I.A. FASTOVA

GENERAL PATHOLOGY

TYPICAL PATHOLOGIC PROCESSES

Manual for third year students of higher educational establishments

ФЕДЕРАЛЬНОЕ АГЕНТСТВО ПО ЗДРАВООХРАНЕНИЮ
И СОЦИАЛЬНОМУ РАЗВИТИЮ

ВОЛГОГРАДСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ

I.A. Fastova

"GENERAL PATHOLOGY. TYPICAL PATHOLOGIC PROCESSES"

Part 3.

(Manual for third year students of higher educational establishments)

Рекомендуется Учебно-методическим объединением по медицинскому и фармацевтическому образованию вузов России в качестве учебного пособия для иностранных студентов медицинских вузов, обучающихся на английском языке

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"General pathology. Typical pathologic processes". Part 3. (Manual for third year students of higher educational establishments in the English-speaking medium).

I.A. Fastova

Reactivity and Resistance of an organism and their role in pathology.
Lipid metabolism disturbances.
Pathology of carbohydrate metabolism.

This manual contains lectures, tests & situational tasks on the following topics: reactivity and resistance of the body and their role in pathology; lipid metabolism disturbances; pathology of carbohydrate metabolism. It caters for third year students in the English-speaking medium for independent work or work in class.

Reviewers: d. m. s., professor Ovsianikov V.G.
d. m. s., professor Chesnokova N.P.

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Рецензенты:

д-р мед. наук, проф. В.Г. Овсянников,

д-р мед. наук, проф. Н.П. Чеснокова

Фастова И.А.

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REACTIVITY AND RESISTANCE OF AN ORGANISM AND THEIR ROLE IN PATHOLOGY.

Reactivity of an organism.

The Definition of the concept "the reactivity of organism".

A well – known pathophysiologist N.Sirotinin who studied the problem of the body's reactivity for over 30 years wrote: "**The body reactivity** is usually understood as its ability to react in a proper way to the influence of the environment. **Resistance** of an organism is its stability under the influence of pathogenic factors".

Reactivity is a characteristic of all living beings. The ability of a human being or an animal to adapt to the environment, to maintain homeostasis largely depends on the reactivity. It is the reactivity that determines the occurrence and the progress of an illness. Therefore, the study of reactivity and its mechanisms is so important for understanding a disease pathogenesis and its purposeful prevention and treatment.

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

Different species of animals change their vital activity under endogenous influence differently; different groups of people react to the same influence in different ways, and every individual has his own peculiar ways of reacting.

The types of reactivity.

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

We can cite animals' seasonal behaviour as an example of the species' reactivity (hibernation, migration of birds and fish, etc.), specific features of pathologic processes in different species (inflammation, fever, allergy, the response of an acute stage, etc.)

Vertebrates' reactivity is manifested stronger and more varied than invertebrates' reactivity.

All warm -- blooded species can produce special antibodies, and this ability of different species is expressed differently. In an experiment one can easily reveal the specific features of the reactions of different species to mechanic, chemical and thermal exposures, ionic radiation (dogs, guinea-pigs and people are the most sensitive, and unicellulars and worms are the least sensitive), hypoxia.

Susceptibility or unresponsiveness to infection is a vivid symptom of the species' reactivity and resistance: dogs' distemper and foot – and – mouth disease are not dangerous for people; tetanus is dangerous for people, monkeys and horses and it is not dangerous for cats, dogs, hedgehogs, tortoises, crocodiles; sharks are never ill with this disease and their wounds never fester; rats and mice can't have diphtheria, dogs and cats – botulism.

Group reactivity is the reactivity of separate groups of people (or animals) sharing a common sign which determines the reaction specifics of all the representatives of this group to external exposure.

Such signs are: age, sex, constitution type, race, blood group, higher nervous activity type, group of people with the same illness, etc.

E. g.: Men are often affected by such diseases as gout, spondylarthritis; pyloric stenosis, ulcer, cancer of the head of pancreas, coronarosclerosis, alcoholism; and women rather have rheumatoid arthritis, cholelithiasis, cancer of cholecyst, myxedema, hyperthyreosis, purpura hemorrhagica; dark-skinned people are not very sensitive to ultraviolet rays. The risk of getting a peptic ulcer is as much as 35% as high for people sharing the 1st blood group, these people died more often in time of epidemics of plague; and people sharing the 2nd blood group more often get stomach cancer, a coronary disease, they are more sensitive to grippe, but they are more resistant to enteric fever.

Individuals of phlegmatic, sanguine, melancholic and choleric types respond differently to a social and emotional stress (their reactivity depends on their temperament).

Children and old people have special reactivity. This fact has resulted in the development of special branches in medicine – pediatrics and geriatrics. Any age is characterized by certain morphological and functional characteristics which determine the character of a body response to external exposures. Children under 1 month never suffer from mumps, scarlet fever, since they have received their mothers' antibodies; newborn babies are very sensitive both to over-cooling and overheating as a result of their imperfect mechanisms of thermoregulation. They need a special diet because of morphofunctional specifics of their gastrointestinal tract and digestive glands, a special water intake schedule, due to the high intensity of their water metabolism. The period of involution is characterized by weakened protective mechanisms, limited adaptability to the environment, weakened regeneration and immune protection, hormonal reorganization. Such people are more subjected to oncological and infectious diseases.

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.

For example, some people have low resistibility to influenza, others have higher resistibility, and there are people who don't get this disease at all, however, the virus can be found in their body (they can be virus carriers).

Individual reactivity of every organism accounts for this fact. The diseases may advance individually for every particular patient. Every case should be treated individually. A particular disease has to be treated (etiologically, pathogenetically, and symptomatically) in a particular patient considering their individual reactivity.

Physiological reactivity means a change of the bodily vital activities, definite forms of reaction to the influence of external agents that don't 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.

In fact, the development of a disease is a manifestation of pathergy which is revealed both in individuals and in groups and species of animals. Besides, there is a belief that species' reactivity can't be pathergy, as it is always aimed at preserving the animals' species.

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).

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

Immunological tolerance is a condition of a specific immunological non-reactivity to a particular antigen caused by the previous contact with this antigen. Immune reactivity to other antigens is preserved.

Immunological tolerance is an active process when the contact with an antigen (tollerogen) causes specific elimination or inactivation of the antigen-reactive clones of lymphocytes (e.g. by means of antibody complexes) or formation of suppressor-cells inhibiting immunocompetent lymphocytes. The types of immunological tolerance are as follows: congenital or natural, acquired (immunological paralysis or high doses, small doses, drug-induced).

Runt disease (homologous disease) is conditioned by the immunological reaction of a transplant to a host. It is usually observed in case of transplanting allogenic immunocompetent lymphocytes of a donor to an adult recipient whose immune system is considerably impaired as a result of earlier roentgeno- or chemotherapy.

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. For example, the changes in the body in response to the hypovolemic or traumatic shock, hypoxia, acceleration or overstrain are the signs of nonspecific reactivity. In infectious, allergic, autoimmune diseases the mechanisms of both specific (production of antibodies) and nonspecific reactivity (inflammation, fever, hypercytosis, changes of function of damaged organs and systems, etc.) are involved.

Both the whole organism and its separate systems, organs, cells may have reactivity. When an environmental agent affects the whole organism, its main regulatory systems – nervous and endocrine – get involved in response to it, when metabolism, blood circulation and respiration change, we can witness the reactivity of the whole organism. If a patient with an ischemic heart disease develops a stenocardial attack as a result of physical exertion, in this case we mainly deal with cardiac reactivity with affected coronary vessels.

The 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. If a disease (pneumonia, tuberculosis, dysentery, etc) takes an intensive, rapid course, with clearly marked symptoms, high fever, sharp acceleration of erythrosedimention rate, high leucocytosis, etc., the course of this disease is considered to be hyperergical. On the contrary, if the symptoms of a disease are poorly marked and the course of the disease is inactive without manifestations of the acute phase, they speak about the hypoergical course of the disease. A perverse (atypical) reaction of the patient to a drug, vasodilation and excessive sweating at low temperatures in patients with disorders of the vegetative nervous system are the examples of disergy. Anergy is a condition when the body doesn't respond to the presence of pathogenic microorganisms in it (carriers), or when the central

nervous system is either deeply depressed or inhibited (coma, shock, anesthesia, inhibitory stage of parabiosis). The condition of immunological tolerance to an antigenic stimulus can be also classified as anergy.

Reactivity should be estimated in relation to a particular intervention. Quite often high 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 doesn't respond to enteric fever and jail fever infection but responds to diphtheria, staphylococcus and streptococcus.

A newborn has low reactivity to hypoxia but high reactivity to overheating. Sometimes when two or several agents affect the body, it can respond only to one of them ignoring the others.

Resistance.

Resistance is the body insusceptibility to pathogenic effects.

The resistance of the body to pathogenic effects manifests itself in different forms: for example, skin and mucous membranes are the structures preventing the penetration of microorganisms and many poisonous agents into the body. They perform the so-called barrier function. Subcutaneous fat tissue has poor thermal conductivity, while bones and other tissues of the locomotor apparatus are characterized by high resistance to deformation under the influence of mechanical agents. These examples testify to the resistance of tissues and the whole body depending on their inherited structure and properties. This is the so-called **primary resistance**.

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.).

Due to hereditary immunity people are not subjected to many infections typical of animals, and in the period of epidemics of smallpox and plague some people who were directly in contact with sick people didn't catch the infection.

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

Gonorrhea is a human disease. Animals cannot be infected with gonococcus. It is possible to infect hens with anthrax only by exposing them to cold, however, they are resistant to it in ordinary conditions.

Secondary resistance is acquired (for example, immunity develops after some infectious diseases, after the administration of vaccines and sera). Resistance to non-infectious interventions can be acquired through exercising resitance to physical exertion, to acceleration and overstrain, hypoxia, low and high temperatures, etc.

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, neutralizition 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, reactivity in breast-fed babies under 3 months is low but resistance to some infections is high as they have received some antibodies from their mothers. A newborn animal has low reactivity and high resistance to hypoxia, while in a mature animal it is opposite. In surgery anesthesia is used to reduce the patient's reactivity and at the same time to boost their resistance to trauma. In animals which are dormant in winter reactivity is low but the resistance to many external agents is high. At the same time old people have a hypoergic course of most diseases and their resistance is low.

Factors affecting the body reactivity and resistance.

Reactivity and resistance are formed on the basis of the constitution type, peculiarities of metabolism, the condition of the nervous, endocrine, immune systems, the system of connective tissue; they also depend on age, sex and environment.

Body type and its role in developing reactivity and resistance.

The body type usually means a complex of fairly stable morphological, functional, mental characteristics of the organism which are developed on the basis of a certain genotype under the influence of environmental factors.

Many scientists noticed that individual forms of reactivity and resistance depend on the constitution type. However, there are different classifications of constitution types with different criteria underlying them. **Hippocrates** divided all people into sanguine, choleric, phlegmatic and melancholic types according to their temperament. He marked in particular that the sanguine type was subjected to plethora, headaches, diabetes mellitus. **C.Signat** divided all people into 4 types according to morphological characteristics: respiratory, digestive, muscular and encephalic. He also emphasized the fact that people of the respiratory type are more subjected to pulmonary emphysema and bronchial asthma; people of the digestive type suffer from obesity, gout and hepatic diseases; people of the muscular type more often have diseases of the cardiovascular, muscular and skeletoarticular systems.

K.Kretschmer singled out 3 constitution types of people: athletic, picnic and asthenic and pointed out that picnics are more subjected to atherosclerosis, ischemic heart disease, maniac-depressive psychosis, while asthenics more often have schizophrenia and severe forms of tuberculosis.

The classification of **A.A.Bogomoletz** is based on the peculiarities of the structure of connective tissue. He singled out 4 types: asthenic – with thin delicate connective tissue; fibrous – with dominant dense, fibrous tissue; lipomatous – with predominant fat tissue; puffy – with predominant loose, edematous tissue. He

considered that people with different kinds of connective tissue have a different course of inflammation, of healing and regeneration of the processes of aging.

I.P.Pavlov singled out 4 types according to the characteristics of higher nervous activity: unrestrained (strong unbalanced excitable); fast (strong balanced mobile); inert (strong balanced calm); weak (weakness of both processes with predominance of inhibition).

Functions of endocrine system and reactivity.

Pituitary, adrenal, thyroid glands, pancreas and sexual glands are of special significance for the mechanisms of reactivity development.

Hormones of the anterior lobe of hypophysis stimulate secretion of hormones of adrenal cortex, thyroid and sexual glands. Removal of hypophysis increases the animal's resistance to hypoxia, while an injection of the extract from the anterior lobe of hypophysis decreases this resistance.

The function of the elements of connective tissue and reactivity.

Connective tissue cellular elements (reticuloendothelial system, the system of macrophages) being connected with other organs and physiological systems are involved in the development of body reactivity. They possess phagocytic activity, perform barrier and antitoxic functions, ensure the intensity of wound healing.

The significance of age.

Persons at any age have their own morphological and functional peculiarities and the body response to external intervention depends on them.

The adaptability to environmental temperature changes is weaker in newborns than in adults as a result of immaturity of their thermoregulatory system.

Children aged 1 – 3 years are highly susceptible to different infections (measles, scarlet fever, whooping-cough, diphtheria) due to functional immaturity of their immune system (inability to produce the required amount of their own antibodies) and the exhaustion of antibodies received from their mothers through placenta and breast milk as well as as a result of immaturity of their barrier systems.

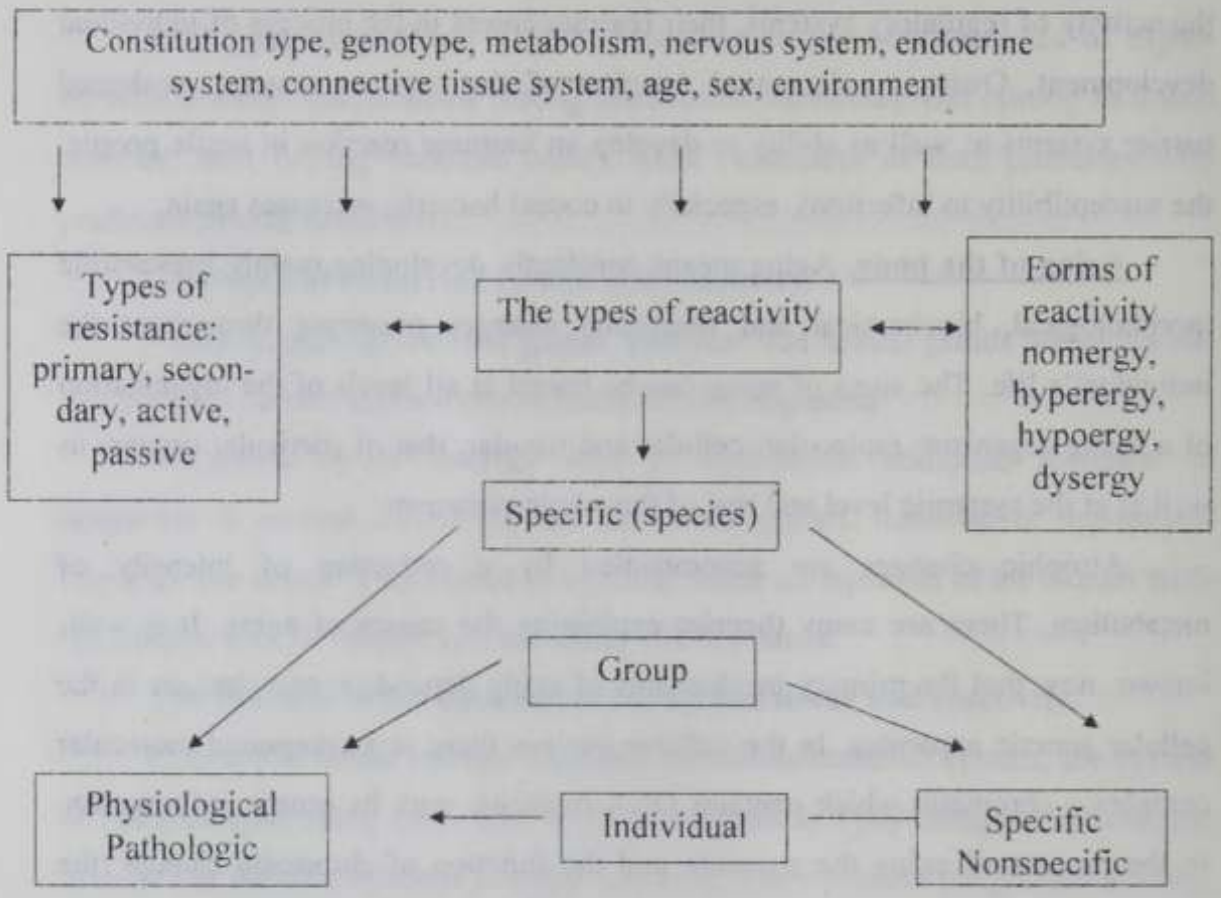
The incidence of malignant tumors, atherosclerosis, ischemic heart disease increases in elderly people. It may be conditioned by age-specific peculiarities of the activity of regulatory systems, their rearrangement in the process of individual development. Owing to decreased function of the nervous system, weakened barrier systems as well as ability to develop an immune reaction in senile people, the susceptibility to infections, especially to coccal bacteria, increases again.

Aging of the body. Aging means constantly developing mainly irreversible morphological, biochemical and functional changes occurring throughout the individual's life. The signs of aging can be traced at all levels of the organization of a living organism: molecular, cellular and tissular, that of particular organs, as well as at the systemic level and that of the whole organism.

Atrophic changes are accompanied by a reduction of intensity of metabolism. There are many theories explaining the causes of aging. It is well-known now that the primary mechanisms of aging depend on age changes in the cellular genetic apparatus. In the cellular nucleus there is a compound molecular complex – chromatin which contains DNA molecule with its genetic information. In the process of aging the structure and the function of chromatin change (the content of inactive chromatin increases). This hampers processing genetic information and causes cumulative damage to the DNA. In aging the number of non-histon proteins (activating genes) diminishes. This changes the functioning of regulatory genes. All these factors change the ratio of synthesis of both single proteins and their blocks coded by different genes. Disorders of genome regulation arising in the process of aging result in the activation of "silent" genes. This gives rise to a protein which has never been synthesized by the cell before. Depending on its type different shifts in cell activity even those causing its death are possible.

Aging mechanisms. As it has already been mentioned before, disorders at the cellular level are important in aging processes. They lead to the development of irreversible changes in protein synthesis as well as to the activation of genes that have not been "at work" before. These changes underlie disorders of cell vital activity, causing their aging.

Social factors produce a great impact on human reactivity (inflation, unemployment, war, food and medicine shortages, etc).



Pic.1. The types and forms of reactivity and resistance of the body. Factors influencing reactivity and resistance.

The estimation of reactivity is important for revealing the mechanism of genesis, development and outcome of a disease. Therefore, a doctor is to determine the peculiarities of the patient's individual reactivity to produce a desirable effect on it to make the treatment more efficient.

TOPICS FOR DISCUSSION

1. The notion of reactivity and its role in pathogenesis.
2. Types of reactivity (specific, group and individual).
3. The significance of a hereditary constitution type. Specific characteristics of the organism essential for reactivity.
4. The significance of the type of the nervous system, sex, age, acquired characteristics of the organism essential for reactivity.
5. Specific (immunological) reactivity.
6. Resistance. The types and basic mechanisms of resistance.
7. The changes occuring in the individual's reactivity. Increased resistance.

Test of the first level. Choose the correct answers.

I. Which of the following statements do you consider to be correct?

1. There is a strict direct interdependence between reactivity and resistance.
2. There is a strict reverse dependence between reactivity and resistance.
3. There is no obligatory direct or reverse dependence between reactivity and resistance; both variants are possible.
4. Resistance is a resultant integrating value reflecting reactivity of the body and its fluctuation from medical and biological point of view.

II. Pick out the factors determining primary (basic) reactivity:

1. Heredity.
2. Neurohumoral regulation.
3. Diseases the person suffers from.
4. Body type (constitution).
5. Environmental factors.
6. Age.
7. Immunization of the organism.
8. Sex.

III. What forms of secondary (acquired) reactivity can be singled out?

1. Specific (immunological).
2. Adaptive.
3. Allergic.
4. Nonspecific.
5. Constitutional.

IV. What determines specific (immunological) reactivity development?

1. Immunity.
2. Allergy of all types.
3. Factors of natural resistance.
4. Specific environmental conditions.
5. Immunodeficiency states.

V. What factors determine the development of nonspecific acquired reactivity?

1. Social.
2. Seasonal.
3. Age.
4. Climatic.
5. Environmental.
6. Psychogenic.
7. Sensitization of the body.
8. Diseases the person suffers from.
9. Conservative and surgical treatment.
10. Nutrition.
11. Belonging to a particular species.
12. Sex.

VI. What individual characteristics of the body are widely used to classify body (constitution) types?

1. Morphologic.
2. Morpho-functional.
3. The characteristics of temperament.
4. The type of high nervous activity.
5. The degree of reaction intensity to a stimulus complex.
6. The capacity of an individual for social adaptation.
7. Tone predominance of one of the sections of the vegetative [involuntary] nervous system.
8. State of the connective tissue.

VII. What is the role of sex in the primary reactivity development of the body?

1. Men and women have different constitution peculiarities.
2. The specific characteristics of neurohumoral regulation of the female organism compared with the male one.

VIII. What determines the peculiarities of reactivity in infants?

1. Morphological and functional nervous system underdevelopment.
2. Immaturity of the endocrine system.
3. Development of immunodeficiency.
4. Musculoskeletal hypoplasia.
5. Deficiency of external and internal barriers.
6. Peculiarities of metabolism.
7. Predominance of the passive resistance over the active one.
8. Predominance of the active resistance over the passive one.

IX. What determines the peculiarities of reactivity in old (senile) people?

1. Irreversible changes in the structure and functions at all levels: molecular, cellular, that of different organs and of the whole organism.
2. Changes of intensity and metabolic disturbances.
3. Summarized changes occuring in the process of the development of acquired reactivity in the body.

X. What parameters are affected by the initial functional condition of the body reactivity systems?

1. The degree of reaction intensity of a system as a response to stimulating and inhibiting stimuli.
2. Condition of the neurohumoral regulation apparatus.
3. Constitutional peculiarities of reactivity.

XI. Pick out the factors of natural resistance (nonspecific protection):

1. Barrier structures of the body.
2. Renal filtration and reabsorption.
3. Thymus.
4. Neuropeptides.
5. Humoral factors.
6. Cellular factors (phagocytes).
7. Normal microflora.
8. All factors.

XII. What formations are included in the notion of "barrier structures of the organism"?

1. Skin.
2. Mucous membrane.
3. Bones.
4. Lymphatic nodes.
5. Histohematic barriers.

6. Thymus gland.

7. Muscles.

XIII. What characteristics of the skin and mucous membranes underlie the barrier function?

1. Mechanical obstruction.

2. Radiative mechanism.

3. Pigmentation.

4. Bactericidal properties.

5. Acid reactions.

6. Normal microflora.

7. Complement.

XIV. What provides bactericidal action of the skin and mucous membranes?

1. Acid reaction.

2. Lysozyme.

3. Secretory immunoglobulin A.

4. Normal microflora.

5. T-lymphocytes

6. Mast cells.

7. Glucuronic acid.

XV. Name physiological and pathologic excretion acts aimed at the removal of infectious, toxic and foreign substances:

1. Cough.

2. Increased mucous secretion.

3. Sneezing.

4. Vomiting.

5. Urinary excretion.

6. Diarrhea.

7. Sweating [perspiration].

8. Epithelial sequestration.

9. Ciliated epithelium activity.

10. All factors.

XVI. What functions of lymph nodes are considered to be barriers?

1. Antigen fixation to tissues of regional lymph nodes with inflammatory reaction development.

2. Immunological reaction formation with lymphocytes of different population.

XVII. Pick out the humoral factors of natural nonspecific resistance:

1. Complement.

2. Lisozyme.

3. Properdin.

4. Endorpherines.

5. ß-Lyzine.

6. Chalones.

7. Somatomedins.

8. Interferon-α..

9. Lymiphotoxin.

XVIII. What are the main effects of humoral natural resistance?

1. Increased permeability and cell membrane disintegration, including membrane microorganisms.

2. Cell lysis coupled with damaged membrane.

3. Stimulation of phagocytosis.

4. The stimulation of the proliferation of cellular elements of T-system immunity.

5. Participation in immune adherence.

6. The transfer of blocking antibodies.

7. Structural and functional maintenance of histohematogenous barriers.

8. The antiviral effect which makes it impossible for virus to multiply in cells (interferones).

XIX. Pick out the cellular factors of nonspecific natural resistance

1. Neutrophils.

2. T-lymphocyte-killers [T cells and natural killer cells].

3. Inflammatory and stable macrophages.

4. Blood basophils.

5. Mast cells.

XX. Pick out the cause of suppressed phagocytosis as a result of the impairment of phagocyte development and differentiation:

1. Leukosis [leukemia].

2. The action of mitotic inhibitors (cytostatic).

3. Genetically dependent block of cell reproduction (hereditary neuropenia, hereditary agranulocytosis).

4. Genetic defect of lysosoma and phagocyte formation with incomplete phagocytosis development (Chediak-Higashi disease).

5. Hereditary enzymopathy in the form of NADF-oxidase deficiency, peroxidase reaction deficiency with incomplete phagocytosis development (chronic granulomatosis).

6. All factors.

Task

Describe the human reactivity mechanisms and develop the strategy for laboratory diagnostics of the workers making frequent meridional journeys (some kinds of nonstandard employments with moving from midlatitudes to trans-polar areas) can develop intensified erythrocytopoiesis, abnormal minute volume, an increase in the respiratory rate along with a decrease in the forced inspiration volume per 1 second. Average respiratory minute volume is 11000 ml, average lung vital capacity is 3800 ml.

What's your diagnosis?

What's the substantiation of the diagnosis?

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LIPID METABOLISM DISTURBANCES

The main research objective of lipid metabolism is to reveal as early as possible **hyperlipidemia** as a risk factor of developing heart disease (one of the leading causes of death).

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

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

Lipid digestion and absorption disorders.

The causes of lipid disintegration and absorption disorder can be as follows:

- **lack of pancreatic lipase** (pancreatitis, sclerosis and acute pancreonecrosis); resulting in the impairment of fat in the upper sections of the small intestine breaking down lipids to high fatty acids, monoglycerides and glycerol;
- **bile acid deficiency** (gallbladder inflammation, umbilical duct obstruction, liver diseases) – **acholia syndrome**. In addition we observe the impairment of fat emulsification, pancreatic lipase activation and external membrane formation of mixed micella in a compound of whose fatty acids and monoglycerides are transported from the site of fat hydrolase to the absorbing surface of the intestine epithelium.
- **small intestinal peristalsis aggravation and its epithelium lesions caused by infective and toxic agents** (enteritis, nervous and humoral control); in this case pancreatic lipase is not activated;

+ **calcium and magnesium excess in food**, in this case bile acid salts, soap, insoluble in water are formed;

+ **avitaminosis A and B, choline deficiency and phosphorylation disturbance** (fat absorption is inhibited);

+ **antibiotic inhibitory effect** (neomycin sulfate, chlortetracycline, etc.) in enterocyte function.

In all cases of digestion and fat absorption disorders **steatorrhea** (i.e. stool contains a lot of high fatty acids and unsplitting fats) develops. The stool becomes loose and butter due to **acholia**, clay-colored and contains lipid drops with whitish pea-soap lumps (calcium and magnesium salts of fatty acids). Calcium is lost together with fat. Coagulopathy and osteoporosis often develop in **chronic steatorrhea**.

Lipid transport disorder and lipid transfer to tissues.

Hyperlipemia (HL) is the main manifestation of fat transport disorder in blood and fat transfer to tissues. **Hyperlipemia** is characterized by more than 2 mmoles/l increase of lipids in blood serum. One can distinguish **alimentary, transport and retention hyperlipemia**.

Alimentary hyperlipemia occurs within 2-3 hours after fatty food intake and aggravates within 3-6 hours. Within 9 hours the level of fat in blood returns to the normal one. It is a physiological phenomenon. In alimentary hyperlipemia blood serum is of milk color and it is slightly opalescent due to increased concentration of chylomicrons (chylos).

In the arterial blood **chylomicrons** interact with **high-density lipoprotein (HDL)**: chylomicrons release apoproteinsA-1, A-2, A-4 and receive esters of cholesterol, apoprotein E and CII in exchange. Apoprotein CII serves as a factor of lipoprotein lipase facilitating chylomicrons and very **low-density lipoprotein (VLDL)** binding with lipoprotein lipase and apoprotein E contribute to

chylomicron capture by hepatocytes with the help of special receptors. An acute form of alimentary hyperlipemia develops due to this physiological process disorder in functional hepatic disturbances, blockage of reticuloendothelial system and splenectomy and also in lipoprotein lipase insufficiency (hyperlipoproteinemia type 1)

Transport hyperlipemia is observed during activation of adipose tissue, disintegration, intensified transfer of fatty acids from depot and lipid transfer from depot to the liver with somatotropic hormone, thyrotropic hormone, thyroxin, adrenalin, glucagons being activated. Transport hyperlipemia is usually accompanied by the increase of triglycerides in plasma level, therefore, it is classified as second hypertriglyceridemia.

Retention hyperlipemia occurs due to the retention of neutral fat transfer from blood to tissues. Decreased concentration of albumin in blood (e.g. nephrosis) which transports free fatty acids, and also decreased lipoprotein lipase activity result in the development of retention hyperlipemia. Lipoprotein lipase activity depends on insulin and glucagon concentration ratio. Insulin stimulates lipoprotein lipase and its antagonists (glucagon and somatotropic hormone) suppress lipoprotein lipase secretion. In case of diabetes mellitus an acute form of hyperlipemia is observed due to the suppression of triglycerides synthesis in adipose tissue, increased lipolysis in the liver and lipocaine deficiency, which activates lipoprotein lipase entering the blood. In case of mechanical jaundice when a lot of bile acids enter the blood and inhibit lipoprotein lipase retention hyperlipemia develops. NaCL is a lipoprotein lipase inhibitor. Retention hyperlipemia occurs due to excessive common salt intake and NaCL removes retardation. Heparin secretion during mast cell degranulation stimulates lipoprotein lipase formation and activates it. In case of atherosclerosis the release of heparin is impaired resulting in hyperlipemia.

Hyperlipoproteinemia.

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 (abnormalities, defects) and environmental factors, or **secondary**, resulted from such diseases as diabetes, liver and kidney pathology, hormone disorders, etc.

Primary hyperlipoproteinemia.

Hereditary factors (predisposition) play a significant role in primary HLP formation. 82% common cholesterol variability is caused by hereditary factors.

In 1967 D.S. Fredrickson suggested to distinguish five types of HLP. HLP classification added by J.Bohm in the early 70s was accepted by WHO. It was based on phenotype serum description in lipid metabolism disorders (table 1).

Type I-hyperchylomicronemia or lipemia induced by fats, resulted from lipoprotein lipase (LPL) deficiency, is usually inherited by autosomal recessive type. The disease is rare (one case per million) and is manifested in childhood, is characterized by the increased content of cholesterol, chylomicrons and triglycerides in plasma, extracellular triglycerides deposit in the skin in the state of eruptive xanthomas. This disease is also characterized by hepatosplenomegalia (much fat in connective tissue of the liver and spleen), abdominal pains (microembolia in vessels), acute form of lipemia in retina vessels during ophthalmoscopy. It is found to be predisposed to acute pancreatitis. Atherosclerosis does not develop since chylomicrons are not associated with atherogenesis.

Type II–hyper–β–lipoproteinemia or familial hypercholesterolemia (tubercular xanthoma multiplex) is inherited by autosomal dominant type. Low density lipoprotein (LDL) receptor defect is found in patients, this leads to low-density lipoprotein (LDL) accumulation in plasma practically from birth. Common cholesterol level is 2-4 times above normal. Two variants occur – the first one is

characterized by the increased low-density lipoprotein (LDL) and cholesterol content with normal very low-density lipoprotein (VLDL) and triglycerides amount; the second one is characterized by the increased low-density lipoprotein (LDL), very low density lipoprotein (VLDL) and triglycerides and cholesterol content.

Table 1. **Hyperlipoproteinemia Classification accepted by WHO.**

Type	Chylomicrons	VLDH	LDL	Cholesterol	Triglycerides	Lipoprotein disorders
I- hyperchylo-micronemia	↑	Norm	Norm	Norm	↑↑	Chilomicron Excess
II a hyper – β – lipoproteinemia	———	Norm	↑↑	↑↑	Norm	LDL Excess
II b hyper – β – lipoproteinemia	———	↑	↑	↑	↑	LDL and VLDL excess
III familial dis–β–lipoproteinemia	———	Floating -β-lipoprotein		↑	↑	Chilomicron remnant and IDL excess
IV hyperpre –β–lipoproteinemia	———	↑	Norm	Norm (↑)	↑	VLDL excess
V combination of hyperpre – β– lipoproteinemia and hyperchylo-micronemia	↑	↑	Norm	Norm (↑)	↑↑	Chilomicron and VLDL excess

Type - III – familial dis – β – lipoproteinemia, or hyperlipemia, induced by carbohydrates, or «floating» β – hyperlipemia is probably inherited by recessive type. VLDL with high content of cholesterol and high electrophoretic mobility, i.e. «pathologic» VLDL has been found. Cholesterol and triglyceride

content of plasma is high. Peculiarity of this disturbance is remnant chylomicron and IDL accumulation in plasma, catabolism of which, usually proceeded in the liver by receptor-indirect way, is impaired due to defective alleles inheritance of apoprotein E and impossibility to bind particles with the receptor (apoprotein B, E). Characteristic features (symptoms) are lipoid arch of cornea, xanthelasmas, ulnar or knee xanthomas lipid deposit of yellowish-brown color in the skin of palmar lines and in the places of the ring pressure.

Atherosclerosis of coronary arteries, peripherial vessels and brain vessels repel atherogenic properties of pathological VLDL which are intensively captured by macrophages. Glucose intolerance, hyperuricemia, obesity, diabetes mellitus, hypothyrosis, sometimes acute pancreatitis are observed in such individuals.

Type IV – hyperpre – β – lipoproteinemia or lipemia, induced by carbohydrates, or familial essential (idiopathic) hyperlipemia which is inherited by autosomal dominant type. Etiology of genetic disease is not clear. VLDL excess is typical, VLDL size is about normal. Higher correlation meaning of triglycerides/apoB with normal (or slightly increased) serum level of cholesterol is also observed. The increased insulin content, general obesity, adiposis liver, diabetes mellitus, chronic kidney diseases, angiopathy on the level of organs, intermittent claudication, fatty deposits in retina are clinically revealed.

Type V – combination of hyperpre –β – lipoproteinemia and hyperchylomicronemia or combined lipemia caused by metabolism disorder of both fats and carbohydrates. It is inherited polygenically. In the blood the content of VLDL, chylomicrons, triglycerides (TG) and plasma cholesterol is increased. Clinical picture (in patients over 20 as a rule) shows symptoms similar to those that occur in I to II types of hyperlipoproteinemia. Acute pancreatitis, eruptive xanthomas, intolerance to glucose, hyperuricemia, neuropathy, arm and leg paresthesia, vascular complications.

Hyper – α – lipoproteinemia is a special type. In practically healthy individuals the increased level (content) of HDD and cholesterol is determined

with normal or reduced level of other lipoprotein fractions. Its carriers have more prolonged life span and coronary heart diseases occur less frequently.

Secondary hyperlipoproteinemia.

The causes of secondary HLP can be:

- pregnancy, since estrogen level is increased, cholesterol and triglycerides (TG) are moderately increased;
- administration of oral contraceptives, treatment by glucocorticoid hormones;
- such diseases as diabetes mellitus of the I and II types, hypothyrosis, nephrotic syndrome, chronic liver deficiency, biliary cirrhosis, fatty infiltration of the liver, obesity, alcoholism, goat, etc.

Hypertriglyceridemia and hypercholesterolemia can be manifested of HLP.

Secondary hypertriglyceridemia develops:

- Due to the stress;
- due to diabetes mellitus,
- due to prolonged somatotropic hormone action;
- due to fasting since.

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

Hypolipoproteinemias and alipoproteinemias.

Familial hypo – α – lipoproteinemia is autosomal dominant disease. The decrease of chylomicron – HD level with the normal lipid level is characteristic feature of such diseases. Apo – a – I and apo – a – II concentration is about 70% above normal one, amino acid compound is not converted. This disease is characterized by coronary heart disease development at tender age.

A – α – lipoproteinemia (hypo – α – lipoproteinemia, Tangier disease) – HDL, apo – A – I and A – II are practically absent, it is inherited by autosomal –

recessive type. In homozygotes general content of chylomicrons and chylomicrons – LDL in the blood serum is about 1/3 of normal meanings; thyrotropic level is normal or slightly increased; normal α – lipoprotein is absent and only converted α – lipoprotein, Tangier lipoprotein is found. Pathogenic mechanism is based on evacuation deficiency of cholesterol ethers. Patients with Tangier disease are found to have early development of coronary heart disease and neuropathy.

A – β – lipoproteinemia (Бассейна – Корнцвейга disease, acanthocytosis) and hypo – β – lipoproteinemia are inherited by autosomal recessive type. Typical features are VLDL, LDL and chylomicron absence in the blood; common lipid, thyrotropic hormone, phospholipids, cholesterol number is decreased; α – lipoproteins are converted. Ataxia, scleral pigmentation, acanthocytosis, essential fatty acid deficiency and liposoluble vitamins in the blood serum are developed in a – β – lipoproteinemia and hypo – β – lipoproteinemia.

Hypo – β – lipoproteinemia can develop during autoimmune processes; in case of liver, alimentary tract discases since lipoprotein formation is impaired. The thyroid gland pathology occurs in this case due to the increase of lipoprotein disintegration. Adipose accumulation is revealed in the intestinal wall of such patients, dietary fat absorption is impaired, steatorrhea occurs, and thus progressive dystrophia develops.

Cell membrane structure is imparied in many systems of the organism. Acanthocytes (styloid protrusions) are found on the erythrocyte surface, anemia with reticulocytosis and hyperplasia of bone marrow is developed. The damage of myelinic membrane leads to peripheral nerves and central nervous system (pyramidal tract and cerebellum) disorders. Atherosclerotic manifestations were not found in such patients during autopsy.

The role of lipid metabolism disorders in pathogenens of atherosclerosis.

Atherosclerotic changes in vessels are typical practically for all individuals over 40, they are differ only in the damage rate. Atherosclerosis

development is closely connected with cholesterol transport to the arterial wall in composition of LDL and VLDL and cholesterol release from the arterial wall with the help of HDL. In healthy individuals 70% of plasma cholesterol are in composition of atherogenic LDL and VLDL, 25-30% are in composition of antiatherogenic HDL. This ratio provides the balance of direct and reverse cholesterol flow and resistance of the organism to atherosclerosis.

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 the most cases the content of atherogenic particles increases in the blood plasma, the main component is cholesterol, apo - B as a protein, but LDL concentration decreases in 30 % of cases.

Phospholipids and polynun saturated fatty acids have antiatherogenic properties. They limit dietary cholesterol absorption in the small intestine, stimulate fatty acid synthesis in the liver, inhibit synthesis and secretion of VLDL by hepatocytes , decrease LDL concentration in the blood plasma, inhibit thrombocsan A synthesis and trombocyte aggregation, stimulate prostacyclin synthesis by endothelial cells.

Cholesterol, thyrotrophic hormones and saturated fatty acids have atherogenic properties.

Atherogenic lipoprotein concentration increase can be caused by the decrease rate of their release from the flood to the liver, by the increase rate of their synthesis, by lipoprotein metabolism injury in plasma including the formation of abnormal modified lipoproteins.

Normally, VLDL and LDL transfer cholesterol from the blood plasma to the cells through receptors, located in cytoplasmic membrane of endothelial and smooth muscle cells. Liver cells, sexual glands and adrenal glands contain a lot of LDL receptors (since cholesterol in them is an essential substance to form bile

acids, sex hormones, corticosteroids). LDL receptors also bind VLDL and IDL remnants.

LDL complexes with LDL receptors being within endocytose vesicles transfer into the cell. Vesicles are mixed with endosomes {LDL and their receptors are catabolised within}. Receptors are restored {recovered} in plasmatic membrane, and LDL is destroyed in lysosomas, apoprotein-B molecule degradation and cholesterol ether hydrolysis occurs.

Free cholesterol regulates its own synthesis rate in the cell by enzyme –3-hydroxymethylglutaryl CoA reductase inhibition. Excessive accumulation of free cholesterol reetherified in cells by enzyme acylcholesterolacyltransferase. Synthesis rate of LDL receptors is regulated by principle of feedback mechanism, sensitive to cholesterol intracellular content. This prevents cholesterol excessive accumulation in cells and atherosclerosis development.

Cholesterol metabolism damage occurs:

- due to the lack of LDL-receptors on cell surface. Specific endocytosis is impossible, as a result LDL level in plasma increases (hereditary hypercholesterolemia - HLP II type) and aspecific endocytosis intensifies: cells of reticuloendothelial system capture LDL, this leads to uncontrolled accumulation of cholesterol and its ethers in the cell;
- due to the increase of lipoprotein affinity to membrane caused by cholesterol saturation of external VLDL layer (HLP, type III);
- due to direct affect of cholesterol excess on endothelium and smooth muscular cells of vessels. Trombocyte adhesion and formation of growing factors occur in the site of injury. The increase of permeability of facilitates capture process of lipoprotein particles by cells, microtraumas, migration of leukocytes from bloodstream into vascular wall and the formation of atherosclerotic plaque;
- the acceleration of atherosclerosis development results from stress developmrent. The increase of adrenaline and angiotensin concentration in blood

causes endothelial cell contraction, enlargement of fissures between them and VLDL and LDL accumulation in the medial layer;

- due to LDL excess in blood plasma rosette forming complex [Golgi complex] develops, stimulation of immune process and injury of vascular wall occur, excessive capture of these complexes by macrophages stimulates their convertion into foam cells;
- due to the low LDL level the contact with fibroblast surface, endothelial and smooth muscle cells is impaired and capture of cholesterol is also damaged, as a result cholesterol etherification is disturbed and cholesterol in HDL combination can't be transported to the liver;
- due to the impairment of cholesterol etherification processes in HDL and its transport between lipoproteins of various classes (hereditary deficiency of lecithin-cholesterol-acyl-transferase). In this case the ability of HDL to remove cholesterol from tissues reduces, the content of triglycerides and VLDL increases, LDL particles abnormally riched in triglycerides occur in plasma;
- due to genetic defect of apolipoproteins and their receptors, enzymes of lipoprotein and cholesterol metabolism (hereditary forms of accelerated atherosclerosis). Synthesis and catabolism rate of circulating lipoproteins in the blood is converted to the liver.

Fatty infiltration and fatty degeneration.

If fats transported into the cells are not disintegrated, or oxidized, or released from cells, it is the evidence of fatty infiltration. In combination with the impairment of protoplasm structure and its protein component we speak of fatty degeneration. The common cause of fatty infiltration and fatty degeneration is considered to be the suppression of oxidizing and hydrolyzing enzyme activity during lipid metabolism (in case of arsenic or chloroform poisoning, in avitaminosis or viral infection). Fatty infiltration is more often observed in the liver since endothelium of capillaries in the liver doesn't have limited membrane and it captures chylomicrons circulating in the blood.

Fatty infiltration in the liver develops

- in the presence of alimentary and transport hyperlipemia;
- due to the impairment of phospholipid formation resulting from insufficient food intake of choline, methionine, containing its proteins (e.g. casein), other lipotropic factors, and also insufficient secretion of endogenic lipotropic factor of lipocaine by pancreas. It activates phospholipid formation and oxidation of fatty acids in the liver. Dispersion of fats and oxidation of fatty acids are impaired, and hydrophilic nature of LDL molecules is reduced due to phospholipid deficiency;
- due to cholesterol excess producing the formation of more hydrophobic LDL fractions, suppressing phospholipid synthesis and fatty acid oxidation. Cholesterol facilitates emulsion formation 'water in fat' that makes triglyceride metabolism difficult. The impairment of lipid intermediate metabolism results in ketasis manifestating the increase of the level of ketonic [ketone] bodies [that is the manifestation of the level increase of ketonic bodies] (acetoacetic acid, β-hydrooxibutyric acid, acetone) in the blood (ketonemia) and their release [excretion] in large amount with urine (ketonuria). Ketonic bodies are group of organic compounds being intermediate products of fat, carbohydrate and protein metabolism. They are synthesized in the liver from acetyl-KoA forming during fatty acid β-oxidation and during oxidized pyruvate decarboxylation in the process of glucose and a number of ketogenic aminoacids metabolism (leucine, phenylalanine, tyrozine, tryptophan and etc).

The causes of ketosis:

- carbohydrate deficiency in the organism. Diabetes mellitus, fasting, fatty diet with limited quantity of carbohydrates (the people of the Far North are adjusted to it), fever, hard physical work lead to the reduction of glycogen supply [storage] in the liver. Glucose utilization is impaired due to insulin deficiency and energy deficiency develops in tissues. The stimulation of lipolysis occurs, the excess of free fatty acids reaches the liver [saturated fatty

acids] where synthesis of ketonic bodies increases but utilization of acetyl-KoA in tricarbonic acid circle is inhibited due to carbohydrate deficiency since all metabolically accessible resources of the organism are converted into glucose, hence, ketosis develops.

- stress during which carbohydrate resources of the organism are depleted [exhausted] due to the activation of sympathetic nervous system and as a result ketosis develops. In addition during stress albuminolysis results from the increase of glycocorticoid production and ketonic bodies are formed from ketogenic amino acids;
- liver injury by toxico - infectious factors. This disturbs its ability to synthesize and store glycogen, excessive supply of free fatty acids occur in the liver.
- vitamin E deficiency inhibits oxidation of higher fatty acids;
- oxidation suppression of ketonic bodies in Krebs cycle is observed during hypoxic hypoxia, the impairment of carbohydrate oxidation in tissues (diabetes), excess of ammoniacal salts (hepatic and uremic coma). Krebs cycle breaks off by ammonia excess which converts ketoglutaric acid to glutaminic one, inhibit oxidation of pyruvic acid and acetyl-KoA, their metabolism transfer to acetoacetic acid;
- glycogenesis type I, II, and IV. Deficient supply of glucose from the liver to the blood leads to its deficiency in tissues and to the oxidation impairment of ketonic bodies;
- resynthesis impairment in higher fatty acids with the deficiency of hydrogen sourses, essential for hydrogenation of β-keto- and unsaturated fatty acids;
- acetonic poisoning (seldom occurs);
- aminoacidopathies with the metabolism impairment of branched-chain amino acids;

- alcoholic intoxication during which ketosis mechanisms are combined since chronic alcoholics affected by alcoholic hepatopathy and pancreatitis and their drinking isn't accompanied by proper food;

An acute form of ketosis leads to the intoxication of the organism, to the impairment of electrolytic balance due to sodium release with urine (sodium forms salts with acetoacetic and β-hydroxybutyric acids) and to acidosis development.

The impairment of lipid metabolism in fatty tissue.

Obesity is a tendency of the organism to increase the body weight excessively under the influence of certain conditions. In this case body weight increseases due to abnormal fat accumulation.

According to the etiology three types of obesity are defined: alimentary, normal and cerebral. Heredity plays an in important role in the pathogenesis of obesity. Obesity develops as a result of three basic pathogenic factors:

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

Overeating may be caused by excessive appetite (bulimia) due to overexcitement of the alimentary [nutritional] centre (ventrolateral nucleus of posterior hypothalamus) or inhibition of «society centre» (ventromedial nucleus of hypothalamus). In this case hypothalamic obesity develops. Reflex excitement of alimentary [nutritional] centre may be due to stimulation of gustatory endings in the oral cavity (e.g. spices) and tasting a little of everything (e.g. a cook or a confectioner). Due to the reduction of nerve ending sensivity in stomach wall, hyperdistention [overextention] of the latter leads to the inhibition of alimentary centre. In individuals with hard physical activity the excitement of the alimentary centre increases, i.e. glucose consumption decreases by 'glucoreceptors' of hypothalamus ('satiety centres' have specific reactivity to glucose).

Overeating occurs when these individual change their way of life to life with less physical activity but their previous excitement level of alimentary centre and

former appetite persist. Elderly people are inclined to put on weight and the cause of it may be explained by relationship between the former excitement level of alimentary centre and less energy expenditure at this age (basal metabolism is decreased, and muscle activity is also reduced). Hypothalamic and diencephalic obesity may develop in patients with brain injury, after meningitis or encephalitis, intracranial hypertension and brain tumor. 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 the sense of satiety [satiation] and individuals refuse to eat. Leptin level increases with the enlargement of fatty tissue. Obesity is considered to be connected with the decrease of tissue sensitivity to leptin. Excessive breast feeding in infancy during the first year of life produces hyperplastic (multicellular) obesity development (abnormal growth of fatty cell number). This obesity has poor prognosis for body weigh reduction. It is constantly associated with hypertrophy and reaches its high degree. Obesity developing in childhood is hypertrophic (the increase of fatty cell size). As a rule it is a result of overeating.

If the function of alimentary centre is normal (that is corresponding to energy expenditure), the cause of obesity may be insufficient consumption of fat from fat depot. This occurs in case of tonus decrease in sympathetic nervous system or tonus increase in parasympathetic nervous system, due to inhibitory affect of cerebral cortex on the centers of sympathetic part of diencephalic region. For example, the accumulation of fat in the abdominal wall increases in pseudopregnancy, painful accumulation of fat on the abdomen, upper extremities and thighs is typical for Dercum's disease (symptoms [signs] of interstitial neuritis are found in nervous branches of fatty tissue).

Since fat mobilization processes [releasing] [the processes of fat releasing] are under the control of hormone and humoral factors, impairment of their production leads to limited fat expenditure. It is observed as follows:

- hypofunction of thyroid gland and pituitary gland [hypophisis]. Adrenocorticotropic hormone (ACTH) directly activates lipolysis and out let of

free fatty acids. At the same time ACTH stimulates glucorticoid secretion. Besides [in addition] glucogen stores in the liver increase and fat releasing from depot inhibits. The increased secretion glucocorticoids inhibits somatotrophic hormone effect [action], its fat-mobilizing and stimulating effects to oxydize fat, and as a result fat accumulation increases in Cushing's syndrome and pituitary [Cushing's] basophilism. P-lipotropin (from adenohypophisis), thyrotropic hormone and thyroxin stimulate lipolysis and oxidation of free fatty acids. Their deficiency also leads to obesity;

- the increase of glucose in the blood. Fat release dereases and absorption of tree fatty acids and chylomicrons by adipose tissue increases. Increased secretion of glucocorticoids produces hyperglycemia due to the increase of gluconeogenesis. Obesity develops in this case;
- exesice insulin production in the presence of hypoglycemia, insulinoma (islet cell tumor) hypertrophy of B-cells pancreatic islet (islet of Langerhans) in pancreas/ Insulun inhibits fatty acid release from depot, decreases glucose level in the blood , this increases appetite and alimentary centre activity. Insulin stimulates glucose absorption by fatty tissue, stimulates fatty acid synthesis and triglycerides from products of carbohydrate metabolism and fi capture by fatty tissue during pinocytosis, it doesn't depend on glucose level. Insulin secretion increases and obesity develops due to the reduction of sexual gland activity and increases reactivity of hypothalamus centers. The increased glucocorticoid level in the blood produces hyperplasia of pancreatic islet and increases insulin production. Obesity in women during lactation and after it is explained by the fact that prolactin stimulates carbohydrate transfer to fatty tissue.

Obesity is a predisposed factor to the development of cardiovascular disease (atherosclerosis), gallstone formation, fatty infiltration of the liver, diabetes mellitus.

QUESTIONS TO DISCUSS.

1. Etiology of lipid metabolism disturbances.
2. Disturbances of entering, digestion and absorption of lipid in the digestive tract.
3. Disturbances of intermediate lipid metabolism.
4. Hyperlipemia state, its types and mechanisms.
5. Hyperlipoproteinemia. Primary hyperlipoproteinemia, its types.
6. The role of lipid metabolism disorders in pathogenesis of atherosclerosis.
7. Obesity.

First Level Tests. Choose the right variants.

I. Which of the following organ injuries cause lipid disintegration and absorption disorder?

1. CNS
2. Lungs.
3. Liver.
4. Kidney.
5. Pancreas.
6. Epinephros.
7. Stomach.
8. Intestines.

II. Match mechanisms which are at the basis of hydrolysis and fat absorption disorders:

1. Amylase deficiency.
2. Fat emulsification insufficiency.
3. Exopeptidase excess.
4. Lipase deficiency.
5. Disorder of fatty acids and glycerin transport to the intestine wall.

III. Select the possible consequences of disintegration and fat absorption disorders:

1. Hypercholesterolemia.
2. Decrease of fatty acid level in lymph and blood.
3. Unsaturated fatty acid deficiency.
4. Lipoprotein lipase plasma activation in the blood.
5. Vitamin A, D, E, K deficiency.
6. Vitamin B, C deficiency.
7. Protrombin synthesis disorder.
8. Energy metabolism disorders and as a result the decrease of endogenous carbohydrate and fat metabolism.
9. Steatorrhea.

IV. Match atherogenic lipoproteins:

1. Chylomicrons.
2. Very-low density lipoproteins.
3. Low-density lipoproteins.
4. High-density lipoproteins.

V. What mechanisms play the main role in pathogenesis of atherosclerosis?

1. Reflex.
2. Hyperlipoproteinemia.
3. Hypoproteinemia.
4. Vascular wall injury.

VI. Indicate diseases which are characterized by hyperlipoproteinemia:

1. Atherosclerosis.
2. Diabetes insipidus.
3. Diabetes mellitus.

4. Thyrotoxicosis (hyperthyroidism).

5. Nephrotic syndrome.

6. Mixydema (hypothyroidism).

7. Cholelithiasis.

VII. Match vessels mostly affected by atherosclerosis:

1. Veins.

2. Aorta.

3. Subclavicular arteries.

4. Coronary arteries.

5. Arterioles.

6. Cerebral arteries.

VIII. Match the major causes of obesity:

1. Polyphagia.

2. Polydipsia.

3. Hypodinamia.

4. Aldosteronism.

5. Hypercorticolism.

6. Hyperthyroidism.

7. Hypothyroidism.

8. Somatotropin deficiency.

9. Injury of ventromedial hypothalamic nuclei.

IX. Indicate the main conditions of fat mobilization increase from adipose depot:

1. Hyperglycemia.

2. Hypoglycemia.

3. Hyperlipemia (hyperlipoidemia).

4. Hyperproteinemia.

X. Match hormones mobilizing fat:

1. Somatostatin.
2. Somatotropin.
3. Adrenaline.
4. Noradrenaline.
5. Aldosterone.
6. Cortisol.
7. Insuline.
8. Melanotropin.

XI. Match the factors having antilipolitic effect:

1. Thyroxin.
2. Beta-hypophysis lipotropins.
3. Prostaglandins.
4. Insulin.
5. Aldosterone.

XII. Indicate the major components combining the notion "ketonic bodies".

1. Neutral fats.
2. Cholesterin.
3. Acetone.
4. Fatty acids.
5. Beta-oxyoily acid.
6. Acetoacetic acid.

XIII. Which of the following substance metabolism disorders result in ketose:

1. Aminoacids.
2. Glycerin.

3. Glucose.

4. Fatty acids.

XIV. Match the natural source of ketonic bodies:

1. Aminoacids.

2. Catecholamines.

3. Choline esterase.

4. Acetyl-CoA.

Second Level Tests

I. Which of the following organ injury leads to direct lipid disintegration and absorption disorders?

1.

2.

3.

4.

II. Which of the following organ and system injury can lead to inderect adipose disintegration and absorption disorder?

III. Match the major mechanisms of hydrolysis and fat absorption disorders.

1.

2.

3.

IV. Name possible consequences of fat disintegration and absorption disorders.

1.

2.

3.

4.

5.

6.

V. Name atherogenic lipoproteins.

1.

2.

3.

VI. What mechanism, except hyperlipoproteinemia, plays the main role in pathogenesis of atherosclerosis?

VII. Which disease does hyperlipoproteinemia play the major pathogenic role in?

VIII. Give examples of diseases during which progressive hyperlipoproteinemia represents as characteristic laboratory feature.

1.

2.

3.

4.

5.

IX. Name the major consequences of atherosclerosis:

1.

2.

3.

X. Which mechanism of hemostasis is primary impaired due to atherosclerosis?

XI. What vessels are most often affected due to atherosclerosis?

XII. Name the major etiological factors of obesity:

1.
2.
3.
4.
5.
6.
7.

XIII. Name the main conditions promoting fat mobilization increase from adipose depot.

XIV. Give the general term for hormones stimulating fat mobilization from depot.

XV. Enumerate hormones stimulating fat mobilization from adipose depot

1.
2.
3.
4.
5.
6.

XVI. Name the factors having antilipolitic effect.

1.

2.

3.

XVII. Form the chain of cause-and-effect connection of emaciation (weight loss) during general starvation.

XVIII. Give the definition for the notion "ketonemia".

XIX. What substances pertain to ketonic bodies?

1.

2.

3.

XX. Name the processes which are characterized by the increase of ketonic bodies in the blood.

1.

2.

3.

XXI. Match the main condition of ketonic body increase in the blood

XXII. What is the natural source of ketonic bodies?

Task 1

Patient H., 38 years, the book keeper by a trade, complains of a progressing obesity, a short wind palpitation, a flaccidity, a sleepiness, the headaches, the raised (increased) sweating, frustration of a menstrual cycle. Appetite is good. Uses much mealy and sweet food. In physical work almost is not engaged.

Objectively: the Patient of a hypersthenic body build. Body height - 150 sm. Weight of-105 kg. Fatty adjournment are distributed (allocated) on all body rather in regular intervals. Integuments wet. In axillary and inguinal folds of an intertrigo. Muscles are flabby. Borders of heart are a little bit expanded. The cardiac jerk is absent. Tones are weakened and mufiled. Pulse is 90 beets per minute. Arterial pressure is 150/100 mm Hg. The liver leaves : from under costal edge (territory) on 2 transversal fingers. The maintenance (contents) of lipoids is revealed in a blood rising.

What possible pathogenesis of an obesity at the patient?

As transport of *adepses is carried out, and in what cases the hyperlipemia develops?*

Task 2

A 26-year-old man got into the cardiologic department for examination. His father was operated on for aortocoronary bypass at the age of 39 after suffering from cardiosclerosis for 3 years. The young man didn't smoke, practically didn't take alcohol. On both hands he had tendinal xanthomas. Blood pressure was 120/70 mm Hg. The pulse was present on all peripheral arteries.

Laboratory analysis:

Cholesterol total 9.0 mmole/l (3.5-6.5)

Triglycerides 1.7 mmole/l (0.5-2.5)

Cholesterol HDL 1.27 mmole/l (>0.9)

Cholesterol LDL 6.9 mmole/l (2.0-5.0)

His 29-year-old sister had the concentration of cholesterol in serum equal to 13.0 mmole/l. His 26-year old brother – 11.3 mmole/l. With the pronounced hypercholesterolemia and heredity the patient is highly predisposed to developing cardiosclerosis.

Treatment:

After 8 weeks of a low-fat (low cholesterol) the concentration of cholesterol in serum dropped to 8.3mmole/l, which was not sufficient. The patient was

prescribed to take stanins (inhibitors GMG-KoA-reduktase) and the total cholesterol was reduced to 5.5 mmole/l., Ch-LPNP to 3.7 mmole/l.

The patient stopped taking the medicine, and the level of cholesterol in serum quickly rose to 8.1 mmole/l

Dynamics of lipid indexes:

Serum index	Upon admission	Diet therapy	Statine therapy	End of treatment
Cholesterol total, mmole/l	9.0	8.3	5.5	8.1
Triglycerides, mmole/l	1.7	1.4	1.3	0.9
Cholesterol HDL, mmole/l	1.27	1.22	1.23	1.21
Cholesterol LDL, mmole/l	6.9	6.4	3.7	6.5

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 3

A nine-year-old boy was taken to the clinic with complaints of stomach pains, which developed after meals (especially after fatty foods), there was rash on his thighs, face, around the elbow- and knee-joints.

After examination and tests hepatomegaly was revealed. The child had been under observation by a dermatologist, his physical and psychomotor development adequate for his age. The boy had history of the following diseases: mumps, quinsy, chronic tonsillitis, stomach pains associated with fatty meals were noted since the age of 3 after a serious abdominal crisis.

Laboratory analysis

Upon drawing the serum was turbid all over the test-tube. After being kept in the fridge for 10 hours it had a turbid a plum-like upper layer of chylomicrons, beneath the serum was clear

Cholesterol 18.4mmole/l (3.5-6.5)

Triglycerides 9.9mmole/l (0.5-2.0)

Ch-LPVP 1.8mmole/l (>0.9)

Lipoproteidlipase 0

Fraction	Result	Reference index
Chylomicrons	4.5%	0-0
LDL	53.7%	40-72
VLDL	29.0%	0-30
HDL	12.7%	10-46

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 4.

A thirty-year-old patient came to see a doctor with complaints of stomach pains, especially after fatty meals, there was rash on the hands, legs, stomach. On examination: the patient was is obese, the liver and spleen were enlarged on palpation, and there were eruptive xanthomas on the skin.

Laboratory analysis

Upon drawing the serum was turbid all over the test-tube. After being kept in the refrigerator for 10 hours a plum-like upper layer appeared over the turbid serum.

Cholesterol	5.2mmole/l (3.5-6.5)
Triglycerides	7.5mmole/l (0.5-2.0)
Cholesterol HDL	0.9mmole/l (>0.9)

Fraction	Result	Reference index
Chylomicrons	5.4 %	0-0
LDL	40.0%	40-72
VLDL	35.6%	0-30
HDL	19.0%	10.46

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 5

A 48-year old man, height 1.91 m gained 98 kg (from 95kg to 193 kg) over 8 years after being discharged from military service. At that period he gave up smoking after his health deteriorated. His diet did not change a lot after demobilization, but the amount of exercise decreased drastically. He began working as a driver. A detailed analysis showed that he consumed 3000-4000 kilocalories with about 40% fat content. He was prescribed a diet with 35%caloric content of the previous diet and he was recommended to swim 3-4 times a week. He began to lose weight by 3-4kg a month, until it reached 145-150 kg. Then he was put on a protein-rich, low carbohydrate and low fat diet. As a result his weight restored to 93 kg.

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 6

A clinical investigation revealed that a 36-year-old woman had a concentration of TG in serum of 7.3 mmole/l, cholesterol – 13 mmole/l. After a close questioning she confessed that she had been suffering from chronic alcoholism: for the last week she had drunk three bottles of vodka and six bottles of wine. When she stopped taking alcohol the TG concentration dropped to 2 mmole/l, of cholesterol – to 5 mmole/l. However, three years later, the woman was admitted a treatment again, this time she had an increased liver as well as a disorder of lipid indexes. Biopsy showed fatty degeneration of liver, hepatocytes infiltrated with lipids.

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 7

After a screening examination it was found out that a 54-year-old woman had hypercholesterolemia, though she did not complain of feeling unwell.

Nevertheless she started a low-fat diet. Eighteen months later she lost three kilos. A lipid spectrum test yielded the following results:

Laboratory analysis:

Cholesterol total 7.9 mmole/l (3.5-6.5)

Triglycerides 0.9 mmole/l (0.5-2.5)

Cholesterol-HDL 3.56 mmole/l (>0.9)

Cholesterol-LDL 3.9mmole/l (2.0-5.0)

What's your diagnosis?

What's the substantiation of the diagnosis?

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PATHOLOGY OF CABORHYDRATE METABOLISM.

Caborhydrates. Description.

Carbohydrates are aldehydes and ketons of multinuclear alcohol. Depending on the carbohydrate atomic number in monosaccharide molecule one distinguishes trioses, tetroses, pentoses, hexoses and etc. Monosaccharides are connected by glycosidic bond forming disaccharides, oligosaccharides (up to 6 monosaccharide residues) and polysaccharides (glycogen, starch). Carbohydrates form combinations with protein (glycoproteins and proteoglycanes), lipoids (glycolipids) and other substances (heteromonosaccharides). Pentoses (included in combination of nucleic acid and coenzyme, NADP in particular) and hexoses (glucose, fructose, galactose) are widely spread in the body. Monosaccharides are found to be in open and cyclic form in the organism.

Carbohydrates are stable and have little activity in cyclic form and in the open form they have highly reactive property and are able to interact with out enzymes with proteins, nucleotides, lipids; this reaction is called **glycosylation**.

Ability to glycosylation is different in various sugars (saccharum) depending upon sugar correlation of open and cyclic sugar forms. Glyconic property of glucose is less than in other sugars (saccharum) and their derivatives because only about 0,002 % of glucose (form total amount in serum) are present in the open form.

It is 7,5 times less than in fructose, 4,7 times less then in galactose, 50 times less than in glucose-6-phosphate, 75 times less then in fructose-6-phosphate.

Nevertheless glucose concentration in blood serum is much higher there in other carbohydrates, that is why glucose is the main substanse (agent) in the glycosylation process of extracellular proteins. According to the above mentioned food glucose substitution by poorly digested fructose might result in complications connecting with the increase of protein glycosylation process. In fructose and

galactose larger percent of molecules interact with proteins nonfermentally. It is probably the reason of toxic galactose effect in children with galactosemia.

Hemoglobin, proteins of erythrocyte membranes , collagen, serum proteins, including albumin, lipoproteins, certain enzymes (alcohol dehydrogenase), protein membranes, endothelial cells are subjected to glycosylation in the blood.

DISFUNCTION OF CARBOHYDRATE METABOLISM occures due to a disorder of any of its three main stages:

1. Splintering and absorption of carbohydrates in a digestive tract.
2. Synthesis and disintegration of glycogen in the liver.
3. Utilisation of carbohydrates by the cells.

DISFUNCTION OF DIGESTION AND ABSORPTION:

Hydrolysis of glycogen and starch starts in the mouth under the influence of alfa-amilase of saliva. Monosaccharides can be absorbed in the mouth. In the stomach there are no enzymes which hydrolyze carbohydrates. In duodenum and in the small intestine under the influence of alfa-amilase they get hydrolyzed up to dextrine and maltose (cavity digestion). Such enzymes as saccharose, maltose, laktose, isomaltose and et cetera are localized on the surface of microvilli which splinter dextrines and disaccharides up to monosaccharides.

In congenital or acquired deficiency of one or more enzymes of disaccharide hydrolyse disaccharide deficiency develops. Disaccharides block the place of absorption so that absorption of monosaccharides gets disturbed. Let's see the pathology of disaccharide deficiency on the example of children with the congenital deficiency of lactose. Undigested lactose enters the large intestine and gets splinted by the bacteria up to organic acids (milky acid, acetic acid). The increase of lactose and organic acids changes osmotic pressure in the lumen of the intestine which appears with the rise of liquid secretion and the volume of fecal masses, the intestinal peristaltics increases, and osmotic diarrhea develops. At the same time the H^+ ions which are formed by the splintering of organic acids enter

the blood circulation and cause acidosis. To remove the excess of H+ ions the lungs take part and the condition is manifested by the increase of the concentration of the oxygen in the expirated air. Due to the absorption of carbohydrates in the intestine of children hypoglycemia and hypotrophy are developed.

In physiological conditions glucose gets absorbed very fast in the small intestine because of the existence of a passive diffusion, easy transport and the active transfer due to the energy which gets free by the ATP hydrolysis. All other sugars like mannose, ksilose, arabinose get absorbed only by the passive diffusion. That's why glucose and galactose get absorbed faster than the other monosaccharides. The functional condition of gastrointestinal tract, the content of food products, vitamins, microelements and etc influences the absorption of carbohydrates. The absorption of glucose abruptly decreases due to disturbance of its phosphorylisation in the cells of the intestinal wall. The main reason of the given disorder is hexokinase enzyme deficiency which develops due to inflammation of the intestinal wall, poisoning by: phloridizin, monoiodacytate. Due to malabsorption of carbohydrates hypoglycemia and loss of body weight occur. As for the synthesis of glucose by the gluconeogenesis fats and protein are expensed. In the intestine the unsplitted carbohydrates are metabolised by the bacteria which cause the osmotic diarrhea.

Pathology of glucose develops more often than the other carbohydrates pathology. So the impairment of carbohydrates metabolism can be seen in the example of glucose impairment.

DISBALANCE OF SYNTHESIS AND SPLITTING OF GLYCOGEN: Glycogen is a deponent form of glucose which doesn't have any osmotic effect. Decrease of glycogen synthesis can be seen in a severe impairment of the liver cells for example in hepatitis, when there occurs a disturbance of glycogen generating function. Glycogen synthesis decreases in hypoxia as in the condition of

hypoxia the synthesis of ATP decreases, which is necessary for the glycogen synthesis.

Glycogen disintegration increases in stress conditions, emotional strain (activation of sympathetic nervous system), heavy physical work, starving, increase of hormonal activation (glucagon, adrenalin) which stimulate glycogenolysis, diabetic ketoacidosis.

Due to a decrease of glycogen in the organism hypoglycemia is observed and energy metabolism is provided by metabolism of fats and proteins (glyconeogenesis). And this results in accumulation of ketone bodies, ketoacidosis, intoxication and loss of plastic material by cells.

Considerable increase of glycogen synthesis causes it's excessive accumulation in the organs and in cells and its damage. It happens in glycogenosis (glycogenic disease) where the congential enzyme deficiency takes place which katalises disintegration or synthesis of glycogen. Glycogenosis are inherited according to the autosomal-recessive type. Usually they appear soon after birth. Till now 12 types of glycogenosis are described. Some of them are very rare.

GLYCOGENOSIS OF Ist TYPE (GIERKE'S DISEASE): is based on a congenital deficiency of glucose-6-phosphatase enzyme in the liver and kidneys. The given enzyme converts glucose-6-phosphate to glucose, which makes easy it's transmembranial motion from the cells of the liver and kidney to the blood. Due to a deficiency from glucose-6-phosphate in the liver and kidneys glycogen accumulated. Liver and kidneys get increased in size and hypoglicemia develops. Patients have to eat very often. In blood The level of lactic acid increases in the blood because glucose-6-phosphate gets converted into it due to a deficiency of glucose-6-phosphatase.Metabolic acidosis develops and children die very early due to the disease or due to acidotic coma.

GLYCOGENOSIS OF THE IInd TYPE (POMPE'S DIASEASE): is seen in congenital deficiency of acidic alpha-1,4-glucosidase. It is a component of in lysosomes. It splitts the remaining glucose from glycogen molecule and splitts maltose. In lysosomal cells of different tissues and organs glycogen is accumulated

which drives cytoplasma away, fills the cell and destroys it. Symptoms of glycogenosis appears in few days or week after birth. A tongue gets increases due to deposits of glycogen on it. In a diaphragm it leads to-respiratory dysfunctions and etc. The Main symptom is cardiomeghalia due to deposit of glycogen. Children die early due to the cardiac deficiency.

GLYCOGENOSIS OF THE IIIrd TYPE (CORRY'S DISEASE); arises due to deficiency of amilo-1,6-glucosidase. The External features are the same with the I st type of glycogenosis. Prognosis is favourable as in pubertate period development of a disease gets slow down.

GLYCOGENOSIS OF THE IVth TYPE (ANDERSON'S DISEASE) is a diffused glycogenosis with the liver cirrhosis. It is due to congenital deficiency of D-1,4-glocon-alpha-glycosine-transferase which provides branching of glycogen with small no. of branching points. Function the of organs especially liver gets disturbed. Symptoms of glycogenosis appear soon after birth. Liver cirrhosis with jaundice and hypoglycemia develop. Children die during the first year of life.

The Given type of glygenosis develops either with the changed structure of glycogen (III, IV-th type) or with out it (I, II-nd type). Besides the given examples there are some rare types and mixed forms of glycogenosis the-V th type is - Mc Ardler's disease (deficiency of the muscular phosphorylase as a result of deposit of glycogen in the muscles, muscular cramps while physical work). The VI type (liver phospholipase-hypoglycemia).

The other classification of glycogenosis is dominated now. According to pathogenesis glycogenosis are divided into hepatic, myopatic and miscellaneous types.

In some pathological condition the **impairment of intermediate metabolism of carbohydrates develops**. For example due to **hypoxia** in tissues dominates anaerobic way of carbohydrate oxidisation, the accumulation of pyruvate acid and lactic acid take place. Tissue acidosis develops.

Liver dysfunction where the normally part of lactic acid gets resynthesised to glucose and glycogen and as a result hyperlactacidemia and acidosis develop.

B hypovitaminosis: Vitamin B1 (thiamine) due to phosphorisation changes to cocarboxylase which belongs to a group of proteolytic enzymes, which take part in carbohydrate metabolism. Decarboxylation of pyretic acid is disturbed and its oxydisation by acetylcoenzyme A takes place. As a result carbohydrates in tissues can't be the source of energy, and transform to the other substances (fats, steroids, acetylcholine). Due to the loss of transketolase pentose cycle is inhibited. Deficiency of gamma-ketoglutarate-dehydrogenosis causes through inhibition of gamma-ketoglutaric acid to the cessation of formation of macroenergetic compounds and to a dysfunction of transferring nervous impulses.

DISFUNCTION OF CARBOHYDRATE METABOLISM REGULATION:

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 one hand and by the speed of glucose utilization on the other. Several types to regulation of carbohydrate metabolism can be distinguished: substrate, nervous, hormonal and renal.

SUBSTRATE REGULATION: is realized by the level of glycemia, increasing or decreasing synthesis of glycogen or glycogenolysis in the liver.

NERVOUS REGULATION: is irritation of the sympathetic nervous system results in hyperglycemia, and of a parasympathetic in hypoglycemia.

Possibility of conditional reflective hyper- and hypoglycemia in an animal was proved. There is also consideration that even experimental neurosis is accompained by the hyperglycemia which is simillar to clinical observations. Different emotions may change the function of endocrine organs and may cause diabetes.

Change in **hormonal regulation** results in hyperglycemia and further in diabetes. The main role in this is played by deficiency of insulin, which may be

due to a low secretion of insulin or to the hypersecretion of conterinsulin hormones. Insulin has a strong hypoglycemic effect and conterinsulin hormones inhibit a decrease of glucose level in the blood. Main effects of hormones on glucose metabolism are:

Adrenalin: increases disintegration of glycogen in the liver, lipolysis in muscles and adipose tissue, speed of glycogenosis in skeletal muscles, which increases the exit of lactate from the muscular tissue to the blood and promotes glyconeogenesis, increases glycogen secretion.

Glucagon: increases disintegration of glycogen in the liver, stimulates gluconeogenosis, increases protein and fats splitting, inhibits synthesis of fats.

Glucocorticoids: stimulate gluconeogenesis in the liver, inhibit the use of glucose by muscles (decrease sensitivity of tissues to insulin), increase glucagon secretion, promote adrenaline action and STH in lipolysis, decrease glucose utilization by the tissues (decreases sensitivity of tissue to insulin), increase lipolysis. (Through catecholamine and thyroid hormones increase sensitivity of adepocytes to tonic litic stimuli along the sympathetic nervous system) activate the enzymes destroying insulin.

Insulin: increases membranial transport of glucose, aminoacids and potassium ions, activates liver glucokinase in the live which deposits glucose in the form of glycogen; and due to this disintigration of glycogen stops. Increases accumulation of glucose in the muscles and adipose tissue in which insulin stimulates transfer of glucose to glycogen (in the muscles) and to fats. (in adipose tissue in the form of triglycerides), the lack of insulin decreases accumulation of glucose in the tissues. From above we can say that in organism we have insulin dependent tissues like liver, muscles, adipose tissue, Langerhan's cells and insulin independent tissues like central nervous system, peripherial nerves, erythrocytes, blood vessels, connective tissue, renal canals, intestine, semen, medullary layer of adrenal gland. Insulin activates enzymes of aerobic glucose oxydisation as well.

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 conterinsular 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. In a healthy person we can see 2 peak of insulin secretion the 1st in 3-10 min after carbohydrate intake and 2nd in 20 min.

RENAL REGULATION: concentration of it in the blood and speed of glomerular filtration and the functional condition of kidney produces make their effect on glucose reabsorption. If glucosemia is more than 8,8-9,9 mmol/lit it results in glucosuria (kidney threshold).

So different stages of carbohydrate metabolism are controlled by a compound complex of stimulators and inhibitors. Disturbance of one stage of carbohydrate metabolism or of regulating mechanism cause disfunction of carbohydrate metabolism and it appears with the change of glucose concentration in blood. (hypo- or hyperglycemia).

Hypoglycemia: Concentration of glucose in blood less than 3,3 mmol/lit is called hypoglycemia. It requires an immediate treatment, because hypoglycemia cause irreversible changes of the nervous cells, first it disturbs the function of cortical layer of the brain than midbrain (cerebral hypoglycemia).

2 types of hypoglycemia exist: physiological and pathological hypoglycemia.

Physiological hypoglycemia can be seen in a healthy person due to the increased muscular work, where utilization of glucose is increased as a source of energy;

neonatal hypoglycemia: is a hypoglycemia of new born babies, specially when the body mass is less than 2500 gr.

Hypoglycemia can be a result of pathological changes:

- hyper dose of insulin during the treatment of diabetes;

- Increased production of insulin due to hyperfunction of pancrease (hyperplasia, insulinoma);
- deficiency of hormones promotinq catalisis of carbohydrates: STH, trioksine, adrenalin, glucocorticoides;
- glycogen splitting deficiency in glycogenosis;
- mobilization of great amount of glycogen from liver;
- liver cell damage;
- disturbed absorption of carbohydrates in the intestine.

When the sugar level decreases to 3-4 mmol/lit symptoms like tachycardia, tremor which resulting from compensating hyperproduction of adrenalin, feeling of hunger (low level of sugar in blood stimulates the ventrolateral nucleus of hypothalamus) develops. The symptoms due to dysfunction of the nervous system develop: weakness, irritation, feeling of fear, with the increase of hypoglycemia. These symptoms are added by a decrease of sensitivity. Sometimes even hallusinations appear. In hypoglycemia the use of oxygen by the brain sharply decreases so long and frequent periods of hypoglycemia cause irreversible change of the nervous cells. First the function of cortical layer of brain disturbed then that of the midbrain (serebral hypoglycemia) are disturbed too.

Concentration of glucose less than 2,5 mmol/lit cause dysfunction of the central nervous system. A decrease of oxydising processes and metabolic disorders, in the brain cause the loss of a vascular tonus, vasodilatation of microcirculation system, the increase of their penetration. Cerebral oedema, epileptical cramps and hypoglycemic coma may develop. Cramps have compensatory character as they help splitting muscular glycogen and due to this from the produced lactic acid liver syntheses glucose and the sugar level in the blood increases.

HYPERGLYCEMIA: Concentration of glucose in blood is more then 5,5 mmol/lit. It can be seen in different conditions:

Physiological HYPERGLYCEMIA: It has an accommodative function as provides easy delivery of utilizing energy material to the tissues;

Alimentary HYPERGLYCEMIA;

Emotional HYPERGLYCEMIA;

Retarding HYPERGLYCEMIA.

Disturbance in carbohydrate metabolism regulation results in a pathological HYPERGLYCEMIA.

Hormonal HYPERGLYCEMIA is caused by a dysfunction of endocrine glands, which takes place in carbohydrate metabolism regulation. In glucogenoma; tumor of Langerhans cell appear, production of glucagon increases. In case of Itsenko-Cushing disease and syndrome-of glucocorticoidosis develops. In feochromocytoma; adrenalin production increases. The excess of these hormones through the written above mechanisms increases the concentration of glucose in blood, in spite of the normal or even increased level of insulin.

HYPERGLYCEMIA due to insulin deficiency is very expressed and firm. It may be accompanied by some specific symptoms like mouth dryness, thirst, polyuria, loss of weight.

DIABETES MELLITUS (Greek diabaio – go through) according to an International Commission of Experts on diagnostics and classification diabetes mellitus in 1997: is a group of metabolic diseases, characterized by HYPERGLYCEMIA which is the result of insulin deficiency or the effect of insulin, or both these combined factors.

It takes the 1st place in endocrine pathology and the 3rd place in death rate(after cardiac diseases, and oncological diseases).

The following types of diabetes mellitus are distinguished:

Primary diabetes mellitus, the common form, is currently divided into 2 major categories;

Type I diabetes mellitus is absolute deficiency of insulin due to a dysfunction of B-cells of pancreas, they say about **autoimmune diabetes** mellitus

(previously called insulin dependent diabetes mellitus IDDM, or juvenile-onset diabetes) and **idiopathic** (etiology is unknown, but mostly African and Asian)

Type II diabetes mellitus: Overtaking insulin resistance with the insulin deficiency up to a defect of insulin secretion with insulin resistance (previously called non-insulin dependent diabetes mellitus NIDDM). It is further of 2 types – **obese and non-obese** type II diabetes.

Symptomatic or secondary diabetes accompanying to endocrine diseases - acromegaly, disease and symdrome of Itsenko-Cushing, pancreatic disease like pancreatitis and diseases of the liver and so on.

Diabetes of pregnant women: Identified first during pregnancy.

Etiology and pathogenesis of diabetes mellitus are presented in lecture and text book.

Diabetic coma is a very serious manifestation of diabetes. The cause of coma development can be inadequate treatment of diabetes or some other concomitant diseases (trauma, operation, stress). The main forms of diabetic coma: ketoacidotic, hyperosmolaric and lactoacidotic.

The complications of diabetes are microangiopathy (retinopathy, nephropathy), macroangiopathy, neuropathy, and cataract.

QUESTIONS TO DISCUSS.

1. Etiology of carbohydrate metabolism disorders.
2. Disturbances of entering, digestion and absorption of carbohydrates in the alimentary tract.
3. Disturbances of synthesis and disassociation of glycogen in the organism.
4. Disturbances of intermediate metabolism of carbohydrate.
5. Hyperglycaemia state, its types and mechanisms.
6. Metabolic changes at diabetes mellitus.
7. Principle of pathogenetic therapy at diabetes mellitus.
8. Hypoglycaemia state, its types and mechanisms.
9. Glycogenoses.

First Level Tests. Choose the right variants.

I. Match the possible causes of carbohydrate disintegration and absorption disorders:

1. Inflammation of the organs in the gastrointestinal tract.
2. Tumour of the organs in the digestive apparatus.
3. Hereditary enzymopathies.
4. Resection of different sections of the gastrointestinal tract.
5. Blood circulation disturbances in the digestive organs (hemorrhage, thrombosis, ischemia).
6. Any pathologic processes and diseases with primary localization outside the gastrointestinal tract.
7. All the above-mentioned factors.

II. Match the possible mechanisms of carbohydrate disintegration disorders:

1. Proteolytic enzyme excess.
2. Excess and high lipase activity.
3. Hydrolase deficiency.

III. Match the major mechanisms of carbohydrate absorption disorders:

1. Disorder of bile flow into the intestines.
2. Disorder of carbohydrate hydrolysis.
3. Disorder of carbohydrate phosphorylation.

IV. Match the major consequences of carbohydrate starvation:

1. Obesity.
2. Hypoglycemia.
3. Hyperglycemia.
4. ATP deficiency.

5. Glycogen synthesis resolution.

6. Glycogenolysis increase.

7. Lipolysis increase.

8. Gluconeogenesis increase.

9. Gluconeogenesis suppression.

10.Organ and system function disorder.

V. Match the major compensatory reactions caused by carbohydrate deficiency:

1. Insulin synthesis and secretion increase.

2. Glycogenolysis activation.

3. Protein synthesis increase.

4. Gluconeogenesis activation.

5. Lipolysis activation.

VI. **Select conterinsulin hormones**:

1. Luteinizing hormone (lutropin).

2. Somatotropin.

3. Glucocorticoids.

4. Estrogens.

5. Mineralocorticoids.

6. Catecholamines.

7. Thyroid hormones.

8. Testosterone.

9. Glucagon.

VII. Indicate the major causes of hypoglycemia:

1. Carbohydrate starvation (exogenous).

2. Diseases of digestive apparatus provided with carbohydrate absorption disorder.

3. Conterinsulin hormone deficiency.
4. Tissue hypoxia.
5. Hyperinsulinemia.
6. Renal diabetes.
7. Renal insufficiency.
8. Respiratory compromise.
9. Hard muscular work.

VIII. Match the major mechanisms of hypoglycemia:

1. Protein synthesis disorder.
2. Insufficiency of glucose absorption into the blood from intestines.
3. Disorder of cholepoiesis and bile excretion.
4. Conterinsulin hormone deficiency.
5. Abundant consumption of glucose due to hyperinsulinism.
6. Insufficient utilization of glucose.
7. Loss of glucose with urine.
8. Diminution of glycogen content in the liver.

IX. Indicate the major consequences of hypoglycemia:

1. Disorders of nervous system function.
2. Disorders of endocrine system function.
3. Disorders of cardiovascular system activity.
4. Disorders of respiratory system function.
5. Disorders of digestive system.
6. Disorders of liver function.
7. Disorders of energy metabolism.
8. Increase of protein synthesis.
9. Increase of protein catabolism.
10. Increase of lipogenesis.
11. Increase of lipolysis.

X. Select the major etiological factors of hyperglycemia:

1. Insulin excess.
2. Insulin deficiency.
3. Abundance of conterinsulin hormones.
4. Deficiency of conterinsulin hormones.
5. Abundant consumption of proteins.
6. Insufficient consumption of proteins.
7. Increase of mineralocorticoids secretion.
8. Abundant consumption of easily available carbohydrates.

XI. Match the major mechanism of hyperglycemia:

1. Abundant utilization of glucose.
2. Insufficient utilization of glucose.
3. Both mechanisms.

XII. What are the possible consequences of hyperglycemia:

1. Energy metabolism disorders.
2. Carbohydrate metabolism disorders.
3. Protein metabolism disorders.
4. Lipid (fat) exchange disorders.
5. Water electrolyte metabolism disorders.
6. Acid-base balance disorders.
7. Oliguria.
8. Polyuria.
9. Glucosuria.
10. Function disorders of all organs and systems.

Second Level Tests

I. Indicate gastrointestinal tract dysfunctions result in carbohydrate metabolism disorders.

1.
2.
3.

II. Name the major mechanism of carbohydrate disintegration disorders.

III. Name the major mechanisms of carbohydrate absorption disorders.

1.
2.

IV. Enumerate the possible consequences of carbohydrate starvation:

1.
2.
3.
4.
5.
6.
7.

IV. Indicate the possible compensatory processes caused by carbohydrate deficiency:

1.
2.
3.

V. What processes of intermediary metabolism of carbohydrates are disturbed due to their deficiency in the liver?

1.
2.
3.
4.
5.

VI. Name contrinsular hormones and match the major mechanisms of their effect.

1.
2.
3.
4.
5.

VII. Enumerate the major causes of hypoglycemia.

1.
2.
3.
4.
5.
6.

VIII. Name the major mechanism of hypoglycemia.

1.
2.
3.
4.
5.

IX. Enumerate the major consequences of hypoglycemia.

X. Name the major causes of hyperglycemia.

1.

2.

3.

XI. Name the major mechanism of hyperglycemia.

1.

2.

XII. Match the major consequences of hyperglycemia.

1.

2.

3.

Task 1

A 30-year-old man consulted the doctor for chronic pains in leg and arm muscles, convulsions on physical exertion. His muscles were always weak, so he never went in for sports. The condition was unchangeable till the moment he decided to strengthen the muscles by going in for sports. On persistent physical exercises pain as a rule subsided in 15-30 minutes and he was able to proceed exercising.

Laboratory analyses. The laboratory studies determined the glucose level in blood to be in norm on moderate physical exertion, but accelerated MM fraction activity of creatine kinase (MM-CK) was noted. During intensive muscular work the level of glucose in blood was increasing insignificantly as well as the level of lactate. The biopsy revealed high content of glycogen in muscles.

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 2

An 18-year-old girl suffering from type I SD consulted the district doctor for health aggravation and loss of weight. She was constantly suffering from thirst and polyuria. Sugar was found in the urine. She recommended to be admitted to the hospital the next day. However, weakness, nausea and sluggishness occurred in the evening. She was hospitalized due to ambulance call. On admission her blood pressure was 95/60 mm Hg, her pulse rate was 112/ min, the extremities were cold. She was developed deep accelerated respiration (Kussmaul respiration), moreover, a smell of acetone was noted.

Laboratory analyses. Serum: natrium 130 m moles per liter [while in norm 135-145]; potassium 5.8 m moles per litre (norm is 3.5-5.0); bicarbonates 5 mmoles per litre (norm is 22-26); urea 18 mmoles per litre (norm is 2,5-3,8); creatinine 110 micromoles per litre (norm is 44-97); glucose 32 mmoles per litre (norm is 3,8-6,1).;

Arterial blood: pH 7,05 (norm is 7,35-7,45); pCO 15 mm Hg (35-45 normally);

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 3

A 42-year-old patient suffered from type I SD since her childhood despite of the insulin dose decrease attacks of hypoglycemia started to occur. This coincided with the period of amenorrhea. Her previous condition was considered to be as controlled diabetes. During the period of hypoglycemia development, the level of Hb was 6,5-7,0%. Thus the dose of insulin within the year was reduced from 48 to 28 Units.

Laboratory analyses. Hb is 6,5 % (N< 6%); LH 1,2 Unit per liter (N 1-20); FSH 1 Unit per litre (N 4-10).

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 4

Describe the state of carbohydrate metabolism and define the strategy for detecting its disorders assuming that the original blood sugar is 8.9 mmole/l. The maximum of 16.6 mmole/l is defined twenty minutes after a single sugar load. The assumed time to original state is six hours. The arteriovenous difference as per sugar level is 0.1 mmole/l. Overall blood protein makes 60.0 g/l, the protein quotient equals 1.4. Lipid content is 4.4 mmole/l, free fatty acids content is 350 mmole/l.

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 5

Patient D., male, 37 years, had the ambulance called in. The patient's condition is grave. He displays the signs of mental confusion and regular tonic convulsions. The skin is wet with a clammy sweat. The blood pressure is 80/40 ml mercury, the pulse is rapid and thready.

The patient's relatives reported his suffering of insulin-dependent diabetes over тапу years. Recently the patient has developed an increased sensitivity to the insulin, even minor dosages of the drug causing hyperexcitability. The patient collapsed shortly after another insulin injection. He was given 40 ml of glucose solution intravenously and 1 ml of adrenaline solution subcutaneously. This done, the patient's state soon restored.

What's the patient's collapse mechanism?

When does the hypoglycemia develop?

How does the insulin act upon the carbohydrate metabolism?

Task 6

Patient E., male, 17 years, complains of abnormal appetite and thirst. The patient is tall (194 cm) and lean (70 kg). Physical examination revealed no inner pathology. Fasting blood sugar is 320 mg%. After a meal, the blood sugar keeps

rising and remains at a high level over 10ng periods.

Insulin treatment does not seriously affect the blood sugar. The daily diuresis (4 1) and the specific weight of the urine (1028) are abnormal. Some sugar is present in the urine.

What's the pyobable hypoglycemia pathogenesis?

What are the counterinsular hormones and how do they act?

Task 7

A six year old girl was nervous and irritable for 6 months, looked sickly, got tired quickly, was often sleepy and had frequent bouts of indigestion

Laboratory analysis

Glucose in blood (1hour after feeding) ≈5 mmole/l

Reference range (3.5-5mmole/l)

Four hours after eating the patient felt unwell with the pulse rate of 110 beats per min.; the glucose lever was 2 mmole/l. The symptoms were relieved by intake of food. Biopsy of liver showed massive deposits of glycogen in the cytoplasm of hepatocytes.

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 8

An elderly woman was taken to hospital after her relatives found her semiconscious. A few days before she had felt well. The analysis showed a pronounced dehydration but without ketone bodies, respiration was normal.

Laboratory analysis:		Norm
Serum: sodium	149mmole/l	135-145
Potassium	4.7mmole/l	3.5-5.0
Bicarbonates	18mmole/l	22-26
Urea	35mmole/l	2.5-3.8
Creatinine	180mmole/l	44-97

Glucose	54mmole/l	3.8-1.6
Protein total	90 g/l	64-83
Osmolarity	370 mosmole/kg	280-300

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 9

A young man had a collapse during a sports competition (during a stayer race). He was conscious, but disoriented with incoherent speech. When he was taken to hospital, the glucometer test showed a very low level of glucose in his capillary blood. A blood sample was sent to the laboratory. He was given intravenous injection of 25gr of glucose, which quickly brought him back to consciousness. It turned out that he suffered from type I diabetes. In the morning he had taken his usual dose of insulin and had a regular breakfast. The laboratory analysis showed glucose in blood equal to 1.6mmole/l.The patient was given carbohydrates internally and the glucose level had become normal by the evening.

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 10

A seventeen-year-old girl lost consciousness three times in the morning. The bout was accompanied by perspiration. There was no inclination to urination. Epilepsy was excluded and reactive or functional hypoglycemia (neurohypoglycemia) was suspected. The glucose level in blood randomly tested (on an empty stomach, while in good health) was 3.2 mmole/l.

The blood sample was taken when the symptoms were absent; the result may be interpreted as corresponding to the normal level of glucose in blood. Reactive hypoglycemia can be diagnosed only by a series of glucose tests after meals or

after a carbohydrate load. A glucose tolerance test was made with a 75 g oral glucose load.

Tolerance test to glucose a 75 g oral glucose load

Time	0	30	60	90	120	150	180	210	240 (min)
glucose	4.5	8.7	11.7	4.2	2.3	5.3	4.6	4.1	4.6 mmole/l

The decrease of glucose level to 2.3 mmole/l 120 minutes after the load was accompanied by intense perspiration and quickened pulse.

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 11

An elderly man couldn't get up in the morning; he developed a stupor condition. The day before he had drunk a lot of alcohol. An ambulance was called. As soon as he was brought to hospital and examined pronounced hypoglycemia was diagnosed. He was given an intravenous injection of glucose but it didn't relieve the signs of intoxication. They went on giving him an infusion therapy, and a few days later he recovered completely.

What's your diagnosis?

What's the substantiation of the diagnosis?

Task 12

A girl was born on the 39th week of gestation by a young but very emaciated mother. The newly born baby was small and weak. In an hour she developed signs of a distress syndrome, including tachycardia and shortness of breath. The glucose level the girl had on her birth was 3.5 mmole/l; in an hour it was 1.5 mmole/l and the girl fell developed a coma at that moment. After glucose infusion and further nourishment with addition of carbohydrates the child's condition quickly improved. Two weeks later she was discharged from the hospital in the normal condition.

What's your diagnosis?

What's the substantiation of the diagnosis?

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I.A. Fastova

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Волгоградский государственный медицинский университет.
400131 Волгоград, пл. Павших борцов, 1

Издательство ВолГМУ.
400049 Волгоград, ул. Рокоссовского, 1 г