to the stick.

The results have to be recorded. On the basis of your findings write a conclusion about the nature of disorder of blood coagulation produced by posthaemorrhagic anaemia.

Experiment 15. Determination of recalcification time of plasma in posthaemorrhagic anaemia.

Method: You have to add 0.2 ml of 0.277% solution of calcium chloride and 0.1 ml of 0.85% solution of sodium chloride into a test-tube, which is in a water bath with a temperature of 37°C. One minute later add 0.1 ml of test plasma and note the time at once. Notice the time of clot formation of fibrin. The investigations are repeated two or three times. The average result is calculated. The normal value is 60-120 sec.

The results have to be recorded. On the basis of your findings write a conclusion about the nature of disorder of blood coagulation produced by posthaemorrhagic anaemia.

Experiment 16. Determination of the prothrombin time by the method of Quick.

Method: Fill a test-tube with 0.1 ml of test plasma, 0.1 ml suspension of thromboplastin and plunge it in the water bath T -38°C. After 1 min add 0.1 ml of 0.277%

sol. of $CaCl_2$. Immediately start a stop-watch and note the time of clotting. Investigations have to be repeated and the average result has to be calculated.

The prothrombin time is the time from the point of placing the plasma of a healthy rabbit to the time of appearance of flakes of fibrin.

Prothrombin time of a healthy rabbit is determined by dilution of the blood 1:4 (1ml of sodium oxalate and 4 ml of blood) for 12-20 sec (depending on the activity of thrombin).

Multiple Choice Questions

Choose the right answer

001. ATYPICAL CHANGE OF HEMATOLOGIC FINDINGS 6-8 DAYS AFTER AN ACUTE BLOOD LOSS ARE

1) moderate hypochromia of erythrocyte (colour index 0.9 –0.8)
2) neutrophilic leukocytosis with nuclear shift to the left
3) normochromia of erythrocytes (colour index 0.9-1.1)

002. ATYPICAL CHANGES OF HEMATOLOGIC FINDINGS IN CHRONIC POSTHAEMORRHAGE ANEMIA ARE

1) increased colour index
2) microanisocytosis and poikilocytosis of erythrocytes
3) decreased colour index

003. MICROCYTOSIS OF ERYTHROCYTES IS CHARACTERISTIC OF ***(choose the right answers)***

1) acute posthaemorrhagic anemia
2) chronic posthaemorrhagic anemia
3) iron deficiency anemia
4) Minkovsky-Shauffard anemia

004. THE FOLLOWING FEATURE IS CHARACTERISTIC FOR B_{12}-FOLATE DEFICIENCY ANEMIA ***(choose the right answers)***

1) hypochromia of erythrocytes
2) macrocytosis
3) megaloblastic type of haemopoiesis
4) presence erythrocytes with Golly bodies and Cabot rings

005. THE CAUSE OF HYPOPLASTIC ANEMIA IS THE FOLLOWING

1) resection of the stomach
2) ionizing radiation

006. DISEASE NOT ACCOMPANIED BY EOSINOPHILIA IS

1) pollinosis
2) echinococcosis of the liver
3) bacterial pneumonia
4) allergic rhinitis

007. DISEASE NOT ACCOMPANIED BY DEVELOPMENT OF MONOCYTOSIS IS

1) measles
2) myocardial infarction
3) infectious mononucleosis
4) roseola

008. ATYPICAL CHANGE OF PERIPHERAL BLOOD IN ACUTE MYELOBLASTIC LEUCOSIS IS

1) onset of blast cells
2) onset of promyelocytes, myelocytes and metamyelocytes
3) absence of promyelocytes, myelocytes and metamyelocytes
4) anemia and thrombocytemia

009. ATYPICAL CHANGE IN PERIPHERAL BLOOD IN ACUTE LYMPHOBLASTIC LEUCOSIS IS

1) onset of blast cells
2) promyelocytes, myelocytes in blood
3) anemia and thrombocytopenia

010. ATYPICAL CHANGE IN PERIPHERAL BLOOD IN NEUTROPHILIC LEUCOCYTOSIS WITH REGENERATIVE NUCLEAR SHIFT TO THE LEFT IS

1) neutrophilia which is accompanied by increased percentage of stab [band] neutrophils
2) onset of neutrophylic metamyelocytes in blood
3) onset of solitary promyelocytes in blood

4) decrease of comparative content of lymphocytes in blood

011. CONDITIONS FOR THROMBORESISTANCE OF A VASCULAR WALL ARE

1) synthesis of tissue plasminogen activator, activation of the system of anticoagulants, synthesis of prostacyclin, binding of thrombin with thrombomodulin
2) excretion of tissue thromboplastin, synthesis of Willebrand's factor, activation of thrombin receptors

012. LYSIS OF A BLOOD CLOT IS CARRIED OUT BY

1) plasmin
2) antithrombin III
3) heparin

013. ANTICOAGULANTS ARE

1) antythrombin III, heparin
2) kallidin, proconvertin, thromboxane A_2

014. PRIMARY HEMOSTASIS IS CALLED

1) vascular-thrombocytic
2) coagulation

015. VASCULAR THROMBOCYTE HEMOSTASIS CAN BE BROKEN DUE TO

1) decrease of quantity of thrombocytes, disorder of thrombocyte function, hereditary angiopathy, deficiency of Willebrand's factor, absence of thrombocytes receptors to Willebrand's factor on a membrane
2) deficiency of the VIIIth factor on a membrane, expression of receptors to fibrinogen on a membrane of thrombocytes, deficiency of the XIIth factor

016. DEVELOPMENT OF HEMORRHAGIC SYNDROME CAN BE DUE TO:

1) increase of procoagulants
2) increase of heparin
3) increase of thrombocytes

017. DEVELOPMENT OF BLEEDINGS IN DIC-SYNDROME IS DUE TO

1) activation of plasminogen system,
   increased consumption of procoagulants,
   thrombocytopenia of consumption
2) increased excretion of tissue thromboplastine,
   consumption of fibrinogen

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of lymphatic system.

Objective of class: To study the causes and mechanisms of lymph formation and lymph circulation disorders.

The term "lymphatic system" denotes the totality of lymphatic vessels penetrating the organs and tissues and containing colorless fluid - lymph, and lymph nodes, in which lymphocytopoesis takes place and a complex of cell-to-cell and cell-to-humour interactions necessary for the immune responce.

Lymphatic system is functionally closely connected with blood circulatory system. On the level of microcirculation the exchange of components between the arterial blood and tissues on the one hand and between tissues and venous blood on the other hand takes place. The exchange takes place according to Starling's law: due to a difference between hydrostatic and colloid-osmotic pressure in the arterial end of the capillary and in the interstitial space the fluid moves towards the tissues. In venules because of a high colloid-osmotic gradient resorption of fluids from tissues takes place except for the transport of protein compounds in the system of blood - tissue - blood. Protein compounds go into the interstitial space through small and large pores, fenestrae, vesicles, intercellular compounds and so on. The return in the blood stream is only possible through the lymphatic vessels. In a healthy person there is a dynamic stability between the process of transport to the tissues and resorption from the tissues.

In case of pathology this stability is impaired and more often lymphokinesia insufficiency (insufficiency of lymphocirculation) occurs.

Lymphokinesia insufficiency includes the following types:

1. Mechanical
2. Resorptional
3. Dynamic

Consequences of acute lymphokinesia are edema, chronic sclerosing of tissues.

Objective of experiment: To study the role of lymphatic system in the processes of resorption of protein and transport of cellular elements from the interstitia in case of burns.

Experiment 1. Change of the protein content in blood and lymph in burns.

Method: To a dog, which is lying under light general anaesthesia in a prone

position, make a cut through the fibular vein. The fat covering it must be ligated bilaterally. Gently stroke the foot of the animal in the cranial direction. Bilaterally we can see swollen lymphatic vessels, which are afferent vessels of popliteal lymphatic node. Take 0.2ml of lymph with a syringe. Collect blood from the vein. Both blood and lymph are to be collected with sodium oxalate, which is diluted in the ratio of 1:5. Burn the hind leg by dipping it into the hot water for 30 sec and 20 min later again take blood and lymph. General protein in the lymph and in the blood plasma is determined with the help of refractometer (IRF-22). For refractometry evaluation use table #1. Compare the results. Draw a conclusion about the role of lymphatic system in the process of protein resorption.

Table 1: Find the refractometry value and value of refraction and the protein percentage.

Refractive index	**Protein** (g%)	**Refractive index**	**Protein** (g%)
1.33705	0.77	1.34070	2.42
1.33743	0.97	1.34048	2.62
1.33781	1.18	1.34086	2.83
1.33820	1.38	1.34124	3.04
1.33858	1.59	1.34162	3.24
1.33934	2.01	1.34199	3.45
1.33972	2.21	1.34237	3.65
1.34275	3.86	1.34500	5.10
1.34313	4.07	1.34537	5.30
1.34350	4.48	1.34575	5.50
1.34370	4.37	1.34612	5.70
1.34426	4.68	1.34650	5.90
1.34463	4.89	1.34687	6.11

Multiple Choice Questions

Choose the right answer

001. LYMPHATIC SYSTEM IS

1) closed vascular system
2) open vascular system

002. BASIC FUNCTION OF LYMPHATIC SYSTEM IS

1) drainage
2) trophic
3) endocrine

003. SUBSTANCES WHICH APPEAR MAINLY IN LYMPH IN INTRAMUSCULAR INJECTION ARE

1) large- molecular
2) small-molecular

004. LYMPH COAGULATION

1) is possible
2) is not possible

005. LYMPHATIC VESSELS WHICH CARRY LYMPH TO BLOOD FLOW ARE

1) right and left thoracic ducts
2) sinuses of lymph nodes
3) mesenteric lymphatic vessels

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of external respiration.

Objective of class: To study the etiological factors and mechanisms of the external respiration disorders, pathophysiological variants of respiratory insufficiency.

External respiration is exchange of gases between alveoluses and atmospheric air.

Pathology of external respiration occurs because of inability of the respiratory organs to provide necessary saturation of blood with O_2 and remove CO_2 from the body.

Respiratory insufficiency is a pathological syndrome, in which partial pressure of oxygen in arterial blood is less than 60 mm Hg, and partial pressure of carbonic gas more than 46 mm Hg.

Pathophysiological variants of respiratory insufficiency:

1. Centrogenic respiratory insufficiency;
2. Nerve - muscular respiratory insufficiency;
3. "Frame" respiratory insufficiency;
4. Respiratory insufficiency due to pathology of respiratory pathways;
5. Parenchymal respiratory insufficiency.

Parenchymal respiratory insufficiency develops more often due to **acute respiratory distress syndrome (ARDS)**, which by definition of the American - European conciliatory conference on ARDS (1994) is not a specific disease, and is considered as a syndrome of inflammation and increase in permeability of the alveolar-capillary membranes, combined with a set of clinical, radiological and physiological disorders which cannot be explained by left auricular or pulmonary capillary hypertension, but can coexist.

An important role in ARDS is played by inactivation of surfactant, which in norm reduces the permeability of the alveolar-capillary membranes and the force of superficial tension in alveolus.

The most common form of a disorder of the respiratory movements is

breathlessness. Breathlessness is characterized by a change of the rhythm, frequency, depth and character of respiratory movements. Depending on duration of inhalation and exhalation we distinguish inspirated, exspirated and mixed forms of breathlessness.

Breathlessness becomes a constant symptom of disorders of external respiration. However breathlessness is not only caused by disorders of the respiratory organs, but also as a compensatory reaction, which is accompanied by some physiological conditions (physical overload), diseases of the cardiovascular system, anemias, bleeding.

Asphyxia (suffocation) is a pathological life-threatening condition caused by acute or subacute insufficiency of oxygen in the blood and accumulation of carbonic gas in the organism.

Asphyxia develops due to: 1) mechanical obstructions of the passage of air in large respiratory pathways (throat, trachea);

2) acute decrease in the amount of oxygen in inhaled air;

3) nervous system disorders and paralysis of respiratory muscles.

Objective of experiment: Familiarization with manifestation of disorder of respiration in some pathological processes.

Experiment 1. Respiratory change of the upper respiratory passages.

Method: Using a two-channel electrocardiograph make a pneumogram (PG) and electrocardiogram (ECG) of a fixed healthy rabbit. You have to bring absorbent cotton moistened with ammonia solution to the rabbit's nose. Strong irritation of sensory endings, which are located in nasal mucosa, by inhalation of ammonia leads to an arrest of respiration for 10-15 sec. After normalization of respiration you have to drop two drops of 5% solution of Novocain into the rabbit's nose. After 10-15 min the experiment is to be repeated. After local anesthesia of the upper respiratory tracts inspiration of ammonia solution doesn't lead to a respiratory disorder.

The results have to be recorded. Comparing the results of the first and second parts of the experiment you have to draw a conclusion about the mechanism of respiration disorder and heart disorder after irritation of the upper respiratory tracts.

Experiment 2. The change in the nature of respiration and heart work upon painful irritation.

Method: This experiment shows a development of reflectory breathlessness in different diseases, when irritation of sensory receptors takes place (in case of pain syndrome).

Using a two-channel electrocardiograph make a pneumogram and electrocardiogram of a fixed healthy rabbit. Under local anesthesia with 2-3% solution of Novocain make a preparation of the sciatic nerve and irritate it with tweezers. Strong painful irritation usually produces a deeper and more frequent respiration. Stronger and more prolonged irritation leads to suppression or even arrest of respiration. Any painful irritation usually leads to stimulation (but more strong irritation - to inhibition) of the cortex; the stimulation (or inhibition) from the cortex spreads to the subcortex, the region where the respiratory center is located.

It is necessary to make an analysis of the PG and ECG in this experiment. Put down the figures.

Experiment 3. Disorders of respiration and heart work in asphyxia.

Method: It is necessary to take the PG, ECG of a healthy rabbit.

After this using a rubber mask make a complete disconnection of the respiratory system from the external environment. Acute asphyxia occurs. There are three periods in it. Soon after imposition of the mask deep or sometimes frequent respiration with long breaths develops. Breathlessness is of inspiratory character. At the end of the first period the respiration becomes slower and expiratory dyspnoea appears. Such a change of breathing is a result of stimulation of the breathing centre by carbonic acid and acid products of metabolism. Further breathing is stopped for a short time; it is caused by paralysis of the respiratory centre. After thissingle infrequent convulsive breathing movements appear, this is terminal breathing. Terminal breathing after apnoea appears because of the impulses, which pass from the additional respiratory centres situated in the cervical section of the spinal cord. Considerable decrease of breathing is explained by a lower degree of automatism of the additional spinal cord compared with the work of the main respiratory centre. Asphyxia is stopped at the second stage in order to avoid killing the animal.

The registered parameters are to be analysed and put down in a table. Draw a conclusion about the mechanism of disorder of breathing and heart work in asphyxia.

Multiple Choice Questions

Choose the right answer

001. STENOSIS OF THE THROAT LEADS TO THE FOLLOWING TYPE OF RESPIRATION

1) deep bradypnoea with difficult inspiration
2) Biot's respiration

002. THE INITIAL AND MAIN LINK IN PATHOGENESIS OF RESPIRATORY DISTRESS SYNDROME IN ADULTS IS

1) increased permeability of vessels in the lungs
2) increased shunting of blood

003. INSPIRATORY BREATHLESSNESS IS OBSERVED IN CASE OF ***(choose the right answers)***

1) Ist stage of asphyxia
2) emphysema of the lungs
3) edema of the throat
4) stenosis of the trachea
5) closed pneumothorax

004. IN CASE OF EXPIRATORY BREATHLESSNESS THE RESPIRATION IS

1) difficult and prolonged expiration
2) difficult inspiration and the expiration

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of digestion.

Objective of class: To study the main mechanisms of digestion disorders in different departments of gastrointestinal tract and pathogenetic principles of therapy in gastrointestinal diseases.

The main role of the digestive system is digestion of the ingested food components (proteins, fats, carbohydrates), intake of digested food (nutrients) and removal from the body of some of the end products of metabolism.

According to modern notions, the pathogenesis of **ulcer disease** in general is an imbalance between the factors of acid-peptic aggression present in gastric fluids and elements which protect the mucous membrane of stomach and duodenum. The protective factors include mucous production by the gastric glands, sufficient production of pancreatic bicarbonates, good regeneration of epithelial cells, persistent gastric mucosal blood flow and normal content of prostaglandins in the gastric wall.

In recent years a significant role in weakening of the protective properties of the mucous membrane of stomach and duodenum is played by microorganisms like **Helicobacter pylori**, found in 1983 by Australian scientists B. Marshall and J. Warren.

These bacteria produce a variety of enzymes (urease, protease, phospholipase) damaging the protective barrier of the mucous membrane as well as various cytokines.

Helicobacter pylori triggers a release of interleukins, lysosomal enzymes, tumor necrosis factor in the mucous layer of stomach which causes the development of inflammatory processes in gastric mucosa. Semination of gastric mucosa by Helicobacter pylori is accompanied by the development of superficial antral gastritis and leads to an increased secretion of gastrin followed by an increased secretion of hydrochloric acid.

Ulcer disease with infection of gastric mucosa with Helicobacter pylori is not always revealed. In approximately 5% of patients with duodenal ulcers and 15-20% of patients with gastric ulcer disease the condition develops without the participation of these micro-organisms. The involvement of Helicobacter pylori into development of intestinal-type gastric cancer has been proved, so these bacteria were included in the group of carcinogens, type 1 (obligate).

Depending on the characteristics of changes in gastric secretory functions, there are several types: inhibitory, excitable, inert, asthenic.

Inhibitory type: Increased latent period of secretion (between the intake of food and the beginning of stimulation of gastric secretion), reduced intensity of the build-up and active secretion, shortened duration of secretion and decrease in secretion. In extreme braking secretion achylia develops - practical absence of gastric juice.

Excitable type: Truncated latent period in the beginning of secretion, increased intensive secretion, increased duration of secretion, increased volume of gastric juice.

Inert type: Increased latent period, slow growth of secretion, slow termination and increase in gastric juice.

Asthenic type: Early truncated latent period and then rapid decline in secretion, slow gastric secretion and a small volume of gastric juice.

Chaotic type: Typically there are no regularities of dynamics and volume of secretion, periods of activation and inhibition are extended over a period of time (several months or years). The total amount of juice is usually increased.

Objective of experiment: To study the role of acidity of gastric juice in the development of gastric disease.

Experiment 1. Determination of acidity of gastric juice in different types of gastritis.

Method: To explore three «dumb» portions of gastric juice with normal, high and low acidity.

Pour 5 ml of gastric juice in the flask, add 1-2 drops of indicator: 1N alcoholic solution of phenolphthalein, alcoholic solution of dimetylaminoazobenzol and titrate with 0.1N solution of sodium hydroxide.

Calculate the amount of the base lost during titration:

a) identify the occurrence of light pink-red color which then changes to the color of salmon;

b) occurrence of unchanging red stain.

First calculate free HCL, then - the total acidity.

Based on the results draw a conclusion.

Experiment 2. Evaluation of disoder of gastric secretory function on the basis of results of clinical tests.

Method: Study «dumb» analysis portion of gastric secretion. On the basis of digital data construct graphs of gastrointestinal secretion and determine its type. Make a conclusion about the nature of disorder of secretory function of the stomach.

Multiple Choice Questions

Choose the right answer

001. ACTIVITY OF PEPSIN IN HYPOACIDIC CONDITION

1) decreases
2) increases
3) does not change

002. ABSENCE OF ENZYMES AND HYDROCHLORIC ACID IN GASTRIC JUICE IS CALLED

1) achlorhydria
2) acholia
3) achylia

003. AN EXCESSIVE TONE OF PARASYMPATHETIC NERVES IN STOMACH LEADS TO

1) decrease of formation of mucus, increase of secretion of gastric juice, increase of excretion of histamine, hypersecretion of hydrochloric acid
2) increase of formation of mucus, decrease of excretion of histamine, hyposecretion of hydrochloric acid

004. FACTORS WHICH PARTICIPATE IN PATHOGENESIS OF THE HEARTBURN ARE

1) hiatus in cardia, gastroesophageal reflux
2) decrease of acidity of gastric juice, decrease of sensitivity of receptors of oesophagus

005. ACUTE INTESTINAL OBSTRUCTION

1) can lead to a painful shock
2) cannot lead to a painful shock

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of the liver.

Objective of class: To study the main types of hepatotropic damaging factors and mechanisms of the development of hepatic syndromes.

Icterus refers to yellow coloration of skin, blood plasma, mucous membranes and tissues. The threshold for visible jaundice (icterus) is bilirubin in blood plasma above 18 mg l^{-1} or 30 mM in most people.

The normal bilirubin in blood plasma is up to 17 mg l^{-1} or 29 mmol l^{-1} (mM).

Three types of icterus can be distinguished:

1.a. **Prehepatic or haemolytic icterus** is caused by excessive destruction of mature or immature red cells. Haemolytic anaemia causes haemolytic jaundice. Increased destruction of red cells (haemolysis) increases the bilirubin production (normally 35 * 6 = 210 mg daily) to the extent that the hepatocytes cannot conjugate the bilirubin as rapidly as it is formed (the key enzyme is glucuronyl transferase). The neurotoxic free bilirubin in blood plasma rises much above normal, and large quantities of urobilinogen are excreted in the urine.

1.b. **Intrahepatic (parenchymatous) icterus** is caused by poor hepatocyte function. Damages of the hepatocytes by infections, tumours, or toxic agents impair the uptake, transport and conjugation of bilirubin. Absence of glucuronyl transferase or inhibition of the enzyme by steroids block conjugation of bilirubin.

1.c. **Posthepatic or obstructive icterus** is caused by cholestasis due to

gallstones or pancreatic tumours. Gallstones or tumour masses obstruct the bile ducts, which is causing extrahepatic cholestasis with impaired excretion of conjugated bilirubin to the intestine. Hereby, conjugated bilirubin reflux to the blood. Most of the bilirubin in plasma is therefore conjugated and some of it strongly bound to plasma albumin.

Hepatic Failure results from destruction of liver cells or impairment of hepatocyte function. Liver failure causes severe jaundice, hepatic encephalopathy, the hepatorenal syndrome, pulmonary veno-arterial shunts, and low coagulobility of the blood.

Objective of experiment: To study the laboratory methods of diagnosing liver pathology.

Experiment 1. Determination of the content of bilirubin in animal blood with obstructive icterus.

Method: For the investigation, the blood taken from the vein of hind leg of a dog is used. Determining the blood bilirubin level is done by the Humans Van Den Bergs method. Pour 1 ml of serum into 2 test-tubes. Add to the first test-tube 1 ml of distilled water and 0.25 ml of Erlich's reactive. Add to the second one 1 ml of ethanol and 0.5 ml of Erlich's reactive. Appearance of red discoloration indicates the presence of direct bilirubin and in the second test-tube indicates the presence of indirect bilirubin. On the basis of the findings draw a conclusion about the character of bilirubin metabolism in obstructive icterus.

Experiment 2. The study of general toxic action of bile in the body.

Method: After counting the respiratory rate and observing the activities of the rat inject 0.2 ml of bovine bile intra abdominally. After 10 min count the respiratory movements again. Changes in the rhythm and activities of the experimental animal are to be written down. Come to the conclusion about the cause of detected changes.

Experiment 3. The influence of bile on the cardiac activity.

Method: After registration of initial ECG of a fixed rat inject 0.4ml sol. of bile intra abdominally. Notice the changes in the cardiac contractions and write them down in the protocol.

Experiment 4. The influence of bile on the blood.

Method: Add a few drops of bile into a test-tube to stabilized blood diluted with isotonic solution. The second test tube with blood is for control. Enter the result into your protocol.

Multiple Choice Questions

Choose the right answer

001. HYPOVITAMINOSIS A, D, E AND K IN CASE OF DISTURBANCE OF THE LIVER FUNCTION

1) can develop
2) cannot develop

002. HAEMORRHAGIC SYNDROME IN HEPATIC INSUFFICIENCY

1) develops due to disturbance of protein synthetic function of the liver
2) develops due to disturbance of lipid synthetic function of the liver

003. SYNDROME OF CHOLEMIA IN MECHANICAL JAUNDICE

1) is characteristic
2) is not characteristic

004. SYNDROME OF CHOLESTASIS IS CHARACTERISTIC OF JAUNDICE ***(choose the right answers)***

1) hepatic
2) mechanical
3) hemolytic

005. PIGMENT WHICH PRODUCES DARK COLOR OF URINE IN MECHANICAL JAUNDICE IS

1) conjugated bilirubin
2) unconjugated blirubin
3) urobilin
4) stercobilin

PART: PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS.

Theme: Pathophysiology of the kidney.

Objective of class: To study the causes and mechanisms of the development of renal syndrome.

Different pathologic disturbances on the part of the kidneys develop under the influence of various damaging factors; at present, they are united in the following syndromes:

1) nephrotic syndrome;
2) acute renal failure (AFR);
3) chronic renal failure (CFR).

Renal insufficiency is a clinical condition, where the glomerular filtration rate is inadequate to clear the blood of nitrogenous substances classified as non-protein nitrogen (urea, uric acid, creatinine, and creatine). The retention of nonprotein nitrogen in the plasma water is called azotemia, and the clinical syndrome is called uraemia. The number of filtrating nephrons falls below 1/3 of normal, as determined by measurement of a CFR below 40 ml/min.

Acute renal insufficiency accompanies extremely severe states of circulatory shock (prerenal cause). The prerenal causes are hypovolaemia with hypotension or impaired cardiac pump function or their combination.

There is also a large group of renal causes. Finally, the postrenal causes are all

types of urinary tract obstruction.

Acute renal failure is a serious disorder, which leads to progressive uraemia and chronic renal insufficiency.

Causes of renal failure:

1) prerenal causes: cardiogenic and hypovolaemic shock.

2) renal causes**:-** ACE-inhibitors and NSAID´s impair renal autoregulation:

- fulminant hypertension;
- renal artery stenosis and embolism;
- vasculitis in glomerular capillaries;
- renal vein thrombosis;
- toxic tubular damage (organic solvents, myoglobin, aminoglycosides, and X-ray contrast).

3) postrenal causes**:**

- urinary tract obstruction is caused by obstructions of the lumen, the wall and by pressure from outside;
- lumen: **t**umours, calculus and blood clots within the lumen of the renal pelvis, ureter, and bladder;
- wall: strictures of the ureter, the ureterovesical region, urethra, and pinhole meatus;
- congenital disorders such as megaureter, bladder neck obstruction, and urethral valve;
- neuromuscular dysfunction in the urinary tract;
- pressure: compression by tumours, aortic aneurysm, retroperitoneal fibrosis or gland enlargement, retrocaval ureter, prostate hypertrophy, phimosis, and diverticulitis.

Two complications to chronic renal failure must be considered:

1. Renal osteodystrophy develops in patients with severe renal failure. The kidneys fail to produce sufficient 1,25-dihydroxy-cholecalciferol. This is active vitamin D or a potent steroid hormone. The active vitamin D metabolite stimulates the Ca^{2+}-transport across the cell and mitochondrial membranes.

Lack of active vitamin D has the following two effects:

a. Poor gut absorption of dietary Ca^{2+}, so that plasma Ca^{2+} falls.

b.The PTH release is stimulated, because the normal inhibitory effect of active vitamin D is lost.

After some time a secondary hyperparathyroidism develops with increased resorption of calcium from bone and increased proximal tubular reabsorption of calcium in an attempt to correct the low serum calcium. The calcium release from bone results in osteomalacia and in osteoporosis. Osteomalacia or soft bones is the result of demineralisation of the osteoid matrix usually caused by insufficient active vitamin D. Osteoporosis or thin bones is characterized by a reduction in all components of the bones.

2. Normochromic, normocytic anaemia. When normal kidneys are perfused with hypoxaemic blood, the peritubular interstitial cells produce large amounts of glycoprotein hormone, erythropoietin, with strong effect on erythrogenesis.

Chronic renal failure leads to erythropoietin deficiency, and thus to anaemia, which is of the normochromic, normocytic type.

Haemodialysis. The aim of haemodialysis is to eliminate nitrogenous wastes in patients with renal failure, and maintain normal electrolyte concentrations, serum glucose and normal ECV. In other words, the haemodialyzer or artificial kidney mimics the normal renal excretion of waste products

Objective of experiment: To get familiarised with pathologic components of urine.

Experiment 1. Determination of pathologic components in urine in condition of renal disease.

Method: Determine the content of glucose, protein, blood and blood pigments consecutively in each of four urine portions.

Determination of urine glucose

Fill a test-tube with 6-8 ml of urine, add 20 drops of Gaines's reagent and put the test-tube into water-bath with boiling water. In case of glucose presence in the urine the contents of the test-tube is coloured yellow.

Determination of urine protein

Fill two test-tubes with 3ml of urine. Add 6-8 drops of 20% solution of sulfasalicylic acid to the experimental test-tube. Compare the experimental test-tube with the control test-tube against dark background. In case of protein presence in experimental test-tube its content is cloudy.

Determination of blood and blood pigments in urine

Fill the test-tube with 5 ml of urine and add several drops of alkali. Boil the contents of the test-tube. A dirty-white sediment gradually turning to brown appears in case of blood and blood pigments presence.

Enter the obtained results into a table and explain the possible common mechanisms of occurrence of pathological admixtures in urine. Make a plan of carrying out additional quantitative laboratory and clinical examinations for elaboration of specific mechanisms of proteinuria, glycosuria and hematuria.

Multiple Choice Questions

Choose the right answer

001. CHARACTERISTIC FINDINGS FOR DISTURBANCE OF RENAL TUBULES ARE

1) aminoaciduria, isostenuria, nonselective proteinuria, decrease of secretion of H^+ ions and ammonium
2) presence of leached erythrocytes in the urine, decrease of creatinine clearance

002. MECHANISMS OF GLUCOSURIA ARE

1) blocking of enzymes of

phosphorylation in the epithelium, structural damage of proximal tubules, exessive amount of glucose in blood (> 10 mmol/l)
2) increase of filtrational pressure in renal tubules, increase of permeability of capillaries of renal tubules

003. THE MAIN MECHANISMS OF DECREASE OF RENAL TUBULAR FILTRATION ARE

1) decrease of arterial blood pressure less than 60 mm Hg, disturbance of the outflow of initial urine, increase of colloid-osmotic pressure of blood plasma, decrease in the number of functioning nephrons
2) decrease of reabsorbtion of sodium ions in renal tubules, decrease of activity of enzymes of renal tubular epithelium

004. CHARACTERISTIC DISTURBANCES OF HOMEOSTASIS AT POLYURA STAGE OF ACUTE RENAL INSUFFICIENCY ARE

1) dehydration of the body, hypoglycemia, development of immunodeficiency
2) increasing azotemia, concentration of urea less than 6.6 mmol/l

005. THE LEADING LINKS OF PATHOGENESIS OF NEPHROTIC SYNDROME IN RENAL DISEASES ARE

1) decrease of oncotic pressure of blood plasma, disturbance of reabsorbtion of protein in renal tubules, disturbance of permeability of glomerular filter, massive proteinuria
2) secondary aldosteronism, hypoproteinemia

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et all

MANUAL
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