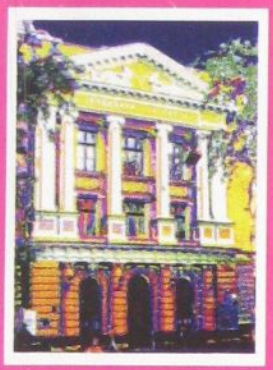

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PATHOPHYSIOLOGY

ОДЕССКИЙ МЕДУНІВЕРСИТЕТ

A.I. Gozhenko
I.P. Gurkalova
I.V. Savitsky

PATHOPHYSIOLOGY

Recommended by the Central methodical study relating to Higher Medical Education of Ministry of Public Health of Ukraine as a textbook for students of Higher Medical Educational Establishments of the IVth level of accreditation using English

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Authors: Professor A.I. Gozhenko, M.D. Honored Sciece and Technique Worker of Ukraine, D.M. Science
I.P. Gurkalova, Candidate of Medical Science, Senior Lecturer I.V. Savitsky, D.M. Science

Reviewers: Professor Yu.V. Byts, M.D., the Head of the Pathophysiology Department of the Kiev National Medical Academy name after A.A. Bogomolets, Honored Science and Technique Worker of Ukraine;
Professor A.V. Kubischkin, M.D., the Prorector on International Communication of the Crimea State Medical University named after S.I. Georgievsky

This textbook presents the data about General and Systemic Pathophysiology for medical students according to the Program of Ministry of Public Health of Ukraine.
The first part deals with the questions on general nosology and typical pathological processes. The second part is devoted to the General regularities disturbances of different organs and systems so that rational therapy can be devised.

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PREFACE

According to the Program of the Ministry of Public Health of Ukraine this book is divided into 33 chapters organized parallel to most standard texts. The first 16 chapters cover general or basic pathology, presenting the major concepts of disease processes viewed as manifestations of a common set of mechanisms of injury. The second part is devoted to systemic pathology, surveying the principal disorders of each organ system.

The last part is devoted to the Comprehensive Examination can be used both as a pretest and as a post test to help identify areas that merit further attention in the chapters or in standard text.

The present edition continues the traditions of the previous edition, continuing and developing Ukraine pathophysiological school of N.Zaiko, Yu.Byts who created a text-book for Ukrainian and Russian speaking students. We express our gratitude and acknowledgment to them.

I. FOUNDATION CONCEPTS OF PATHOPHYSIOLOGY

UNIT 1

THE SUBJECT, METHODS AND AIM OF PATHOPHYSIOLOGY. THE GENERAL TEACHING ABOUT DISEASE ETIOLOGY AND PATHOGENESIS

Pathophysiology should form the basis of every physician's thinking about a patient. The study of the nature of a disease, pathological processes, pathological conditions, which form general pathology may be used by the genetist, biochemist, clinical diagnostician, etc., and it is difficult function of the pathologist to attempt to bring about a synthesis, and present diseases in as whole or as true an aspect as can be done with present knowledge.

Pathophysiology — it is the study of the mechanism underlying a disease, the main laws of the development and complications of the disease. The final aim is to discover the laws of the disease development so that rational therapy can be devised. Pathophysiology analyzes the general processes for all the diseases or for some groups of disease syndromes that's why pathophysiology is a transition stage between the main theoretical biological and clinical disciplines.

The main aims of pathophysiology are:

1) to define the external and internal causes of disease, the effect of pathological factors of environment upon the human organism;

2) to learn the general laws of patient resistance, adaptation reactions and mechanisms of convalescence;

3) to form the student's conception about the disease, pathological process, pathologic state and its mechanisms;

4) to learn the typical pathological processes such as inflammation, tumor, fever, hypoxia, allergy, shock and others;

5) summarizing all these conceptions will be used in creating the modern medical technologies.

Pathophysiology can use the following methods:

1) the modeling of various forms of pathologic processes, protective

and adaptive reactions of humans;

2) experimental therapy as an important method of studying and introducing the new ways of treatment;

3) clinical studying of various diseases with functional, biochemical, immunological and other tests due to pathophysiology groundation therapy.

General pathophysiology includes a very important part of nosology or the general teaching about etiology and pathogenesis of the disease and such terms as the "health", "norm", "disease", "pathological process", and "pathological condition".

Traditionally, the study of pathophysiology is divided into two general disciplines: the General Pathophysiology and Special or Systemic and Clinical Pathophysiology.

The General Pathophysiology focuses on the injurious stimuli undergoing in the cells, tissues, organs and the whole organism (etiological factors) and also on the mechanisms of the development of pathological process, its conditions and diseases (pathogenesis), the role of self defense mechanisms (heredity, constitution, reactivity, immunity, sex and age), the general studies of disease, the determination of "the disease".

Special and clinical pathophysiology has to learn morphological, biochemical, functional disorders in different organs and systems (pathophysiologic alterations).

THE GENERAL TEACHING ABOUT THE DISEASE

The disease and the health are the main forms of living process. It is necessary to determine what normal healthy life means to understand the essence of the disease.

The normal condition of the organism is characterized by:

a) the balance of the organism and environment;

b) organism integrity;

c) ability to work.

The health is a condition of total physical, mental and social well-being, but not only the absence of the disease and physical defects (World Health Organisation, 1946).

Health is the normal condition of a human, who is able to work and adapted to the changes of environment (I. Petrov).

According to N. Zaiko, health is the organism's normal condition,

when its structure and functions conform to each other and its regulatory systems are able to maintain homeostasis.

The norm is the biologic optimum of functioning and developing of the organism.

The disease is the abnormal activity of the human organism un- dur the influence of injurious agents, it is characterized by the limitation of adaptability to work, leading to harm to the life of the organism.

The disease is a complicated process in the organism with the two quite opposite processes:

1) "a measure against the disease" (by I. P. Pavlov) — which means the compensatory reactions;

2) "pathologic process proper" with functional, morphological, biochemical and other disorders.

So, the disease is a unity of opposites, which always contend (law of dialectics). The doctor must find out the pathologic process proper and stimulate the protective processes.

There are four stages of disease:

1) latent period (incubation period of the infectious diseases);
2) prodromal period;
3) period of expressed manifestations;
4) the outcome of the disease.

Tlie disease includes (a) pathologic process, (b) pathologic condition.

A pathologic process is a combination of pathologic and protective reactions in the damaged organs or organism. The simplest form of the pathologic process is called "pathologic reaction" (hyperemia, ischemia and others).

Pathologic condition is reflected in the dynamic development of pathologic process. It develops slowly (for example condition after amputation of foot, resection of the stomach).

THE GENERAL ETIOLOGY

Etiology is a study about the causes and conditions of the disease, which provoke the disease and determine its specific features.

Etiologic factors may be 'divided into two groups: external and internal. According to nature there are:

1) biological (microbes, viruses, parasites);
2) mechanical (trauma);
3) physical (atmosphere pressure, electric current, ionizing radiation, X-rays, space flight factors and others);

4) chemical (drugs, narcotics, alcohol, acids and others);

5) mental (emotional stress).

Endogenous factors are heredity, constitution, sex, age (Down's syndrome, diathesis).

There are internal and external conditions, which favour the disease, for example, old age, early childhood, poor nutrition, overcooling, overheating, oxygen and clean water deficit and others.

Pathogenesis (from Greek "***pathos***" — suffering, "***genesis***" — origin) is a study on mechanisms of the development and outcome of the disease.

Pathogenesis of every disease depends on the cause and resistance (reactivity) of the human organism.

There are four periods of pathogenesis:

1) the latent (incubation) period;

2) the prodromal period;

3) the period of expressed manifestations;

4) the outcomes.

The outcomes of every disease may be:

— recovery (complete, incomplete);

— the turning to chronic course or the pathologic condition;

— preagony, agony, clinical death and biological death.

What is the connection between the cause and the pathogenesis?

There are three variants of interconnection of the cause and pathogenesis:

1. The etiologic factor initiates the pathologic process and then disappears, so pathogenesis develops without etiological factor (trauma, radiation).

2. The cause continues its action throughout all the period of the development of the disease (infectious disease), as a consequence, the etiological factor penetrates into pathogenesis, exists in it and influences it.

3. Persistence of the cause agent, which causes the disease, is delayed in the organism (healthy bacilli-carrier).

Causes and consequences constantly change their places.

The cause (etiological factors) causes the pathologic reactions (process) and then these reactions return to the first agent (etiological factor) and intensify it. So "vicious circle" is formed in pathogenesis.

For example, if arterial pressure decreases it causes hypoxia and then vasomotor center is depressed. It leads to the prolonged decrease of

arterial pressure.

What is "the main stage" in pathogenesis?

The main stage of pathogenesis is the process, which initiates the development of others. The time of elimination of the main stage is the time of elimination of the whole process. So, in diabetes mellilus "the main stage" of pathogenesis is lack of insulin. Its elimination (introduction of the hormones) leads to the disappearance of other manifestation of the disease (hyperglycemia, ketosis, coma).

COMPREHENSION CHECK

Try to answer the following questions.

1. What is pathophysiology?
2. Why is pathophysiology important?
3. Name the methods and aim of pathophysiology.
4. Give the definition of the term "disease".
5. Characterize differences between "pathological process", "pathological condition" and "disease".
6. Define "etiology", "pathogenesis" and the connection between them.

UNIT 2

PATHOGENIC EFFECT OF ENVIRONMENTAL FACTORS: ATMOSPHERIC PRESSURE, ELECTRIC CURRENT, IONIZING RADIATION, SPACE FLIGHT FACTORS NEGATIVE EFFECT OF CHANGES OF ATMOSPHERIC PRESSURE

A man feels the effect of decreased atmospheric pressure during ascent on plane, or in mountains. The pathologic changes, occurring in it, are caused by two main factors: decrease of partial pressure of oxygen in inspired air and decrease of atmospheric pressure (decompression). Lack of oxygen in inspired air causes state, described in the unit "Hypoxia". Range of phenomena, connected with decrease of atmospheric pressure, is called **decompression syndrome.**

It is known, that some physical characteristics of gases and liquids (volume and solubility of gases in liquids, point of boiling of liquids) depend on atmospheric pressure. Decrease of atmospheric pressure leads to expansion of internal gases of the organism. That's why their solubility in liquid medium decreases. Point of boiling of blood and other liquids is so low, that they can begin to boil at body temperature. The degree of manifestation of these phenomena depends on velocity of decompression and its degree. Pilots, flying in nonhermetically sealed cabin, can have some symptoms, caused by decompression: expansion of air in intestines, pain in ears and frontal sinuses because of expansion of air in these cavities, nasal bleeding because of bursts of small vessels. Liquids begin to boil at body temperature at the height of 19,000 m.

Explosive decompression syndrome develops when quick change of atmospheric pressure.

The main cause is barotrauma of lungs, heart and big vessels is quick increase of pulmonary pressure. Rupture of alveoli and vessels of the lungs causes the gas bubbles to penetrate into circulatory system (gas embolism). In case of depressurization of a space ship or high-altitude plane momentary death occurs because of boiling of blood and other liquids of the organism, and also because of quick form of hypoxia.

A man feels effect of increased atmospheric pressure in water during diver's or caisson works. One can have pain in ears because of pressing tympanic membranes. Rupture of lung alveoli is possible at quick increase of atmospheric pressure. But the most important is the fact that

in conditions of hyperbaria the man breathes with air or other gas mixture under increased pressure. That's why additional quantity of gases dissolves in blood and tissues of the organism (saturation). Nitrogen is the most important in breathing with compressed air. It was considered for a long time, that nitrogen, as inert gas, didn't make a biological effect, and only experience of underwater medicine has showed another thing.

Nitrogen causes syndrome of specific changes in people, working under increased pressure. The nitrogen quantity of the organism can increase sometimes, especially in organs, containing a lot of lipids. It's known, that nervous tissue contains a lot of lipids, so it is mostly affected. The first manifestation of it is a light excitement, like euphoria. The next are phenomena of narcosis and intoxication. Oxygen-helium mixtures are used in underwater mechanisms for avoiding these phenomena (helium is dissolved less than nitrogen).

But not only nitrogen is toxic at increased pressure. Surplus of oxygen (hyperoxia) exerts a favorable effect only in the beginning, improving processes of tissue respiration. But oxygen gas realizes its toxic effect later. Optimum concentration of oxygen in inspired air exists for every depth of immersion. For example, concentration of oxygen in gas mixture is about 2% in immersion at the depths of 100 m.

MECHANISM OF TOXIC EFFECT OF OXYGEN UNDER INCREASED PRESSURE

At first those reactions of the organism develop, which are directed to maintenance of optimum oxygen regime in the brain tissue and limitation of excessive increase of oxygen concentration in it. Decrease of excitability of blood channel chemoreceptors has great importance in formation of these protective reactions, breath

and pulse are rare, circulating blood volume is decreasing, and brain vessels are narrow.

Suffocation can develop later. The cause of it is that hemoglobin molecule is blocked by oxygen and losses ability to take out carbon dioxide. It can be explained as follows: tissues use oxygen physically dissolved in plasma, it encourages dissociation of oxyhemoglobin. Content of dissoluble in blood oxygen is increased at increased pressure.

The quantity of dissolved oxygen corresponds to normal consumption of oxygen by tissues. The result is that oxyhemoglobin

practically doesn't dissociate and carbon dioxide isn't taken out.

Toxic effect of high concentration of oxygen is similar to that one of radiation. In both cases formation of free radicals and peroxides with strong oxidative abilities causes affection of DNA and tissue enzymes.

Sensitivity of the organism to toxic action of oxygen is defined by level of tissues antioxidants (tocopherols, glutathione, and others), which suppress free-radical oxidation. They can be used for treatment and prophylaxis at oxygen action on the organism under high pressure.

Desaturation (excretion of excessive quantity of dissolved gases via blood and lungs) develops at return of men into conditions of normal atmospheric pressure (decompression). Decompression must be done slowly, so that speed of gas formation doesn't exceed excretory opportunity of lungs. In an opposite case bubbles of air cause occlusion of blood vessels press on cells and irritate receptors (gas embolism). Clinical picture of this disease is defined by location of gas bubbles. The most often signs are pain joints, skin itch. In serious causes — disorder of vision, paralysis, loss of consciousness and other signs of brain affection and spinal marrow. This syndrome is called **decompression (caisson) disease.**

PATHOGENIC INFLUENCE OF ELECTRIC CURRENT

Person is exposed to effect of natural (lightning) or technical electricity. Lightning influences like transitory (part of a second, seconds) penetration through the human body of current with high tension (to millions of volt). Death results from cardiac arrest and (or) respiratory standstill (Ju. R. Petrov). In consequence of lightning thermoeffect, burns, haemorrhages like special branch figures, blackening and necrosis of tissues remain on the body; there may be mechanical influence — tearing off of the tissues and even part of the body.

Pathogenic effect of technical electricity (electrotrauma) depends on kind of current (constant, variable), strength, tension, direction and duration of penetration through the body and also of tissue resistance and condition of the body reactivity.

Current strength. At the same strength alternating current is more dangerous than direct current. Current with strength of 100 mA is mortally dangerous. Alternating current of 50-60 Hz with strength of 12-25 mA causes cramps ("unleaving"). Its basic danger is "chaining"

of the person to the electric object.

Tissue resistance. Full resistance of the human body to alternating current is called ***impedance.*** The most resistant to electric current is external epidermal layer of the tissue (to 2,000,000 Om), after that tendons, bones, nerves, muscles, blood come. The least resistant is the cerebrospinal fluid. General resistance of the human body is on the average 100,000 Om (from 1,000 to a million Om). The dry skin is more resistant than the wet skin.

Direction of electric current through the human body. Ascending direct current (anode is lower — cathode is higher) is more dangerous than descending one (opposite localization of electrodes) in the same direction. With ascending current in the sinus node of the heart is under exciting influence of cathode, and the apex-under- suppressing influence of anode.

Frequency of alternating current. It is considered, that alternating current with frequency of 40-60 Hz has steady effect (arise of ventricle fibrillation). Alternating current frequency of 1,000,000 Hz and more isn't pathogenic, but in high tension Tesl's, d'Arsonval's, diametric currents exert the thermal effect and are used for treatment.

Condition of the organism reactivity. Tiredness, weakening of attention, slight or moderate alcohol intoxication, hypoxia, overheating, thyrotoxicosis, cardiovascular insufficiency decrease the reaction of electrotrauma. Severity of defect decreases significantly in emotional exertion, which is a result of waiting for current influence, necrosis or a condition of deep intoxication.

Mechanisms of the injurious effect of electrical current. Electrotrauma may cause local (current marks, burns) and general changes in the organism.

Local reaction of the organism to electrotrauma. Current marks, burns arise in outlet and inlet points current in consequence of transformation of electrical energy into thermal (Joul-Lens' warmth). Current marks arise on the skin, if the temperature in the place of penetration isn't more than 120 °C; they are small formations of white-gray color ("parchment" skin), of hard consistency, bordered by dilating eminence.

When the temperature in the penetrative place of current is more than 120 °C, burns arise: contact due to heat — production with current penetration through the tissues and thermal — in consequence of flame effect of volt arch. The latter are more dangerous.

General reactions of the organism to electrical current. Penetrating

through the body current causes an excitement of the nervous receptors and conductors, smooth and skeletal muscles, glandular tissues. It results in tonic cramps of the muscles that may be accompanied by abruptive fractures, extremity dislocation, spasm of the vocal cords. Arrest of breathing, increase of blood pressure, involuntary urination and defecation. Excitement of the nervous system and organs of the internal secretion leads to "ejection" of catecholamines (adrenaline, noradrenaline), changes many somatic and visceral functions of the organism.

The main significance in the mechanism of current injurious effect has its electrochemical effect (electrolysis). Having got over skin resistance, electric current causes disbalance in different cells, changes their biological potential and results in polarization of the cell membranes: at some areas of tissues positively charged ions (acid reaction) are concentrated at the cathode, negatively charged ions (alkaline reaction) are concentrated at the anode. In consequence functional condition of the cells is changed significantly. Coagulation of protein is a result of motion of albuminous molecules under the anode (coagulation necrosis) in alkaline areas under the cathode — swelling of colloids (colliquative necrosis). The processes of electrolysis in the cardiac synticium may cause the shortening of refractor phase of the cardiac cycle, which causes development of circular increase of its rhythm. Injury of the respiratory and vasomotor centers in electrotrauma is brought about by injury of the nervous cells due to depolarization of their membranes and protoplasm coagulation.

In non-normal electrotrauma cramping muscle contraction occurs with temporary loss of consciousness, cardiac activity disorder and (or) respiratory disorder; clinical death (imaginary) may
come. In timely rendering of medical care the patient feels vertigo, headache, photophobia, nausea; disorders of skeleton muscles may persist. Immediate cause of death in electrotrauma are respiratory standstill and cardiac arrest.

Respiratory standstill may depend on:

— injury of the respiratory center;

— spasm of the vertebral arteries, which bring blood to the respiratory center;

— spasm of the respiratory musculature;

— disorder of potency of airways due to laryngospasm.

Cardiac arrest may arise due to:

— ventricle fibrillation;
— spasm of the coronary vessels;
— injury of the vasomotor center;
— increase of the nervous vagus tension.

THE EFFECT OF IONIZING RADIATION

Etiology

The general property of ionizing radiation is the ability to penetrate into the radiated environment and produce ionization. The rays of high energy (X- and y-rays) and ***a- and P***-particles (radionuclides) possess this ability. There are the external radiation when the source of it is outside the organism and the internal one when radioactive substances get into the organism. The latter is called incorporated radiation. This kind of radiation is considered to be more dangerous. Combined radiation is possible. The character and degree of radiation injury depend on radiation dose. However there is direct dependence on the dose only for high and median doses. The effect of low doses of radiation is subject to other laws and it will be clarified while studying pathogenesis of radiation injuries (Table 1).

Pathogenesis

Physical, Chemical and Biochemical Disturbances

Energy of ionizing radiation exceeds energy of the intramolecular and intraatom bonds. Absorbed by macromolecule, it may migrate in the cell realizing in the most vulnerable places. It results in ionization, excitation, and break of less stable bonds, tearing off of radicals, which are called free. It is a direct effect of radiation. The primary target may be a highly molecular compound (proteins, lipids, nuclear acids, and molecules of complex proteins — nucleoprotein complexes, lipoproteins). In the molecule of DNA is a target genetic code may be disturbed.

Ionization of water molecules is the most significant of all primary radiochemical transformations. Ionization of water molecule results in formation of free radicals (OH-, H), which begin to interact with excited water molecule, tissue oxygen and produce additional hydrogen peroxide, radical of hydroperoxide, atomic oxygen (H_2O_2, HO_2, O). More active reduction agents catch energy of free radicals. The products of water radiolysis have a very big biochemical activity and are capable of causing oxidation reaction by any bonds including stable ones in

usual oxidation — reduction transformation. The effect of ionizing radiation conditioned by products of water radiolysis is called ***indirect effect of radiation.***

Tabie 1. Biologic significance of a single whole-body exposure to various doses of ionizing radiation on a man

Dose (roentgens)	Biologic response
10	No detectable somatic effects. Detectable morphologic and functional alterations in specific subpopulations of lymphocytes; probable chromosomal abnormalities.
100	Mild radiation sickness in some persons with nausea and vomiting, decrease in mitotix index of bone marrow and transient leukopenia.
1,000	Extensive damage to bone marrow with leukopenia, thrombocytopenia and anemia; necrosis of gastrointestinal mucosa; severe radiation sickness; death within 30 days.
10,000	Intermediate disorientation or coma; death within hours.
100,000	Acute death of most types of mammalian cells.

Free radicals and peroxides are capable of changing chemical structure of DNA. Radiation of chemical oxidation of pyrimidine and desamination of purine bases are observed in radiation of solutions of nuclear acids.

Unsaturated fatty acids and phenols are oxidized resulting in formation of lipids (LRT) (lipid peroxides, epoxids, aldehydes, ketones) and quinone radiotoxins (QRT). Radiotoxins inhibit synthesis of nucleic acids, influence upon the molecule of DNA as chemical mutagens, change the enzyme activity, and react with lipid- protein and intracellular membranes.

Thus, primary radiochemical reactions consist of direct and indirect (through the products of water radiolysis and radiotoxins) injury of the most important biochemical cell components — nucleic acids, proteins, and enzymes. Later on, fermentative reactions are violently changed — fermentative lysis of proteins and nucleic acids is increased, synthesis of DNA is decreased, biosynthesis of proteins and enzymes is disturbed.

Disturbance of Biological Processes in the Cells

The above-described physical, chemical and biochemical changes lead to disturbance of all manifestations of the cell vital activity. We can see signs of radiation injuries of the nucleus in the electronic and light microscope. There are observed chromosome aberration (breakdowns, reconstruction, fragmentation). Chromosome mutations and more subtle disturbances of the genetic apparatus (gene mutations) lead to disturbance of hereditary properties of the cell, inhibition of synthesis of DNA and specific proteins. Cell division is inhibited or has an abnormal course. The cell may be destructed at the moment of division as well as the interphase.

All cell organoids are injured. Ionizing radiation injures the intracellular membranes — membranes of the nucleus, mitochondria, lysosomas, and endoplasmatic reticulum. The injured lisosomas release ribonuclease, desoxiribonuclease and catepsins having an injurious effect on nucleic acids, cytoplasmatic and nuclear proteins. Oxidative phosphorillation is disturbed in mitochondrion membranes.

Disturbance of cell energy metabolism is one of the most probable cause of cessation of synthesis of nucleic acids, nucleic proteins and mitosis inhibition. So, radiation injury of the nucleus is connected not only with direct effect of ionizing radiation of the DNA molecules and chromosome structure, but also with processes in other organelles.

Summing up the above given findings of pathogenesis of the cell's iadiation injury, it may be concluded that the most typical manifestation, namely the nuclear damage, inhibition of division or destruction of the cells is a result of impairment of the genetic apparatus, disturbance of the cell energy metabolism in injury of mitochondria and release of lytic ferments from the injured lysosomas.

The cell's nucleus has especially high radiosensitivity in comparison with cytoplasm, disturbance of the nuclear structures influences more significantly on the viability and vital activity of the cell. Therefore it is easy to understand the phenomenon revealed during the comparison of radiosensitivity of the tissues: the highest radiosensitivity have those tissues where processes of cell division is more intensively marked, and in radiation even by low doses there is their mitotic destruction. First of all they are the thymus, sexual glands, hemopoietic lymphoid tissue where renewal of the cells is constant. Then comes the epithelial tissue, especially glandular epithelium in the digestive and sex glands,

pegment epithelium of the skin and the endothelium of the vessels. Cartilaginous, osseal, muscular and nervous tissues are radioresistant. The nervous cells are not able to divide and that's why they are destructed only in high over-dose radiation (interphase destruction). Mature lymphocytes are the exception; they are destructed even in radiation by 0.01 Gy.

Dysfunctions of the Organism and Common Symptoms

In lethal and superlethal radiation doses interphase destruction of the cells prevails and death comes within first minutes (hours) after radiation. In median radiation doses the life is possible but in all functional systems without exception there are pathologic changes, which are marked depending on comparative radiosensitivity of the tissues.

The most characteristic are disturbances of hemopoiesis and blood system. There is decreased amount of all formed blood elements as well as their functional deficiency. During first hours after radiation there is lymphopenia, later — deficit of granulocytes, thrombocytes and at least — erythrocytes. Loss of the bone marrow is possible.

Immune reactivity decreases. Phagocytosis is reduced, formation of antibodies is inhibited or completely suppressed. Therefore, infection is the earliest and severe complication of radiation. Tonsillitis is of necrotic character. Frequently the cause of the patient's death is pneumonia.

Infection develops violently in the intestines. Pathology of elementary canal is one of the causes of death. The barrier function of the mucus membrane of the intestines is disturbed that results in absorption of toxins and bacteria in blood. Dysfunction of the alimentary glands, intestinal autoinfection, severe condition of the oral cavity leads to exhaustion of the organism.

The characteristic sign of the radiation disease is hemorrhagic syndrome. The most important for pathogenesis of this syndrome is reduction of thrombocytes containing biological factors of blood coagulation. The cause of thrombocytopenia is disturbance of thrombocyte maturation in the bone marrow rather than their destruction. Disturbance of thrombocyte ability to adhesion is of great significance as biological factors of blood coagulation are released in aggregation of thrombocytes. Probably, disturbance of thrombocyte ability to aggregation is connected with changes of their membrane

ultrastructure. Besides, thrombocytes play an important role in maintaining integrity of the vascular wall, its elasticity and mechanical resistance. There is reduction of ability of fibrin fibers to contractility and blood clot to retraction. The activity of fibrinolysis and anticoagulation system increases. Anticoagulants appear in blood, for example, heparin, which is released in degranulation of tissue basophiles (mast cells). Synthesis of proteins of coagulation system of blood decreased in the liver.

The changes of the vascular wall, mainly of small vessels are very important in pathogenesis of the hemorrhagic syndrome in radiation disease. The endothelium becomes pathologically changed *end* peels off; the ability of its cells to produce polysaccharide-protein complexes to construct basal membrane is disturbed. The perivascular connective tissue, which is the mechanical base of the vessel, undergoes great destructive changes. The tension and resistance of the vessels are disturbed. The injured cells release biologically active substances (BAS) — proteolytic ferments from the injured lysosomas, kinines, hialuronidase, which aggravate damage of the vascular wall increasing its permeability.

Destructure of the vascular wall leads to functional deficiency of the vessels and disturbance of blood circulation in those vessels where there is metabolism between blood and cells.

The hereditary properties of the cell are changed if the cell isn't destructed due to chromosome injuries. The somatic cell may have malignant regeneration, and chromosome aberration in the sex cells leads to development of hereditary diseases.

Pathogenesis of Nervous System Disorders

Severe structural changes and destruction of the nervous cells occur in higher doses of radiation. However, structural changes do not always correspond to the functional ones, so the nervous tissue is very sensitive to any influences, including radiation. In the few seconds after radiation the nervous receptors are stimulated by products of radiolysis and tissue disintegration. The impulses come into the nervous centers changed by direct radiation, disturbing their functional condition. The changes of the bioelectrical activity of the brain can be registered within first minutes after radiation. Thus, neuroreflex activity is disturbed before appearance of other typical symptoms of radiation disease. At first functional and then deeper dysfunctions of the organs and systems are connected with it.

In the organs of the endocrine system the initial signs of increased activity are replaced by inhibition of the function of the endocrine glands.

Similar to other pathologic processes, compensatory-adaptive reactions are observed in radiation injury. They develop at all levels of the organism organization. At the molecular level the pathologic changes are compensated by natural antioxidant systems. These are compensated by natural antioxidant systems. These are captors of free radicals, inactivators of peroxides (catalase), of sulfhydrilic group (glutathione). The ferments of reparation of the injured DNA, inhibitors and inactivators of BAS function in the cell. Correction of radiation injury includes a number of measures directed at prevention of infection, intoxication and hemorrhagic signs. The preparations of symptomatic therapy are variable and include correction of dysfunction of the endocrine glands, nervous and alimentary system. Restoration of hemopoiesis is of special importance. In its respect transplantation of the bone marrow is the most effective measure. Hypothermia, hypoxia increase radiostability of the animals in experiment. There is a special group of preparations of antiradiation chemical protection. These are substances blocking the development of chain of radiation chemical reactions by capture of active radicals, antioxidants creating tissue hypoxia (methemoglobin producers).

Acute Radiation Disease

All the described disturbances of hemopoiesis, function of the nervous and alimentary systems are marked in all forms of radiation injury. But the degree of changes, development rate and prognosis depend on the absorbed dose of total radiation.

Medullar Form (dose 0.8-10 Gy)

There are four clinical periods: (1) the period of initial reactions, (2) the latent period, (3) the period of marked clinical signs and (4) the outcome of the disease.

The first period, duration of which is several hours to 1-2 days is reactions of the nervous and hormonal mechanisms to radiation: excitation, instability of the vegetative functions, lability of the arterial pressure and pulse, dysfunctions of the inner organs ("X-ray hangover"). Disturbance of the alimentary canal motility is manifested in vomiting and diarrhea. The body temperature may increase due to central disturbance of thermoregulation. There is shot- term

redistribution leukocytosis, which is accompanied by lymphocytopenia. In severe cases radiation shock is possible in this period. Pituitary-adrenal system becomes activated.

The second period is a period of alleged health. The signs of over-exertion of the nervous system, dyspeptic disorders disappear but still there are some signs of the disease: instability of arterial pressure, lability of the pulse, leukopenia (progressing of lymphocytopenia, development of granulocytopenia).

The third period is characterized by marked manifestations of radiation disease. There are leukopenia, thrombocytopenia and anemia in blood. There are inevitable infectious complications, which are the main cause of the patient's sufferings. Development of autoinfections of the oral cavity is typical of this period. They are inflammation of the tongue and gums, necrotic tonsillitis. Intake of food becomes difficult. Radiation disease may be complicated by pneumonia, which is very severe on the background of decreased immunologic reactivity and may become the cause of the patient's death. The appearance of the patient is quite typical — the skin is covered with numerous hemorrhages. There is blood in urine, feces and sputum. At the height of the disease the patient may die.

The signs of recovery are improvement of health, normalization of blood picture and young blood cells. However, residual signs may persist for a long time, they are asthenia, fatigue, general weakness, instability of hemopoiesis, sexual dysfunction, weakening of immunity, trophic disorders leading to premature aging and marasmus. The follow-up consequences are tumors.

The intestinal form develops in the dose of 10-20 Gy. **The toxemic form** is observed in radiation of 20-80 Gy. In these forms of injury there are stopping of mitotic division of cells of the intestinal epithelium and their mass interphase destruction, loss of proteins, electrolytes and tissue dehydratation. The surface of the mucous membrane of the intestines becomes bare that promotes penetration of infection. Shock is possible due to the effect of toxic substances of microbe and tissue origin.

The clinical picture is characterized by vomiting, anorexia, flaccidity, blood in feces, increased body temperature and pain in the intestines. There develops paralytic obstruction of the intestines, peritonitis due to disturbance in the barrier function of the intestinal wall. Lethality is 100%.

The cerebral form is observed in radiation dose over 80 Gy. The fatal outcome may occur during radiation or in a few minutes (hours) after it. The most severe changes are observed in the nervous system due to direct injury of ionizing radiation of the nervous tissue. There are significant structural changes and even destruction in the nervous cells of the brain cortex and hypothalamus, severe damage of the vessels endothelium. Severe and irreversible disorders in the central nervous system lead to development of spasm-paralytic syndrome, disturbance of the vascular tension and thermoregulation.

The Pathogenic Effect of the Factors of Space Flight

There are such factors, which influence on the human organism in space flight:

1. Acceleration and overloads at the active parts of flight (in taking-off the space ship at the time of descent).
2. Weightlessness.
3. Stressor action.

The Acceleration, Overloads

The acceleration is marked at the beginning of the flight in taking-off the space ship and at the end of flight in descent of the ship from the orbit and at the end of flying under lowering of ship from orbit (entering the compact strata from the atmosphere and landing).

The acceleration is a vector quantity size, which is characterized by the quickness of exchange of movement speed. In movement with acceleration in the opposite direction the inertion strength acts. For its determination we usually use such a term as 'overload".

In the aviational and cosmic medicine the overloads are differentiated by some indices, including quantity and duration (long — more than 1 s, shock — less than 1 s), speed and character of increasing (even and pick). As to relation of the vector of overload to the longitudinal axis of the human body we have a positive (from head to legs) and longitudinal negative (from legs to head), transversal positive (back — chest), lateral positive (right — left) and lateral negative (left — right).

The significant overloads condition redistribution of blood mass in the vessel flow, the disturbances of lymphatic outflow, displacement of the organs and soft tissues and then the disturbance of blood circulation, respiration and condition of the central nervous system. The displacement of great mass of blood is accompanied with overfilling of the vessels of some region of the organism and blood deficiency of

other organs. The recurrence of blood to the heart and of the amount the cardiac output change, the reflexes from baroreceptor zones are realized, that take part in the regulation of the heart work and vessel tonus. A healthy man endures the transversal positive overloads (back — chest) easier. Most of healthy men endure easily the even overloads at this direction for one minute with quantity to 6-8 units. In short pick overloads their endurance increases. In transversal overloads (above the level of individual endurance) the function of the external respiration is disturbed, the blood circulation changes in the vessels of the lungs and the contractions of the heart increase. In increasing of the quantity of the transversal overloads the mechanic compression of some parts of the lungs becomes possible.

The longitudinal overloads are more difficult to endure. In positive longitudinal overloads (heart — legs) the recurrence of blood to the heart becomes more difficult; the blood supply of the cavities becomes decreased (and consequently the ejection cardiac), the blood supply of the cranial parts of the body and brain is reduced.

The receptor apparatus of the sinocarotid zone reacts on decrease of the arterial pressure. Tachycardia appears, and sometimes we can see the disturbances of the cardiac rhythm. In increasing of the level of individual stability we can see marked arrhythmia of the heart, the disturbances of vision and respiration.

The longitudinal negative overloads are more difficult to endure (pelvis — head). The vessels of the head are overfilled with blood. The increase of the arterial pressure in the reflexogenic zones of the carotid arteries cause reflex slowing down of the contractions of the heart. In increase of the levels of individual stability the headaches, vision disturbances, arrhythmia of the heart appear, the respiration is disturbed, prefaint condition arises and then the man loses consciousness.

As to ***weightlessness***, we can say that at present we have enough experience of the long space flights, which proved the possibility of the human adaptation to that condition.

The adaptation to weightlessness is based on active reorganization of some systems on the new level of functioning. The significant changes can be noted in the system of blood circulation. As a result of going out of the hydrostatic component of the arterial pressure, we can see the redistribution of blood with increased blood supply of the vessels of the upper part of body. The stimulation of the volumoreceptors and inhibition of excretion of vasopressin and aldosterone result in

reorganization of hydroelectrolytic metabolism (the increased excretion of Na^+ and H_2O through the kidneys). The volume of circulative blood decrease, the overloads with H-ion leads to decrease of heart activity. This is an unloading reorganization. The decrease of energy expenditures promotes it (because there are no muscular effects to overcome the strengths of Earth gravity).

In weightlessness we can see intensified excretion of K^+, Cl^-, Fe^{2+}. The negative asotic balance and loss of water explain the decrease of body mass, which we can see in cosmonauts. The changes in the locomotor apparatus deserve a great attention. Ca^{2+} and Ph are excreted; the structure of the bones changes, osteoporosis appears. The mass of the skeleton muscular tissue decreases, the signs of atrophy appear. The changes in the muscles and bones result from hypokinesia, decrease of gravitation overload on the locomotor apparatus, decrease of mechanic compression of the bones.

For prophylaxis we recommend the physical trainings, muscular electrostimulation, vibromassage.

In the pathogenesis of the changes in the muscular and bone tissues the nervous trophicity takes place. The adequate afferentation is the necessary link of the trophic reflex and in weightlessness the locomotor apparatus is in the condition of the functional diafferentation. The appeared changes of the muscles are not only atrophy without action but also neurogenic dystrophy, and prophylactic measures are aimed at keeping and imitating the locomotor function and maintaining the afferent link of the trophic reflex.

Evaluating the influence of weightlessness on the organism we must remember, that new level of functioning of blood circulation system and locomotor apparatus, and energy and hydro-electrolyte metabolism for conditions of weightlessness, may be more adequate but it is unfavorable for conditions of Earth life, and to these conditions a cosmonaut must return. After coming back to the Earth we can see the decrease of functional possibilities of the systems opposing to the gravity.

Under the conditions of flight the pathogenesis factors act not isolately, but in the different combination and sequence. We must remember that the final effect may be different from the expected. **In** particular it was shown in that overloads the reactivity of the organism changes and so the course of other pathologic processes changes too (hypoxia, overheating, intoxication and cooling). It is known, that the organism having had the overloads reacts differently on the medicine

for curative aim. In the long stay under the weightlessness the organism condition also sharply changes and makes the unfavourable background for the action of other pathogenic factors of flight.

COMPREHENSION CHECK

Try to answer the following questions.

1. What is the pathologic action of decreased atmospheric pressure?
2. Characterize hyperbaria, hyperoxia, caisson disease as the effect of increased atmospheric pressure.
3. Describe pathogenic action of electric current, its manifestations and mechanisms.
4. Describe the effect of ionizing radiation, dysfunctions of the organism and common symptoms.
5. What is acute radiation disease?
6. Characterize the pathogenic effect of the factors of the space flight.

UNIT 3

CELLINJURY

Knowledge of the structural and functional reactions of cells and tissues to injurious agents, including genetic defects, is the key for the understanding of disease processes. Currently diseases are defined and interpreted in molecular terms and not just in general descriptions of altered structure. Altered cellular and tissue biology can be the result of adaptation, injury, neoplasia, aging, or death. Adaptation occurs in response to both normal, or physiologic, conditions and adverse, or pathologic, conditions. For example, the uterus adapts to pregnancy — a normal physiologic state — by enlarging. Enlargement occurs because of increase in the size and number of uterine cells. In an adverse condition, such as high blood pressure, myocardial cells are stimulated to enlarge by the increased work of pumping. Like most of the body's adaptive mechanisms, however, cellular adaptations to adverse conditions are usually only temporarily successful. Severe or long-term stressors overwhelm adaptive processes, and cellular injury or death ensues.

Cellular injury can be caused by any factor that disrupts cellular structures or deprives the cell of oxygen and nutrients required for survival. Injury may be reversible (sublethal) or irreversible (lethal) and is classified broadly as chemical, hypoxic (lack of sufficient oxygen), free radical, or infectious. Cellular injuries from various causes have different clinical and pathophysiologic manifestations.

Cellular death is confirmed by structural changes seen when cells are stained and examined under a microscope. No biochemical indicators of cellular death are universally applicable because we still do not know precisely what biochemical functions must be compromised before a cell dies.

Cellular aging causes structural and functional changes that eventually lead to cellular death or a decreased capacity to recover from injury. Mechanisms explaining how and why cells age are riot known, and distinguishing between pathologic changes and physiologic changes which occur with aging is often difficult. Aging clearly causes alterations in cellular structure and function, yet senescence is both inevitable and normal.

First of all it is necessary to recall prerequisite knowledge.

The intact, normally functioning plasma membrane is selectively permeable to substances; it allows some substances to pass and excludes

others. Water and small, uncharged substances move through pores of the lipid bilayer by passive transport, which requires no expenditure of energy. This process is driven by the forces of osmosis, hydrostatic pressure, and diffusion. Larger molecules and molecular complexes are moved into the cell by active transport, which requires the expenditure of energy, or ATP, by the cell. In active transport, materials move from low concentrations to high concentrations. The largest molecules and fluids are ingested by endocytosis and expulsed by exocytosis after cellular synthesis of smaller building blocks. When t tie plasma membrane is injured, it becomes permeable to virtually everything and substances move into and out of the cells in an unrestricted manner. Notably, such substances may affect (a) the nucleus and its genetic information or (b) the cytoplasmic organelles and their varied functions; then, there is altered cellular physiology and pathology (Table 2).

Homeostasis is the concept of a dynamic steady state, turnover of bodily substances that maintains physiologic parameters within narrow limits. Stressors cause reactions that alter this dynamic steady state or homeostasis. Deviations from normal values, or homeostasis, cause disease (Fig. 1).

DESCRIPTION OF THE CELLULAR ADAPTATIONS OCCURRING IN ATROPHY, HYPERTROPHY, HYPERPLASIA, DYSPLASIA, AND METAPLASIA

At first we identify conditions under which everybody can occur. When confronted with stresses that disrupt normal structure and function, the cell undergoes adaptive changes that permit survival and maintain function. An adapted cell is neither normal nor injured — it is somewhere between these two states. These changes may lead to atrophy, hypertrophy, hyperplasia, metaplasia, or dysplasia. These adaptive responses occur in response to a need and appropriate stimulus. Once the need is no longer present, the adaptive response ceases.

Cellular atrophy decreases the cell substance and results in cell shrinkage. The size of all the structural components of the cell usually decreases as the cell atrophies. Causes of atrophy include difuse, denervation, lack of endocrine stimulation, decreased nutrition, or ischemia. Difuse atrophy is seen in muscles that are not used. Denervation atrophy occurs in the muscles of paralyzed limbs. Lack of endocrine stimulation causes changes that may occur in reproductive structures during menopause. During prolonged periods of malnutrition, the body may undergo a generalized wasting of tissue mass. Ischemia

reduces blood flow and delivery of oxygen and nutrients to tissues.

Table 2. Cellular Accumulations

Accumulation	Causes	Injury
H_2O	Extracellular H_aO shifts into cell, reduced ATP and ATPase, sodium accumulates in cell	Cellular swelling, vacuolation, hydropic degeneration
Lipids, carbohydrates	Imbalance in production, utilization, or mobilization of carbohydrates	Vacuolation, displaced nucleus and organelles, lead to fibrosis and scarring
Glycogen vacuolation	Genetic disorders, diabetes mellitus	Cytoplasmic
Proteins	Enzymes digest cellular organelles, renal disorders, plasma cell tumor	Disrupted function and intracellular communication, displaced cellular organelles
Pigments	Exogenous particle ingestion, UV light stimulates melanin production, malignancy, loss of hormonal feed-back, genetic defects, bruising and hemorrhaging increases hemosiderin, liver dysfunction	Membrane injury
Calcium	Altered membrane permeability, influx of extracellular calcium, excretion of H^+ leading to more OH- which precipitates Ca^{++}, endocrine disturbances	Hardening of cellular structure, interferes with function
Urate	Abscence of enzymes	Crystal deposition, inflammation

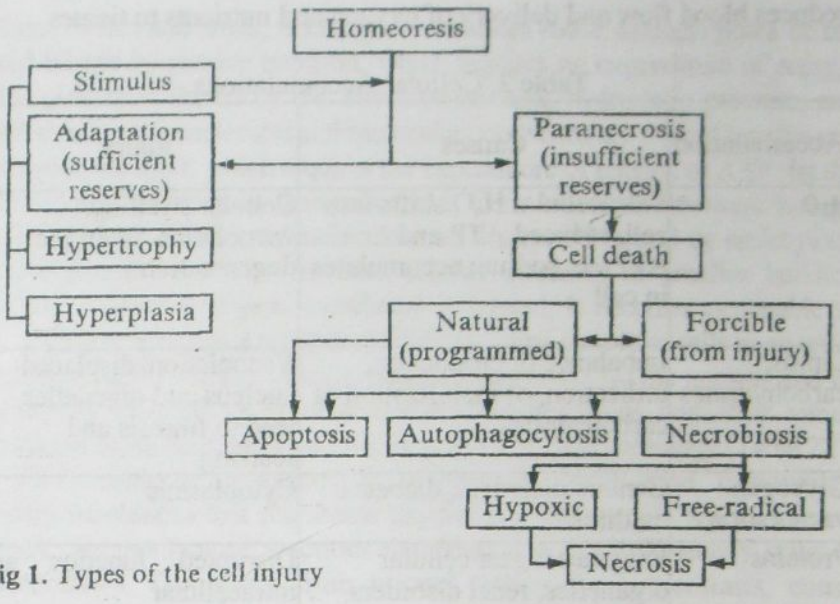

Fig 1. Types of the cell injury

Hypertrophy increases the amount of functioning mass by increasing cell size. This allows the cell to achieve an equilibrium between demand and function. Hypertrophy usually is seen in cardiac and skeletal muscle tissue. These tissues cannot adapt to increased workload by mitotic to form more cells. The increase in cell components is related to limitations in blood flow. Hypertrophy may be either physiologic or pathologic. In myocardial hypertrophy, initial enlargement is caused by dilation of the cardiac chambers in response to valvular disease or hypertension. This adaptation is short-lived and is followed by increased synthesis of cardiac muscle proteins that allows cardiac muscle fibers to do more work. Ultimately, advanced hypertrophy becomes pathologic and can lead to heart failure.

Hyperplasia is an increase in the number of cells of a tissue or organ. It occurs in tissues where cells are capable of mitotic division. Hyperplasia is a controlled response to an appopriate stimulus and ceases once the stimulus has been removed. Breast and uterine enlargement during pregnancy are examples of a physiologic hyperplasia that is hormonally regulated. A pathologic hyperplasia occurs when the endometrium enlarges because of excessive estrogen production. Then, the abnormally thickened uterine layer may bleed excessively and frequently. Compensatory hyperplasia enables certain

organs, like the liver, to regenerate after loss of substance.

Dysplasia is deranged cell growth that results in cells that vary in size, shape, and appearance of mature cells and is related to hyperplasia. Minor degrees of dysplasia occur in association with chronic irritation or inflammation in the uterine cervix, oral cavity, gallbladder, and respiratory passages. Dysplasia is potentially reversible once the irritating cause has been removed. Dysplastic changes may progress to neoplastic disease. This makes dysplasia a phenomenon of importance.

Metaplasia is a reversible conversion from one adult cell type to another adult cell type. It allows for replacement with cells that are better able to tolerate environmental stresses. In metaplasia, one type of the cell may be converted to another type of the cell within its tissue class (i.e., an epithelial cell cannot change to a connective tissue cell). An example of metaplasia is the substitution of stratified squamous epithelial cells for ciliated columnar epithelial cells in the airways a habitual cigarette smoker.

THE MAIN CAUSES AND MECHANISMS OF CELLULAR INJURY

There are different causes of the cell injury: hypoxia, chemicals, infectious agents, immunological and inflammatory responses, genetic factors, nutritional imbalances, ionizing radiation, and physical trauma.

Hypoxia

Hypoxia deprives the cell of oxygen and interrupts oxidative metabolism and the generation of ATP, as oxygen tension within the cell reverts to anaerobic metabolism. One of the earliest effects of reduced ATP is acute cellular swelling caused by failure of the sodium-potassium membrane pump, intracellular potassium levels decrease and sodium and water accumulate within the cell. As fluid and ions move into the cell, there is dilation of the endoplasmic reticulum, increased membrane permeability, and decreased mitochondrial function as extracellular calcium accumulates in the mitochondria. If the oxygen supply is not restored, there is continued loss of essential enzymes, proteins, and ribonucleic acid through the very permeable membrane of the cell. Hypoxia can result from inadequate oxygen in the air, respiratory disease, decreased blood flow due to circulatory disease, anemia, or inability of the cell to use oxygen.

An important mechanism of membrane damage is caused by free radicals, especially by activated oxygen species. A free radical is an atom or group of atoms with an unpaired electron. The unpaired electron makes

the atom or group unstable. To gain stability, the radical gives up an electron to another molecule or steals an electron. These radicals can bond with protein, lipids, and carbohydrates, which are key molecules in membranes and nucleic acids. These reactive species cause injury by (1) lipid peroxidation, which destroys unsaturated fatty acids, (2) fragmentation of polypeptide chains within proteins, and (3) alteration of DNA by breakage of single strands. Free radicals are difficult to control, and they are initiated within cells by the absorption of ultraviolet light or X-rays, oxidative reactions that occur during normal metabolism, and enzymatic metabolism of exogenous chemicals or drugs.

Toxic Chemical Agents

Toxic chemical agents can injury the cell membrane and cell structures, block enzymatic pathways, coagulate cell proteins, and disrupt the osmotic and ionic balance of any cell. Chemicals may injure cells during the process of metabolism or elimination. Carton tetrachloride, for example, causes little damage until it is metabolized by liver enzymes to a highly reactive free radical and then it is extremely toxic to liver cells. Carbon monoxide has a special affinity for the hemoglobin molecule and reduces its ability to carry oxygen.

Alcohol (ethanol) is the favorite mood-altering drug in the United States and other countries. Liver and nutritional disorders are serious consequences of alcohol abuse. The hepatic changes, initiated by ethanol conversion to acetaldehyde, include deposition of fat, enlargement of the liver, interruption of transport of proteins and their secretion, increase in intracellular water, depression of fatty acid oxidation, increased membrane rigidity, and acute cell necrosis. In the CNS, alcohol is a depressant initially affecting subcortical structures. Consequently, motor and intellectual activity become disoriented. At high blood alcohol levels, respiratory medullary centers become depressed.

Lead acts on the central nervous system by interference with neurotransmitters; this may cause hyperactive behavior. Manifestations of brain involvement include convulsions and delirium. Peripheral nerve involvement may cause wrist, Finger, and foot paralysis. Lead inhibits enzymes involved in hemoglobin synthesis; anemia is seen in lead toxicity.

Infectious Agents

They produce injury by invading and destroying cells, producing toxins, or inducing hypersensitivity reactions.

Immunologic and Inflammatory Injury

It is an important cause of cellular injury. Cellular membranes are

injured by direct contact with cellular and chemical components of the immune and inflammatory responses. Such mediators are lymphocytes and macrophages and chemicals such as histamine, antibodies, lymphokines, complement, and proteases. Complement, a serum protein, is responsible for many of the membrane alterations that occur during immunologic injury. Membrane alterations are associated with rapid leakage of potassium out of the cell and rapid influx of water. Antibodies can interfere with membrane function by binding to and occupying receptor molecules on the plasma membrane.

Genetic Disorders

Genetic disorders may alter the cell nucleus and the plasma membrane structure, shape, receptors, or transport mechanisms.

Nutritional Imbalances

They are important because cells require adequate amounts of proteins, carbohydrates, lipids, vitamins, and mineral substances normally. If inadequate or excessive amounts of nutrients are consumed and transported, pathophysiologic cellular effects can develop.

Proteins are the major structural units of the cell and participate in many enzymatic and hormonal functions. With lowered plasma proteins, particularly albumin, fluids move into the interstitium and produce edema. Children suffering from protein malnutrition are very susceptible to and often die from infectious diseases.

Glucose is the major carbohydrate obtained from the breakdown of starch. Hyperglycemia, excessive glucose in the blood, if caused by excessive carbohydrate intake may lead to obesity. Deficiencies of glucose result from starvation or from inadequate use, as in diabetes. In both of these conditions, the body is compensated by metabolizing lipids to obtain cellular energy. In lipid deficiency, the body is compensated by mobilizing fatty acids from adipose tissue. This causes an increase in the production and circulation of acidic ketone bodies. Severe increases in ketone bodies can cause coma or death. Hyperlipidemia, or an increase of lipoproteins in the blood, results in deposits of fat in the heart, liver, and muscle.

Vitamins are involved in many reactions including metabolism of visual pigments (vitamin A), calcium and phosphate metabolism (vitamin D), prothrombin synthesis (vitamin K), and antioxidation reactions (vitamin E). Vitamin B affects amino acid transfer reactions; FAD, FMN, and NAD help transfer electrons. Deficiencies in vitamin C cause poor wound healing and scurvy. Vitamin D deficiency causes

rickets and problems with healing of fractures. Folate deficiency is associated with plasma and membrane changes of the red blood cell and is particularly a problem in individuals with severe liver dysfunction. Vitamin deficiencies are associated with several other disease states including cancer.

Injurious Physical Agents

They include temperature extremes, changes in atmospheric pressure, radiation, illumination, mechanical factors, noise, and prolonged vibration. Physical injury is often environmental.

The temperature extremes of chilling or freezing of cells cause hypothermic injury directly by creating high intracellular sodium concentration. This results from the formation and dissolution of ice crystals. Indirect forms of injury like vasoconstriction paralyze vasomotor control and vasodilation follows with increased membrane permeability.

This causes cellular and tissue swelling. Hyperthermic injury, from excessive heat, ***varies depending on*** the nature, intensity, and duration of the heat. Burns cause extensive loss of fluids and plasma proteins. Also, intense heat damages temperature-sensitive enzymes and the vascular endothelium and causes coagulation of the blood vessels.

Sudden increases or decreases of ***atmospheric pressure*** cause blast injury. In air blast or explosive injuries, tissue injury is due to compressed waves of air against the body. The pressure changes may collapse the thorax, rupture solid internal organs, or cause widespread hemorrhage. In increased pressure caused by immersion blast, water pressure is applied suddenly to the body, and the body is forced up out the water. The positive pressure compresses the abdomen and ruptures hollow internal organs such as the spleen, kidneys, and liver. With sudden decreases in pressure, carbon dioxide and nitrogen normally dissolved in the blood leave solution and form tiny bubbles, gas emboli, which obstruct blood vessels. This is seen in rapidly ascending deep sea divers and underwater workers. At low atmospheric pressure, such as occurs at altitudes above 15,000 feet, there is a decrease in available oxygen; this causes hypoxic injury. The compensatory vasoconstriction shunts the blood from the peripheral circulation to the visceral organs including the lungs. The combination of increases in pulmonary blood flow and systemic hypoxic cause pulmonary edema, interstitial water excess.

Ionizing radiation

It is any form of radiation capable of removing orbital electrons from atoms. Ionizing radiation is emitted by X-rays, gamma rays, and the

process of radioactive decay. Radiant energy from sunlight can also injury cells. DNA is the most vulnerable target of radiation, particularly the bonds within the DNA molecule. Irradiation during mitosis produces chromosome abberation, and other cell injury and enzymes are also damaged by radiation. Radio- sensitivity depends on the rate of mitosis and cellular maturity. The more numerous the mitotic figures, the greater the sensitivity; more maturity, less sensitivity. Particularly vulnerable cells of the bone marrow, intestinal, and ovarian follicles are susceptible to injury because they are always undergoing mitosis.

IDENTIFICATION OF THE MAJOR TYPES OF CELLULAR NECROSIS

Necrosis is local cell death and involves the process of cellular self-digestion known as autodigestion or autolysis. As necrosis progresses, most organelles are disrupted, and karyolysis, nuclear dissolution from the action of hydrolytic enzymes, becomes evident. There are four major types of necrosis: coagulative, liquefactive, caseous, and fat. Gangrenous necrosis is not a distinctive type of cell death but refers to large areas of tissue death.

Coagulative necrosis occurs primarily in the kidneys, heart, and adrenal glands and usually results from hypoxia caused by severe ischemia. Protein denaturation causes coagulation. An increased intracellular level of calcium may be a critical event in coagulation necrosis.

Liquefactive necrosis is common following ischemic injury to r eurons and glial cells in the brain. Because brain cells are rich in digestive hydrolytic enzymes and lipids, the brain cells are digested by their own hydrolases. The brain tissue becomes soft, liquefies, and is walled off from healthy tissue to form cysts. Liquefactive necrosis can also result from bacterial infections. Here, the hydrolases are released from the lysosomes of phagocytic neutrophils that are attracted to the infected area to kill the bacteria; these hydrolases also destroy brain tissue. The accumulation of pus is; present in liquefaction necrosis.

Caseous necrosis is commonly seen in tuberculosis pulmonary infection and is a combination of coagulative and liquefactive necrosis. The necrotic debris is not digested completely by hydrolases, so tissues appear soft, granular, and resemble clumped cheese. A granulomatous inflammatory wall may enclose the central areas of caseous necrosis.

Fat necrosis found in the breast, pancreas, and other abdominal structures is a specific cellular dissolution caused by lipases. Lipases break down triglycerides and release free fatty acids that then combine

with calcium, magnesium, and sodium ions to create soaps, or saponification. The necrotic tissue appears opaque and chalk white.

Gangrenous necrosis refers to death of tissue, usually in considerable mass and putrefaction. It results from severe hypoxic injury subsequent to arteriosclerosis or blockage of major arteries followed by bacterial invasion. Dry gangrene is usually due to a coagulative necrosis, and wet gangrene develops when neutrophils invade the site and cause liquefactive necrosis. Gas gangrene, a special type of gangrene, is due to bacterial infection of injury tissue by a species of Clostridium. These anaerobic bacteria produce hydrolytic enzymes and toxins that destroy connective tissue and the cellular membrane; bubbles of gas likely form in the muscle cells.

DESCRIPTION OF THE MECHANISMS OF APOPTOSIS

Apoptosis is an important, distinct type of cell death that differs from necrosis. It is an active process of cellular self-destruction in both normal and pathologic tissue changes. Apoptosis likely plays a role in deletion of cells during embryonic development and in endocrine-dependent tissues that are undergoing atrophic change. It may occur spontaneously in malignant tumors and in normal, rapidly proliferating cells treated with cancer chemother-apeutic agents and ionizing radiation. Unlike necrosis, apoptosis affects scattered, single cells and results in shrinkage of a cell; whereas in necrosis, cells swell and lyse (Fig. 2).

THE MAIN THEORIES OF AGING

There are two general theories of aging: (I) aging is caused by the accumulations of injurious events, sometimes termed damage-accumulation theories, or (2) aging is the result of a genetically controlled developmental program. In support of these two categories, the mechanisms of aging have emerged: the cells of the endocrine, immune, and central nervous systems, are responsible for aging; and (3) degenerative extracellular and vascular alterations cause aging.

Regardless of injurious environmental factors, some believe that each cell may have a finite life span during which it can replicate. Fibroblasts have been demonstrated to be limited to 40 to 60 cell doublings. Alternatively, an intrinsic program within the human genome progressively slows or shuts down mitosis.

Alterations of cellular control mechanisms include increased hormonal degradations, decreased hormonal synthesis and secretion, and decreased receptors for hormones and neuromodulators. This suggests

that a genetic program for aging is encoded in the brain and relayed through hormonal and neural agents because of shared common receptors within these systems.

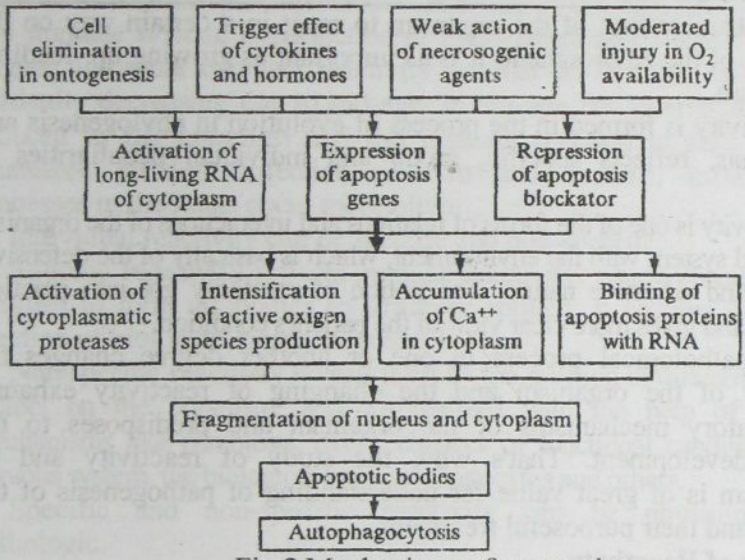

Fig 2 Mechanisms of apoptosis

Immune function declines with age and the number of autoantibodies that attack body tissues increases with age. These observations implicate the immune system in aging.

A degenerative extracellular change that affects the aging process is collagen cross-linking, which makes collagen more rigid and results in decreased cell permeability to nutrients. Free radicals of oxygen are believed to damage tissues during aging. These reactive species not only permanently damage cells but also may lead to cell death. Damage accumulates over time and reduces the body's ability to maintain a steady state.

COMPREHENSION CHECK

Try to answer the following questions.

1. Describe the cell responses on various injurious factors (hypoxia, chemicals, infectious agents, physical trauma).
2. Explain what atrophy, hypertrophy, hyperplasia, dysplasia and metaplasia mean.
3. Identify the major types of cellular necrosis.
4. Describe the mechanisms of apoptosis.

UNIT 4

REACTIVITY AND ITS ROLE IN PATHOLOGY

REACTIVITY

The characteristic of the organism to react in a certain way on the influence of the environment. It is as important as growing up, feeding, metabolism.

Reactivity is formed in the process of evolution in phylogenesis and ontogenesis, reflects specific, group and individual peculiarities of reaction.

Reactivity is one of the forms of relations and interactions of the organism as a united system with the environment, which is basically of the defensive, adaptive and adjustive nature. The notion of reactivity got into practical medicine and gives more clear view of the patient's condition.

Any pathological process in one or another degree changes the reactivity of the organism and the changing of reactivity exhausts compensatory mechanisms of the organism and predisposes to the disease development. That's why, the study of reactivity and its mechanism is of great value for understanding of pathogenesis of the diseases and their purposeful treatment.

Types of Reactivity

Biological or specific reactivity is defined as hereditary and expresses the ability of all representatives of the given species to react in the same way, which is the defensive-adaptive nature due to different changes of the environment. This reactivity is also called primary. It defines specific immunity to infectious diseases, for example: hibernation of animals, seasonal migration offish and birds. Gophers infected in winter hibernation by pests and tuberculosis do not get sick, sleep raises stability to strychnine and other poisons. On the base of the specific reactivity group and individual reactivity is formed.

Group reactivity is possessed by people who have some hereditary constitutional peculiarities: such as constitutional type, blood group, antigens of leukocytes and others. It is known that the people from the first blood group are more often fall ill with peptic ulcer of the stomach, but people who have antigen HLA-B_8 have high risk to get diabetes mellitus.

Individual reactivity is stipulated by heredity and obtained by factors, depending on the conditions of the external environment, in which the organism develops, for example, climate, contents of oxygen in the atmosphere, nature of feeding and others.

Reactivity depends on the sex. In the female organism reactivity changes in connection with menstrual cycle, pregnancy. The women are

more stable to hypoxia, blood loss, starvation.

Age peculiarities play a significant role in reactivity. In babies the form of reaction is simple, as a rule, with low reactivity. This is connected with the incomplete development of the nervous, endocrine and immune system, imperfection of the external and internal barriers. Higher and more complex reactivity is observed in maturity and it is gradually decreasing due to old age. In old age the barrier function is reduced in the organism and the immune reaction is also reduced. Therefore purulent infection of skin and mucous, inflammatory processes in the lungs occur more often.

Individual reactivity can be specific and non-specific.

Specific reactivity reflects immune reactivity, which consists of the abilities to form antibodies to irritating antigen. It ensures immunity, reaction of biological tissue incompatibility.

Non-specific reactivity reveals itself by the reaction of different external factors on the organism, and it's realized with the help of different mechanisms like parabiosis, stress, changes of functional candition of the nervous system, the biological barriers, phagocytes and others.

Specific and non-specific reactivity can be physiologic and pathologic.

Physiological reactivity covers the reactions of the healthy organism in normal circumstance of existence, for example, immunity (specific reactivity), and also reactions of the organism on the action of the different factors of the external environment, which do not change homeostasis (non-specific reactivity).

Pathologic reactivity reveals itself in the action of the pathogenic factors on the organism. Examples of specific pathologic reactivity are: allergy, immune deficit condition. Example of non-specific pathologic reactivity can be change of reactivity under traumatic shock, narcosis (phagocytosis, sensitivity to medicines).

By the forms of manifestations we distinguish: increased (hyperergia), lowered (hypoergia) and perverted (dysergia) reactivity.

In the development of pathologic process (allergy, inflammation) it's possible to observe the change of reactivity on different levels: molecular, cellular, systems of the organs and the organism on the whole.

RESISTANCE. TYPES. INTERACTION WITH REACTIVITY

Resistance

Resistance is the stability of the organism due to the action of the

pathogenic factors. During the evolution the organism has gained mechanisms of adaptation which ensure its existence in conditions of non-stop-actions connected with the environment, but many factors can cause impairment of vital activity and even death in the absence of these mechanisms.

The resistance of the organism is connected with reactivity. Ability of the organism to withstand harmful influences determines its reactions as a whole so that's why resistance is one of the main effects and manifestations of the organism reactivity. Resistance can be active and passive.

Passive resistance is connected with the anatomic-physiological peculiarities of the organism: aging of the skin, mucous layers, bone tissue, thick coverings.

Active resistance is stipulated by switching on defensive-adaptation mechanism. So, stability to hypoxia is connected with the activation of the ventilation of the lungs, acceleration of the blood circulation, increase of the quantity of erythrocytes and hemoglobin in the blood, stability to infectious influence-immunity — is connected with the formation of antibodies and the activation of phagocytosis.

Resistance can be primary which is connected with hereditary factors and secondary, which is acquired.

Usually reactivity and resistance are changed in the same way. But other correlation can be possible, so in conditions of hibernation the reactivity of the animals falls ***but*** their resistance increases .

Under two or more kinds of (extreme) stimuli the organism often responds to only one, staying "deaf to the action of the others. Such a form of reactions cannot be named resistance, because the organism reacts only when it's vital activity is deeply affected. Such form of reactivity is named tolerance. It is usually observed in less developed organisms, when transmission to more ancient and resistant though economic way of release of energy — "glycolysis". Reactivity as contrasted with tolerance ensures active protection of the organism from the pathogenic factors due to protective-adaptive mechanisms, which help the organism to maintain homeostasis.

Reactivity by Bogomolets

The study of A. Bogomolets shows a great role of connective tissue in specific and non-specific reactivity. He proposed the term — physiological system of connective tissue (PhSCT), as an important system of the defense. This system includes:

a) endothelium of vessels;
b) lymphocytes and lymph nodes;
c) cells of bone marrow;

d) reticular cells of the liver, spleen, kidneys, lungs;

e) micro- and macrophages, as such cells of blood as neutrophils, monocytes, lymphocytes (moving phagocytes), histiocytes of connective tissue.

There are protective-adaptive mechanisms, which help the organs to maintain homeostasis.

Bogomolets created antireticular cytotoxic serum. Introduction of this serum in the organism stimulates all elements of reticuloendothelial system and then reactivity increases.

According to Selye, adaptation insufficiency causes adaptation diseases. The Selye's theory (one of the achievement of modern medicine) is the important role of the endocrine glands, in particular, the system of the pituitary-adrenal cortical substance. It is known that after introduction of large doses of desoxicorticosterone (DOCS) to the experimental animals it was observed elevation of blood pressure, development of hypertension, nephrosclerosis, hyalinosis of the organs, intensification of the inflammatory reactions. Introduction of glucocorticoids (anti-inflammatory hormones) to the animals inhibits inflammation but at the same time they depress immune reaction and cause impairment of the stomach and duodenum, create conditions for myocardial necrosis.

Insufficiency of glucocorticoid secretion promotes hyperergic course of the pathogenic effects. Seley considers rheumatism, bronchial asthma, some diseases of the kidneys, heart and vessels, a number of skin diseases and others to be diseases of adaptation. Such condition factors as overcooling, overheating, physical overstrain, aggravated heredity, excess intake of salt are of great significance.

Combined introduction of corticosteroids and sodium chloride creates the background for development of necrotic changes of the myocardium by different stimuli.

W. Cannon and L. Orbelly created a study of adaptational- trophic role of the sympathetic part of the vegetative nervous system in the protective compensatory reactions.

Reactivity and Biological Barriers

Biological barriers are special tissue structures, which protect the organism or its separate parts from pathogenic influence of the environment and preserve homeostasis. There are two types of the barriers: external and internal.

External barriers include the skin, the mucous layer which protect the organism from pathogenic influence of the environment, the respiratory

organs which hold back harmful materials pressure in atmosphere, the digestive organs (antibacterial action of gastric juice, deprivation of nutrients of antigenic properties), the liver has desintoxicating function, the spleen and the lymph nodes, as well as other organs also have the same function, including mononuclear cells of phagocytes.

Internal barriers are the necessary energetic material, preventing the penetration of the foreign and poisonous material arriving from the blood to the organs and tissues.

In 1929 L. S. Stern made a supposition that there was a defence mechanism between the blood and the liquid of the tissue, which she named histo-hematic barriers. Each organ has its own medium because the blood does not contact with the cells of the organs. The functional characteristics of the barriers depend on the morphological and physiological peculiarities, corresponding to the organs and tissues. The peculiarity of each barrier is its selective permeability.

Special barriers are a particular group which defend certain organs which are in need of its own strictly constant media. They are hematoencephalic, hematoophthalmic, hematotesticular, hematoplacentar barriers.

The structural elements of the barriers are capillaries, whose endothelium in different organs possesses their own distinctive peculiarities, and that is the principal morphological selective permeability.

In different organs in respect of different materials the barrier function may not be alike. In the study of the penetration of serum proteins into the organs, several types of barriers were shown. Hematoencephalic barrier is mainly present in the vascular walls, the barrier of the thyroid gland has an organisation on the tissue level and with the help of the paranchymatous cells divides the organs into zones where protein does not penetrate. The sarcolemma acts as a barrier in the muscles.

Hematoencephalic barrier has the most difficult organization. Besides endothelium and basal membrane, it has also argirophil material, the brain layers and glia with astrocytes.

It is known that microorganisms, toxins, medicines, antigens, antibodies do not penetrate into the brain. As to metabolites, hormones, biologically active materials, these barrier acts selectively, with respect to them regulating the penetration of these materials into the cells of the brain.

The main function of the barrier is the mechanism of dialysis, ultrafiltration, osmosis, as well as the metabolic function of the cells, which are included in the structure of the barrier.

Biological barriers, executing protective and adjusting function, support an optimum composition of medium for the organ and promote a conservation homeostasis to maximum.

Intensive transport through the barrier depends on the functional needs of the organ, hemodynamic, hormonal and nervous effect and also presence and absence of morphological and functional disturbances.

The function of the barrier may change depending on the age, sex, nervous and hormonal effects and many influences of external and internal media. The functional state of the barrier may change when in sleep and staying awake, tiredness, trauma irradiation with infra-red, ultraviolet and X-rays, influence of ultrashort and high-frequency waves, ultrasound.

Introduction of alcohol, acetylcholine, histamine, kinines, hialuronidase, agitating the central nervous system, increases the permeability of the barrier in the organism. Materials, with an opposite effect of lowering permeability include catecholamines, salts, calcium, vitamin PP, sleeping medicines.

Permeability of barriers is changed under different pathologic processes, such as trauma, inflammation, alcoholic intoxication, virus infection and others.

Increase of permeability makes the organ more sensitive to poisons, intoxications, intensifies tumor growth. In impairment of permeability of the barriers there is possibility of autoimmune damage of the organs (for instance the thyroid gland, the brain). Particular value for developing fetus has the hematoplacental barrier, which defends the fetus in the period of pregnancy. Impairment of permeability of this barrier (virus infection, alcoholic intoxication) can be harmfully reflected in the embryonal development of the fetus, which results in the development of different types of postnatal pathology.

COMPREHENSION CHECK

Try to answer the following questions.

1. Define reactivity an its types.
2. What is specific and non-specific reactivity?
3. Explain the term "physiological system of connecting tissue" and name elements of this system by Bogomolets. What is the role of this system in maintenance of organism's homeostasis?
4. Characterize biological histohematic barriers as protecting and adjusting mechanism in reactivity.

UNIT 5

THE ROLE OF HEREDITY AND CONSTITUTION IN PATHOLOGY

We should remember, that the disease and its pathogenesis depend on etiologic ("extreme") factors and such properties of the organism as heredity, constitution, reactivity.

The most important questions are when and how hereditary diseases appear. Depending on the scope of the damage of hereditary apparatus in reproductive cells (genetic or chromosomal mutations) molecular and genetic and chromosomal diseases are distinguished.

ETIOLOGY

The factors that cause mutation are called mutagens. They are physical, chemical and biological. Among the physical mutagens ***ionizing*** and ***ultraviolet*** radiation are on the first place. Radiation may change hereditary substance of the reproductive cells and cause mutation in such a minimal dose of radiation, that doesn't :ause death. But the posterity of a person, who underwent radiation, is at risk of developing this disease.

There are hereditary diseases, hereditary predisposition and congenital diseases.

Hereditary diseases are caused by mutation of the reproductive cells. Their manifestations doesn't depend on exogenic (etiological) factors.

Hereditary predisposition is connected with genetic damage of regulatory apparatus. Their manifestations depend on etiological factors. Without injurous factors hereditary predisposition doesn't i:urn into disease. For example, the development of diabetes mellitus depends on the interaction of genetic factors and the environment.

Congenital (innate) diseases are caused by the mother's diseases during pregnancy (tuberculosis, alcoholism, syphilis, toxoplasmosis). They imitate hereditary diseases, such as deaf-mutism, microcephaly, cataract and others.

Harmful mutation causes diseases and anomalies, which may be lethal and non-lethal for the carrier.

The hereditary disease manifestation sometimes depends on age. Hemophilia, ichthyosis, hereditary deaf-mutism are manifested at birth, Hungtington's chorea is found at 30-35 years of age, gout — at the old age.

There are following ways of inheritance:

Inheritance of a ***dominant type*** means that hereditary traits or anomalies are transmitted directly from parents to children and are manifested at the first generation.

Inheritance of a ***recessive type*** is manifested only in that case when the children get the pathological gene from both parents.

The recessive type is connected with X-chromosome — it means that in women who have X-chromosome pathology it may be compensated by another normal one. So the disease is manifested only in males, while the females remain healthy (conductor), being, however, the carriers of this trait. The juvenile defects as microcephaly, deaf-mutism, deafness and dumbness, blindhess, some psychiatric diseases, phenylketonuria, retinitis pigmentosa, enzymopathies and others belong to a recessive type.

Hemophilia, albinism transmitted by a recessive type is linked with the sex chromosome.

To anomalies inherited by a dominant type belong skeletal and other anomalies (sex digital, shot finger, Polydactyly, horse foot, brachydactyly, accreted fingers, muscular atrophy, otosclerosis, progressive Huntington's chorea, Marphan's syndrome, achondroplasia). They don't impair reproduction, don't shorten the life span and hence they undergo selection to a lesser extent. The most dangerous diseases of this group are polyposis of the rectum that tends to malignance and neurofibromatosis.

Chromosomal Diseases

Klinefelter's Syndrome

Klinefelter's syndrome is a genetic disorder in which there are three sex chromosomes, XXY. Total number of chromosomes 47,
48, 49. Affected individuals are apparently male, but they are: (1) (all and thin, (2) have small testes, with failure of normal sperm production, (3) azoospermia, (4) enlargement of the breasts — gynaecomastia, absence of facial and body hair, (5) less intelligence, (6) insufficient physical and genetical development.

When X-chromosome more than two (three, four) — XXXY, XXXXY — oligofrenia may be present; when Y-chromosome more than one (XYY, XXYYY) — increase of aggressiveness.

Down's Syndrome

Most individuals with Down's syndrome have 47 chromosomes (i.e., one extra chromosome 21, or trisomy 21) and are born to parents with normal karyotypes. This type of aneuploidy is usually caused by non-

disjunction during meiotic segregation, which means the failure of two homologous chromosomes to separate, or disjoin, from each other at anaphase. In contrast, aneuploid conditions that affect part of an autosome or sex chromosome must, at some point, involve DNA breakage and reunion. DNA rearrangements are an infrequent but important cause of Down's syndrome and are usually evident as a karyotype with 46 chromosomes in which one chromosome 21 is fused via its centromere to another acrocentric chromosome. This abnormal chromosome is described as the Robertsonian translocation and can sometimes be inherited from a carrier parent. Thus, Down's syndrome may be caused by a variety of different karyotypic abnormalities, which share in common a 50% increase in gene dosage for nearly all of the genes on chromosome 21.

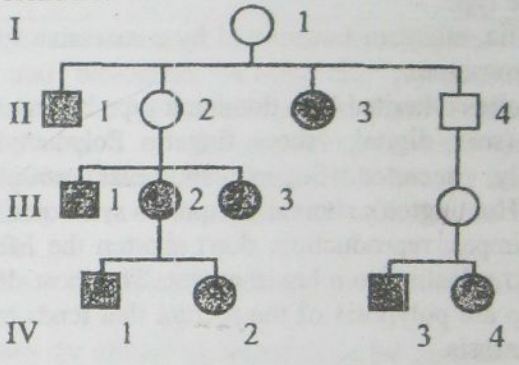

Fig. 3. Scheme of the generation with X-associated mental retardation syndrome

Clinical manifestations. Down's syndrome occurs approximately once in every 700 live births and accounts for approximately one third of all cases of mental retardation. The likelihood of conceiving a child with Down's syndrome is related exponentially to increasing of maternal age. However, screening programs detect most Down's syndrome pregnancies in pregnant women over 35 years of age. The condition is usually suspected in the perinatal period from the presence of characteristic facial and dysmorphic features such as brahycephaly, epicanthal folds, small ears, transverse palmar creases, and hypotomia. Approximately 50% of affected children have congenital heart defects that come in the immediate perinatal period because of cardiorespiratory problems. Strong suspicion of the condition on clinical grounds is usually confirmed by

karyotyping within 3 4 days.

The natural history of Down's syndrome in childhood is characterized mainly by developmental delay, growth retardation, and immunodeficiency. Developmental delay is usually apparent by 3- 6 months of life as a failure to attain age-appropriate developmental milestones and affects all aspects of motor and cognitive function. The mean IQ is between 30 and 70 and declines with the age. However, there is a considerable range in the degree of mental retardation in adults with Down's syndrome, and many affected individuals can live semi-independently. In general, cognitive skills are more limited than affective performance, and only minorities of affected individuals are severely impaired. Retardation of linear growth is moderate, and most adults with Down's syndrome have the heigt shorter than the most of the general population. In contrast, weight growth in Down's syndrome exhibits a mild proportionate increase compared with that of the general population, and most adults with Down's syndrome are overweight for height. Although increased susceptibility to infections is a common clinical feature at all ages, the nature of the underlying abnormality is not well understood, and laboratory abnormalities can be detected in both humoral and cellular immunity.

One of the most prevalent and dramatic clinical features of Down's syndrome — premature onset of Alzheimer's disease — is not evident until adulthood. Although frank dementia is not clinically detectable in many adults with Down's syndrome, the incidence of typical neuropathologic changes — senile plaques and neurofibrillary tangles — is nearly 100% by the age of 35. The major causes of morbidity in Down's syndrome are congenital heart disease, infections, and leukemia. Prognosis depends to a large extent on the presence of congenital heart disease. Survival to the age of 10 and 30 years is approximately 60% and 50%) respectively for individuals with congenital heart disease, and approximately 85% and 80% respectively for individuals without congenital heart disease.

Fragile-Associated Mental Retardation

Fragile X-associated mental retardation syndrome produces a unique combination of phenotypic features that affect the central nervous system, testes, and cranial skeleton.

In some respects, fragile X-associated mental retardation syndrome is similar to other genetic conditions caused by X-linked mutations — affected males are impaired more severely than affected females, and the condition is never transmitted from father to son.

Penetrance of fragile X-associated mental retardation syndrome. This artificial pedigree of the syndrome shows the each individual will manifest phenotypic features of the condition (penetrance). Penetrance increases with each successive generation owing to the progressive expansion of a triplet repeat element. Expansion is dependent on maternal allele; thus, daughters of normal transmitting males (indicated with T in II-4) are non-penetrant **(Fig. 3).**

PATHOPHYSIOLOGY OF SELECTED GENETIC DISEASES

Osteogenesis Imperfecta

Osteogenesis imperfecta is a condition inherited in a mendelian fashion that illustrates many principles of human genetics. It is a heterogeneous and pleiotropic group of disorders characterized by a tendency toward fragility of the bone. More then 100 different mutant alleles have been described for osteogenesis imperfecta: the relationships between different DNA sequence alterations and the type of disease (genotype-phenotype correlations) illustrate several pathophysiologic principles in human genetics (Table 3).

Phenylketonuria

Phenylketonuria presents one of the most dramatic examples of how the interrelationship between genotype and phenotype can depend on environmental variations. Phenylketonuria was firstly recognized as an inherited cause of mental retardation in 1934, and systematic attempts to treat the condition were initiated in 1950-s. Treatment outcomes have been hailed, perhaps prematurely, as the pinnacle of success in applying biochemistry and molecular biology to social problems that stem from inherited disease. The term "phenylketonuria" denotes elevated levels of urinary phenylpyruvate and phenylacatate, which occur when circulating phenylalanine levels, normally between 0.06 and 0.1 mmol/L, rise above 1.2 mmol/L. Thus, the primary defect in phenylketonuria is hyperphenylalaninemia, which itself has a number of distinct genetic causes.

Clinical Manifestations

The incidence of hyperphenylalaninemia varies among different populations. In American blacks it is about 1:50,000; in Yemenite Jews — about 1:5,000; and in most Northern European population, about 1:10,000. Postnatal growth retardation, moderate to severe mental retardation, recurrent seizures, hypopigmentation, and eczematous skin rashes constitute the major phenotypic features of untreated phenylketonuria.

Table 3. **Pathophysiological characteristics of the types of osteogenesis imperfecta**

Type	Phenotype	Genetics	Molecular pathophysiology
Type 1	Mild: short stature, postnatal fractures, little or no deformity, blue scleras, premature hearing loss	Autosomal dominant	Loss-of function mutation in pro al (1) chain resulting in decreased amount of mRNA; quality of collagen is normal; quantity is reduced twofold
Type 2	Perinatal lethal: severe prenatal fractures, abnormal bone formation, severe deformities, blue scleras, and connective tissue fragility	Sporadic (autosomal dominant)	Structural mutation in pro al (1) or pro a2 (1) chain that slows heterotrimer assembly; quality of collagen is abnormal; quantity often reduced also
Type 3	Progressive deforming: prenatal fractures, deformities usually present at birth, very short stature, usually nonambulatory, blue scleras, hearing loss	Autosomal dominant (rare cases autosomal recessive)	Structural mutation in pro al (1) or pro a.2 (1) chain that has mild or no effect on heterotrimer assembly; quality of collagen is mildly abnormal; quantity can be normal
Type 4	Deforming with normal scleras: postnatal fractures, mild to moderate deformities, premature hearing loss, normal or gray scleras, dentinogenesis imperfecta	Autosomal dominant	Structural mutation in pro a2 (1) chain that has little or no effect on heterotrimer assembly; quality of collagen is mildly abnormal; quantity can be normal

Metabolic Fates of Phenylalanine

Because catabolism of phenylalanine must proceed via tyrosine, the absence of phenylalanine hydroxylase leads to accumulation of phenylalanine. Tyrosine is also a biosynthetic precursor for melanin and

certain neurotransmitters, and the absence of phenylalanine hydroxylase causes tyrosine to become an essential amino acid.

The different genetic forms of phenylketonuria illustrate two important pathophysiologic mechanisms by which inborn errors of metabolism can cause disease: end-product deficiency and substrate accumulation. The mental retardation in phenylalanine hydroxylase is caused not by deficiency of tyrosine or its metabolites but instead by accumulat ion of the substrate for phenylalanine hydroxylase. In contrast, the progressive hypotonia and developmental regression seen in disorders of BH4 metabolism are caused by a decrease in the metabolic products of tryptophan hydroxylase and tyrosine hydroxylase.

Finally, a thorough understanding of the pathophysiology of phenylketonuria is a prerequisite for the development of gene therapy. For example, since most phenylalanine hydroxylation occurs in the liver, attempts to deliver a normal phenylalanine hydroxylase gene to affected individuals have focused on strategies to express the gene in hepatocytes. However, since individuals with benign hyperphenylalaninemia have phenylalanine hydroxylase activities that may be as low as 5% of normal, successful gene therapy of phenylketonuria might be accomplished by expressing phenylalanine hydroxylase in only a small proportion of hepatic cells.

THE ROLE OF BODY CONSTITUTION IN PATHOLOGY

The constitution, or the make up of the body is a unified complex of morphological, functional, psychological peculiarities of the body. These peculiarities are quite stable; they define the body reactivity, being formed on the hereditary basis under the influence of the environmental factors.

Constitution determines the individual reactivity of the body, its adaptational peculiarities, the distinctive traits of physiological and pathological processes, and pathological predisposition to certain diseases. The course of any disease, its prognosis and treatment depend not only on the character and severity of the pathogenic activity, but also on the individual peculiarities of the human body.

In constitution it is extremely important to see the ratio of the inherited and acquired peculiarities. The environment is a source of condition of existence and manifestation of inherited peculiarities, which can be termed as potential possibility of a body. At the same time

the environment may promote the formation of new peculiarities having constitutional significance. It is well known for instance, that infection and/or intoxication, avitaminosis and radiation can considerably change the make up of the body, its reactivity and resistance. Such pathological influence is especially harmful at the stage of intrauterine development and in childhood. Beyond doubt, the social and hygienic factors, as every day conditions, work-site conditions, food habits, etc. have a special significance for a man.

Hippocrates offered the first constitutional classification. He attracted his attention at the differences existing in various people, which reflected peculiarities in temperament and social behavior. Precisely these observations were assumed by Hippocrates as the basis for his classification. They were **choleric, sanguine, phlegmatic and melancholic types** according to Hippocrates' terminology, this ancient typology exists up to the present time. Choleric personality is impetuous, easily irritated and angered, sometimes uncontrollable. His workability is high, but not constant. Sanguine personality is communicable, vivacious, lively, active, and emotional. Phlegmatic personality is calm, apathetic, unexcitable, but stable. Melancholic personality is unsociable, sometimes depressed, and hesitating.

The ancient doctors have in general noted some predispositions of one or the other personality type to certain diseases and tried to give people recommendations as to the rational behavior and life style. The sanguine personality has a predisposition to fullbloodedness apoplexy, headache and diabetes mellitus. It is useful for such type to have bloodletting, which was so popular among the ancients.

One of the most, popular morphological classifications was made by ***Sigaud.*** Basing upon the pronounced development of one or the other physiological feature he differentiated the following four **constitutional types**: respiratory, digestive, muscular and cerebral. Sigaud belonged to the group of scientists who believed that main constitution is forming throughout his life, but mainly in the childhood and the process of training.

Kretschmer's classification is widely spread. He singled out three constitutional types: **athletic, asthenic and pyknic.** Kretschmer, being a psychiatrist by profession, attempted to connect the morphological peculiarities of a man not only with the specific character traits, psyche and temperament, but also with the mental disease morbidity. Among the schizophrenics one can meet the asthenic type more often than other

ones, while epileptics are encountered mainly among individuals of an athletic constitution; the pyknic type is spread among those patients who suffer from manic-depressive psychosis.

In the clinical practice ***M. V. Chernorutsky's*** classification has received acknowledgement in this country. Each of the constitutional type **(hyposthenic, hypersthenic and normosthenic types)** was given a characteristic from the standpoint of the main functions and metabolism. Thus, he indicates that a hyposthenic type has a low blood pressure and absorptive intestinal function, but metabolism is elevated. High blood pressure, slower metabolic processes, lower carbohydrate tolerance, slow matabolic waste excretion are characteristic for the hypersthenic type. This type also has a predisposition to obesity.

A. A. Bogomolets, a Ukrainian physician described leading significance to the connective tissue physiological system in the structural and functional peculiarities of the human body. Hence, he laid the active mesenchymal peculiarities as a basis for his classification of constitutional types. According to A. A. Bogomolets, the **asthenic type** is characterized by predominantly thin, tender connective tissue, **the fibrotic type** has a denser and more fibrillar connective tissue; **the lipomatous type** has an abundant adipose tissue, his mesenchymal elements have a leniency to fatty infiltration and to various decomposition of a lipoid character, and **pastly type** (from latin ***pastosus***) has a predominantly edematous, loose (friable) connective tissue.

I, P. Pavlov in classifying the humans and animals into constitutional types leaned upon the idea that the inner unity of all bodily parts, body reactivity and balance with the environment are insured by the central nervous system. The higher nervous activity. as it is known, is characterized by the following main peculiarities: the intensity of the stimulating and inhibiting processes, their agility and the balancing ability. From this stand point I. P. Pavlov singled out the following constitutional types: the strong, unstable excitable type, or unrestrained one (with intensive stimulation and inhibition processes, but with a relative prevalence of stimulation), the strong, stable lively (agile); strong, stable, composed or slow (inertia of the main nervous processes); weak (weakness of both stimulation and inhibition processes with a relative prevalence of inhibition).

For humans I. P. Pavlov suggested one more classification where he indicated the prevalence of the 1st or 2nd signal system. Depending on this prevalence there are discerned the reasoning and the artistic types.

When studying the constitutional types it becomes evident that the minority of people can be referred to pure types, the majority present transitional types. There were attempts to describe those transitional constitutional types, but up to the present the issue did not find its solution.

The significance of constitution was well understood by the ancient doctors. They knew of the stronger and weaker peculiar traits of every constitutional types. They have discovered, for instance, that the tall type had a predisposition to respiratory diseases, while the short stature type had a predisposition to apoplexy (status apoplexicus). For instance, in tuberculosis the primary infection does not depend on constitution, but for asthenics the course of the disease is more severe and lethal outcomes occur more often. Atherosclerosis and coronary disease are more often observed in pyknics. While gastric ulcer, hypertension, neurasthenia is characteristic of people with excitable type of the nervous system. It has also been noticed that the specificity of neurotic symptoms is connected with the constitution. For example, hysteria and depression are more common among the athletic pyknic types, while fear and anxiety are more common for asthenics.

At present the aim of the science is to study the nature of the established connections, which is probably genetically conditioned. Evidently one chromosomal locus controls simultaneously a group of features, which are morphological, functional and psychic. The mechanisms of environmental influence on constitution formation necessitate their investigation too.

The study of the most vulnerable sides of constitution makes it possible to prognose their traumatic consequences, to determine the disease predisposition, to prognose the disease course, to have an individual approach to the treatment course.

COMPREHENSION CHECK

Try to answer the following questions.

1. Define hereditary disease, hereditary predisposition and congenital (innate) disease.
2. Characterize different ways of the inheritance.
3. Describe chromosomal abnormalities and the main syndromes.
4. What is the role of constitution in pathology?
5. Name different types of constitution and their role in determination of disease predisposition, and prediction of the disease course.

UNIT 6

PATHOPHYSIOLOGY OF THE PERIPHERAL BLOOD CIRCULATION

Circulation in the peripheral vessels (small arteries, arterioles, metarterioles, capillaries, preferential channels, postcapillary venules and small veins) provides an exchange of water, electrolytes, gases, essential nutrients and metabolites in the system "blood — tissue — blood".

The most common forms of the local disturbances of microcirculation are arterial and venous hyperemia, ischemia, stasis, thrombosis and embolism.

ARTERIAL HYPEREMIA

Arterial hyperemia means increasing of an organ blood supply due to excessive blood inflow from arterial vessels.

It is characterized by the following ***functional changes and signs:***

— spread redness;
— dilatation of small arteries, arterioles, veins, capillaries;
— pulsation of small veins and capillaries;
— increasing of the number of function vessels;
— local hyperthermia,
— increasing of the volume of the region with hyperemia;
— increasing of the tissue turgor;
— increasing of the pressure in arterioles, capillaries and veins;
— speeding up of blood flow and intensifying of metabolism and organ function.

Pathogenesis

There are two types of arterial hyperemia recognized according to pathogenesis: neurogenic (of neurotonic and neuroparalytic type) and caused by local metabolic (chemical) factors.

Neurogenic arterial hyperemia was first reproduced by Clod Bernard by stimulation of chorda tympani — the branch of the facial nerve, containing ***parasympathetic vasodilating fibers.***

In a case if vessels don't have parasympathetic stimulation, hyperemia is caused by the ***sympathetic (cholinergic, histaminergic and p-adrenergic) system.***

Sympathetic cholinergic nerves dilate small arteries and arterioles of skeletal muscles, facial muscles, mucous membrane of the cheeks, intestine. Their mediator is also ***acetylcholine.***

In some cases hyperemia is caused by formation prostaglandins E and A (PGE, PGA), they have a vasodilating effect upon arterioles, metarterioles, precapillaries and venules.

Neurogenic arterial hypertension of the neuroparalytic type can be observed in clinic and experiment on animals after cutting the sympathetic a-adrenergic vasoconstrictor fibers and nerves.

Clod Bernard (1857) observed hyperemia and hyperthermia of the skin on a rabbit's head (ear) on the side of cutting the cervical node of the sympathetic trunk. Their mediator is norepinephrine.

The neuroparalytic mechanism of the arterial hypertension partially takes part in developing of inflammatory hyperemia, ultraviolet erythema, etc.

Local metabolic (chemical) factors are caused by:

1) reduction of $P0_2$ value in blood and tissues of vessels' walls;

2) increase of $PC0_2$;

3) excess of nonspecific metabolites and nonorganic ions (lactic acid, ATP, ADP, adenosine, local BAS as bradykinin, histamine, PGE, PGA, PGI_2, (x-aminobutyric) prostacyclin has a very strong antiaggregational effect upon platelets.

The outcome of the arterial hyperemia may vary. In the majority of cases arterial hyperemia is accompanied with speeding up of the metabolism and intensifying of organ's function. However, unfavorable outcomes are also possible. For instance, under atherosclerosis rapid dilation of a vessel can lead to its rapture and hemorrhage. Such phenomena are especially dangerous in the brain.

VENOUS HYPEREMIA

Venous hyperemia means increasing of organ or tissue blood filling due to inadequate venous drainage.

The causes of its development are the following:

1. Obstruction of veins with a thrombus or an embolus.

2. Compression by a tumor, enlarged uterus, in the region of inflammation by exudates, in kidneys under hydronephrosis.

3. Predisposition to venous hyperemia may be of a genetic nature (in some cases — weakness of venous elastic apparatus, low tonicity of the smooth muscle elements of the walls.

4. Professional peculiarities (vertical position for a long period of time).

5. Under right ventricle's failure, exudative pleuritis, hemothorax, pneumosclerosis, emphysema, left ventricle's failure.

The basic factors causing local changes under venous hyperemia is lack of oxygen (tissue hypoxia), it leads to disturbance of the tissue metabolism and causes atrophic and dystrophic changes and excessive growth of the connective tissue (cirrhosis).

The sequence of events of venous hyperemia:

1. Slowing of the microcirculation.
2. High hydrostatic pressure.
3. Increasing permeability of the wall of the vessels due to unoxygenated condition.
4. Transudate formation.
5. Increased viscosity of the blood.
6. Thrombosis.

The local clinical signs of venous hyperemia are:

1. The loss of temperature.
2. Enlarging of organs tissue region due to swelling.
3. Cyanosis as a result of hypoxia.

Pathogenesis

Congestion of capillary beds leads to intravascular thrombosis (mechanical factors). But weakness of venous elastic apparatus, inadequate development and low tonicity of the smooth muscle elements of the walls can be predisposing factors of venous hyperemia.

Consequences may be following:

1) Dystrophic changes of an organ or region.

2) Substitutive excessive growth of the connective tissue so called cirrhosis (in lung, liver, kidney).

Stasis

Stasis (from Greek "***stasis***" — remaining at the same place) is ***slowing down and stopping of blood flow*** in capillaries, small arteries and veins.

There are the following types of stasis distinguished: ***true*** (capillary) stasis, developing as a result of pathologic changes in capillaries or abnormality of reologic qualities of blood, ***ischemic*** stasis occurs in case of a total stop of blood inflow and venous stasis.

Venous and ischemic stasis is the consequences of simple slowing down and stop of the circulation. These conditions are caused by the same factors as venous hyperemia and ischemia. Venous stasis can result from compression of veins, occlusion with the clot or embolus, and the ischemic stasis — a consequence of a spasm, compression or occlusion of arteries. Elimination of the cause leads to restoration of normal circulation. However the progression of the ischemic and

venous stasis promotes the development of the true stasis.

Under the ***true*** stasis the blood in capillaries and small veins becomes still, homogenizes, erythrocytes swell and loose most of their pigment. Plasma together with the released hemoglobin escapes from the vessel. The tissues in the focus of capillary stasis show the signs of severe dystrophy and necrosis.

The ***cause*** of the true stasis can be physical (cold, heat), chemical (poisons, concentrated solution of sodium chloride or other salts, turpentine, mustard oil) and biological (toxins of microorganisms) factors.

The ***mechanism*** of the true stasis development is based on intracapillary aggregation of erythrocytes, meaning their adherence and formation of conglomerates, which make the flow difficult. This also causes increasing of the peripheral resistance.

Aggregation occurs as a result of changing the physical properties of erythrocytes plasmolemma under the direct effect of factors, entering the capillary. It turned out to be that the surface of erythrocytes, which is smooth under normal conditions, becomes "fuzzy".

A significant role in the pathogenesis of the true stasis belongs to slowing down due to thickening of blood and increasing permeability of capillary walls. This is promoted by etiological factors, causing stasis and metabolites, produced in tissues. A special significance in the genesis of stasis belongs to biologically active substances (serotonin, bradykinin, histamine), and also acidic shift of the interstitial medium and its colloid state. This results in increasing of vessels permeability and dilatation of vessels leading to thickening of blood, slowing down of blood flow, aggregation of erythrocytes and, consequently, to stasis.

Ischemia

Limiting or complete stop of arterial blood inflow is called ischemia.

Ischemia is characterized by the following signs:

1) paleness of the ischemic region;
2) hypothermia;
3) paresthesia (disturbance of sensibility, feeling of numbers, tingling);
4) pain (ischemic pain is very strong);
5) slowing down of the blood flow;
6) diminishing of organ's size;
7) disturbance of an organ or tissue's function;
8) dystrophic changes.

Etiology

Various agents can cause ischemia:

1) compression of an artery by ligature, cicatrix, tumor, foreign

body, etc.;

2) obstruction of its lumen by thrombus or an embolus;

3) functional disturbance — angiospastic types of ischemia.

Angiospastic ischemia develops as a result of stimulation of vasoconstrictor apparatus of vessels and their reflex spasm caused by

1) emotional factors (fear, pain, rage);

2) physical factors (cold, injury, mechanic stimulation);

3) chemical agents;

4) biological factors (toxins of bacteria).

Angiospastic ischemia can have a conditioned reflex nature.

Pathogenesis

Mechanism of ischemia developing depends on permeability of smooth muscle cells' membranes for Na^+, Ca^{2+}, K^+ and Cl- ions. Also the first place due to activation of neurogenous a-adrenergic, H-histaminergic, serotoninergic, dopaminergic mechanisms. Angiotensin II is one of the strongest vasoconstrictor substances. It directly effects smooth muscle cells causing their depolarization as a result of increasing of Na^+ permeability.

Na^+ ions accumulate in muscle fibers of vessels and increase their sensibility to vasoconstrictor substances — catecholamines, vasopressin and angiotensin.

Injury of endothelium takes away its ability to produce the relaxation factor that leads to increasing of spastic reactions.

The outcome of the ischemia is determined by the degree of oxygen starvation, which depends on:

a) the time of development;

b) type of ischemia, its duration, localization, condition of the collateral circulation, functional state of the organ or tissue.

Ischemia of vital organs (brain, heart) has more severe consequences than ischemia of kidneys, spleen, lungs. Skeletal muscles and especially connective tissue are more resistant to the conditions of ischemia due to a lower metabolism level in them.

Thrombosis

Thrombosis — is formation of clots, containing blood's elements, on the internal surface of vessels in a living organism.

The thrombi can be parietal (partially decrease vessel's lumen) and obstructing.

Depending on the components thrombi can be pale (which is formed out of platelets, leukocytes and a small amount of plasma proteins); red

(they contain erythrocytes) and mixed (they have alternating white and red layers).

The basic factors of clot formation are known as the Virchow's triad:

1. Injury of a vessel's wall (by mechanic factors, electric current, chemical, biological factors). These abnormalities also accompany atherosclerosis, hypertension and allergic process.
2. Disbalance between coagulation and fibrinolytic systems.
3. Slowing down of the blood flow and its abnormalities. It explains why thrombosis of veins occurs 5 times more often than that one of arteries.

Mechanism

The process of a platelet plug formation could be divided into two stages:

1. The cellular stage of coagulation of platelets.
2. The plasma stage of coagulation.

The cellular stage consists of changing of the membrane potential of a vascular wall; the change of platelets and other blood cells; increasing of the adherence and aggregation ability of platelets;
precipitation on the injured surface of vessels' endothelium (adherence) and sticking to each other (aggregation).

There are various aggregation stimulators (PGD_2, PGH_2, thrombin, serotonin, epinephrine PGI_2 (prostacyclin) norepynephrine). Shift of the ATP — ADP ratio to the increase of ADP content and as a result further and progressive increase of adherence and aggregation.

In normal flow the larger particles, such as white and red cells, occupy the central column, most rapidly moving axial stream. The smaller platelets are carried in more slowly moving laminar stream outside the central column.

In injury of endothelium white and red cells, platelets of blood activate electricity and steak to endothelium. Than various coagulant factors and thrombogenesis begins.

The thrombus may: (1) propagate and by its enlargement actually cause obstruction of some critical vessel; (2) give rise to an embolus; (3) be removed by fibrinolytic action; (4) become organized and possibly recanalyzed.

The main outcomes of thrombosis:

— aseptic (enzymatic, autolytic) lyses;
— organization (resorption, substitution with connective tissue);
— recanalization;

— septic (purulent) desintegration.

The septic outcome is especially dangerous because it may cause septicopyemia and formation of numerous abscesses in various organs.

The consequence of thrombosis may be a adaptation phenomenon (after mechanical injury) and caused by severe disturbance of circulation in the region of the plugged vessel (ischemia under thrombosis of arteries, congestion under thrombosis of veins). Development of necrosis (infarction, gangrene) is the terminal stage of thrombosis.

Embolism

An embolus is a detached intravascular solid, liquid or gaseous mass that is carried by the blood to a site distant from its point of origin. About 99% of all emboli arise in thrombi (thromboembolism). Rare forms of emboli:

— a fragment of bone or bone marrow;
— droplets of fat;
— air or gas:
— bits of tumor;
— foreign bodies such as bullets.

Inevitably emboli lodge in vessels too small to permit their further passage, resulting in partial or complete occlusion of the vessels.

Depending on emboli site of origin, emboli may come to rest anywhere. Thrombotic occlusion of pulmonary artery is the most common preventable cause of death in hospitalized patients. Whatever the underlying heart disease (myocardial infarction, rheumatic heart disease), arrhythmias increase the risk of embolisation.

COMPREHENSION CHECK

Try to answer the following questions.

1. Name the main disturbances of microcirculation, its functional peculiarities and clinical signs and mechanisms.
2. Define thrombosis and name the basic factors of clot formation.
3. Characterize embolism and the main forms of emboli.

UNIT 7

INFLAMMATION

Inflammation is a fundamentally protective response whose ultimate goal is to save the organism from both the initial cause of cell injury (microbes or toxins) and its consequences. Humans could not long survive injury without the protective responses of inflammation.

Inflammation is a typical pathological process, which causes different diseases (for example, gastritis, meningitis, nephritis, pneumonia, angina and others). It is the most numerous pathological process, which has perfected in evolution as a protective response. Different side of this process — own pathological and defense with various compensatory mechanisms are presented. Although inflammation and repair are basically defense mechanisms, they are potentially harmful. Indeed, an overactive inflammatory response (hypersensitivity) to a bee sting can cause death.

Inflammation has local and common breaches of biochemical, morphological, structural characters with functional and vascular changes. This components accounts for the classical signs of acute inflammation, written by Celsus:

1) heat (calor);
2) redness (rubor);
3) swelling (tumor);
4) pain (dolor).

A fifth clinical sign, loss of function (function laesa), later added by Virchov. Common clinical manifestations:

1) fever;
2) headache;
3) neutrophilia;
4) insomnia;
5) decreased appetite;
6) haemodynamic effects (chock).

Causes of inflammation:

1. Microbes and its toxin, parasites, viruses.

2. Environmental factors — ultraviolet rays of sunlight, X-rays, nuclear fission, radionuclides, Roentgen rays.

3. Chemical agents — alcohol and other drug abuse, medicine.

4. Mechanical trauma.

5. Thermal injury (thermal burns).

6. Electrical injury.

7. Ionizing radiation.

8. Tissue-destructive enzymes.

9. Activation of the B-cell system, as a result production of antibodies, some of which are directed against self-constitutions.

Inflammation has three major components, which are caused by various exogenous and endogenous stimuli. It is complex reaction with structural and vascular changes and increased function of connective tissue:

I. Alteration.

II. Vascular changes with emigration of the leukocytes and exudation.

III. Proliferation.

ALTERATION

There is primary and secondary alteration. When phlogogen (injuring factor) acts on the tissue, the first massive tissue destruction develops. Cell organelles progressively degrade and there is leakage of cellular enzymes. Consequences of these disorders increase metabolic processes ("the fire of metabolism"), local hypoxia and its result — acidosis (normal pH equals 7.34- 7.36; under acute inflammation — 5.6-6.0; under chronic inflammation — 6.0-7.5).

It induces lasting tissue damage (secondary alteration) and may also prolong inflammation because leakage of enzymes, chemical mediators and toxic carbooxygen breach metabolism. In the tissue osmotic and oncotic pressure increase, because developing acidosis stimulate those processes. Then the next phase of inflammation develops.

VASCULAR CHANGES (CHANGES IN MICROCIRCULATION)

The vascular phenomena and changes in microcirculation (it involves arterioles, precapillaries, capillaries, venules) breach local blood circulation. It is a very important phase because increased blood flow to the injured area and opening of capillary beds form exudates and its stimuli to phagocytosis and repair. Changes in vascular flow and caliber begin very early after injury and develop at varying rates, depending on the severity of the injury.

The changes occur in the following order:

1. ***Vasoconstriction*** of arterioles, lasting a few seconds (it occurs very rapidly). The mechanism is connected with binding to receptors of

sympathetic nervous system and released adrenalin (noradrenalin), which at ones degraded.

2. ***Arteriole hyperemia*** (arteriole dilatation) is the longest phase, because it accounts for sustained not only nervous but humoral stimuli.

The first involves the arterioles and then results in opening of new microvascular beds in the area. Thus there comes about increased blood flow and the cause of the heat (calor) and the redness (rubor). This is by far the most common mechanism of vascular leakage and is elicited by histamine, bradykinin, H^+-ions, and virtually all other chemical mediators.

3. ***Venous hyperemia*** — venular dilatation is characterized by following signs: (1) slowing of blood circulation; (2) high hydrostatic pressure; (3) increased permeability by mediators of inflammation; (4) the outflow of protein — rich fluid into the extravascular tissue (edema, the local sign is swelling); (5) increased viscosity of blood; (6) concentration of red cells in small vessels; (7) platelet adhesion as a result of endothelial cell detachment; (8) thrombosis (dilated small vessels packed with red cells); (9) prestasis.

4. ***Stasis*** — it is the last phase of the vascular changes.

Emigration of Leukocytes. Phagocytosis

Under venous hyperemia the process of so-called leukocytic margination starts: leukocytes, principally neutrophils, stick to the endothelium due to the lowering electric potential, at first transiently, then more avidly, and soon afterwords they migrate throughout the vessel's wall into the interstitial tissue — the process called emigration.

Cellular events: leukocyte emigration and phagocytosis.

A critical function of inflammation is the delivery of leukocytes to the site of injury. Leukocytes kill bacteria and other microbes and degrade necrotic tissue and foreign antigens. Unfortunately, leukocytes may also prolong inflammation and induce tissue damage by releasing enzymes, chemical mediators and toxic oxygen radicals.

The sequence of events in the leukocyte journey can be divided as following:

1. Margination, rolling, and adhesion.
2. Emigration toward a chemotactic stimulus.
3. Phagocytosis and intracellular degradation.
4. Leukocyte activation with extracellular release of leukocyte products.

Margination, rolling and adhesion. In normally flowing blood erythrocytes and leukocytes are confident to a central axial column, leaving a cell-poor layer of plasma in contact with endothelium. As blood flow slows early in inflammation (as a result of the increased vascular permeability) white cells fall out of the central column, tumble slowly and roll along the endothelium of venules, and finally rest at some point where they adhere. The initial process is called margination and in time the endothelium appears to be virtually lined by white cells, a phenomenon called pavementing. When the leukocytes adhere, they resemble pebbles or marbles over which a stream runs without disturbing them. This process of leukocyte-endothelial adhesion is a necessary prelude to all the subsequent leukocytic events.

Chemical mediators such as interleukin stimulate leukocyte adhesion and expression on endothelial cells "an endothelium — dependent effect".

Emigration and chemotaxis. Following adhesion leukocytes move along the endothelial surface, ***insert*** pseudopods into the junction between the endothelial cells squeeze through interendothelial functions, and assume a position between the endothelial cell and the basement membrane. Eventually they traverse the basement membrane and escape into the extravascular space.

Neutrophils, monocytes, lymphocytes, eosinophils and basophils use the same pathway.

In most types of acute inflammation, neutrophils emigrate first and monocytes later. In the first 24 to 48 hours most acute inflammatory infiltrates are predominantly neutrophilic. By 48 hours, however, monocytes take over, owing to three factors:

1. Short-liver neutrophils disintegrate and disappear after 24 to 48 hours, whereas monocytes survive longer.

2. Monocyte emigration is sustained long after neutrophil emigration.

3. Chemotactic factors for neutrophils and monocytes are activated at different phases of the response.

Both exogenous and endogenous substances can act as chemotactic agents for leukocytes, among them (1) soluble bacterial products; (2) components of complement system; (3) arachidonic acid (AA) and its product leukotriene (result disorders metabolism).

But how does the headless leukocyte "see" or "smell" the chemotactic agents and how do these diverse substances actually induce

directed cell movement? Although not all the answers are known, several important steps and second messengers are recognized.

Binding of chemotactic agents to specific receptors on the cell membranes of leukocytes results in activation of phospholipase C (mediated by a unique G protein) and may release calcium (intra- and extracellular). It is the increased cytosolic calcium that triggers the assembly of contractile elements responsible for cell movement. It also activates phospholipase A_2, which as we shall see converts membrane phospholipids to arachidonic acid. In addition, prostoglandin D and through its activation of protein kinase C, is involved in various phases of leukocyte activation, degranulation, and secretion, which occur when these is a very strong chemotactic stimulus or during phagocytosis.

Phagocytosis consists of recognition and attachment of the particle to be ingested by the leukocyte.

Opsonins, which bind to specific receptors the leukocytes, and other fragment of complement generated by immune or nonimmune mechanisms.

Pseudopods flow around the object to be engulfed, eventually forming a phagocytic vacuole. The vacuole then fuses with the limiting membrane of a lysosomal granule, resulting in discharge of the granule's contents into the phagolysome and degranulation of the leukocyte.

The ultimate step in phagocytosis of bacteria is killing and degranulation. Bacterial killing is accomplished largely by reactive oxygen species.

Microbes can also be killed by non oxygendependent substances in the leukocyte granules, including bacterial permeability — increasing (BPI) protein, lysozyme, lactoferrin, and a group of newly discovered arginine-rich cationic peptides called defensins.

The pH of the phagolysosome drops to between 4 and 5 after phagocytosis, allowing acid hydrolases to degrade the dead microorganisms.

Summary of the Acute Inflammatory Response

The vascular phenomena are characterized by increased blood flow to the injured area, resulting mainly from arteriolar dilatation and opening of capillary beds. ***Increased vascular permeability results*** in ***the collection of protein-rich extravascular fluid, which forms the exudate.*** Plasma proteins leave the vessels, either through widened interendothelial cell junction of the venules or by direct endothelial cell

injury. The leukocytes, predominantly neutrophils, first adhere to the endothelium via adhesion molecules, then leave the microvasculature and migrate to the site of injury under the influence of chemotactic agent.

Phagocytosis of the offending agent follows, which may lead to the death of the microorganism. During chemotaxis and phagocytosis activated leukocytes may release toxic metabolites and proteases extracellularly, potentially causing endothelial and tissue damage.

Kinds of Inflammation

Serous inflammation is marked by the outpouring of thin fluid that, depending on the site of injury, is derived from either the blood serum or the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities.

Fibrinous inflammation — it's a result of greater vascular permeability, larger molecules pass the vascular barrier. A fibrinous exudate is characteristic for inflammation in body cavities, such is the pericardium and pleura. Fibrinous exudates may be removed by fibrinolysis, and other debris by macrophages. This process called ***resolution,*** may restore normal tissue structure, but when the fibrin is not removed it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring. Conversion of the fibrinous exudate to scar tissue (organization) within the pericardial sac will lead either to opaque fibrous thickening of the pericardium and epicardium in the area of exudation or, more often, to the development of fibrous strands that bridge the pericardial space. It is evident, that fibrinous exudation may have more serious consequences than serous exudation.

Purulent inflammation (suppurative) is characterized by the production of large amounts of pus or purulent exudate.

A common example of an acute suppurative inflammation is acute appendicitis, abscesses. Abscess has a central region that appears as a mass of necrotic white cells and tissue cells. There is usually a zone of preserved neutrophils about this necrotic focus, and outside this region vascular dilatation and parenchymal and fibroblastic proliferation occur, indicating the beginning of repair. In time, the abscess may become walled off by the connective tissue that limits further spread. Furuncle, carbuncles — purulent inflammation (called cellulitis) tends to track rapidly through large areas of tissue such as the whole arm, the face, or the abdominal wall.

Pathogenesis

The mechanism of inflammation development depends in different

chemical mediators, which can by released by microbes, or macrophages, or killed cells. There are various clinical and morphological effects of such mediators (Fig. 4), (Table 4, 5).

Repair — Proliferation

After leukocyte emigration and phagocytosis repair begins — endothelial cells proliferate and form new blood vessels ***(granulation tissue).*** Death "gives birth" to life. For the life threading loss of fluid, the endothelial cells differentiate and form intercellular junction — it's characteristic for healing inflammation (Fig 5).

During repair, endothelial cells proliferate and form new blood vessels (granulation tissue). These capillary sprout remain leaky until the endothelial cells differentiate and form intercellular junctions, accounting for the edema characteristic of healing inflammation.

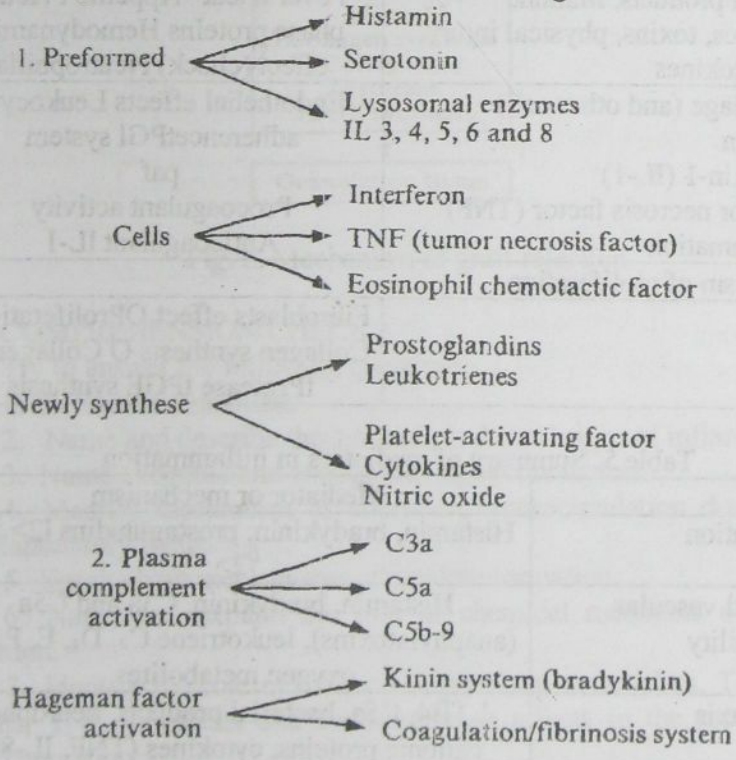

Fig 4. Chemical mediators of inflammation

It should be noted that outcomes of acute inflammation depend on the nature and intensity of the injury, the site and tissue affected and the

ability of the organism to defence. Acute inflammation generally has one of 4 outcomes:

1. **Complete resolution** involves neutralisation or removal of the chemical mediators.

2. **Scarring or fibrosis** happens when inflammation occurs on tissues that don't regenerate.

3. **Abscess formation** may occur in the setting of certain bacterial of fungal infections.

4. **Progression to chronic course.**

Table 4. Major effect of interleukin-1 (IL-1) and tumor necrosis factor (TNF) in inflammation

Mediators	Acute phase reaction
Bacterial products, immune complexes, toxins, physical injury, other cytokines	Fever tHeat ^Appetite t Acute phase proteins Hemodynamic effect (chock) Neutrophilia
Macrophage (and other cell) activation Interleukin-1 (IL-1) and tumor necrosis factor (TNF) in inflammation	Endothelial effects Leukocyte adherencetPGI system paf Procoagulant activity Anticoagulant IL-1
Mechanism of proliferation	
–	Fibroblasts effect OProliferation f Collagen synthesis O Collagenase fProtease tPGE synthesis

Table 5. Summary of mediators in inflammation

Event	Mediator or mechanism
Vasodilation	Histamin, bradykinin, prostaglandins I2> ^{E}2> ^{D}2>
Increased vascular permeability	Histamin, bradykinin, C3a and C5a (anaphylatoxins), leukotriene C_4, D_4, E, PAF-oxygen metabolites
Chemotaxis	LTB4, C5a, bacterial products, neurophil cationic proteins, cytokines (TNF, IL-8)
Fever	IL-1, TNF (tumor necrosis factor)
Pain	PGE_2 bradykinin, histamine
Tissue damage	Oxygen free radicals, lysosomal enzymes

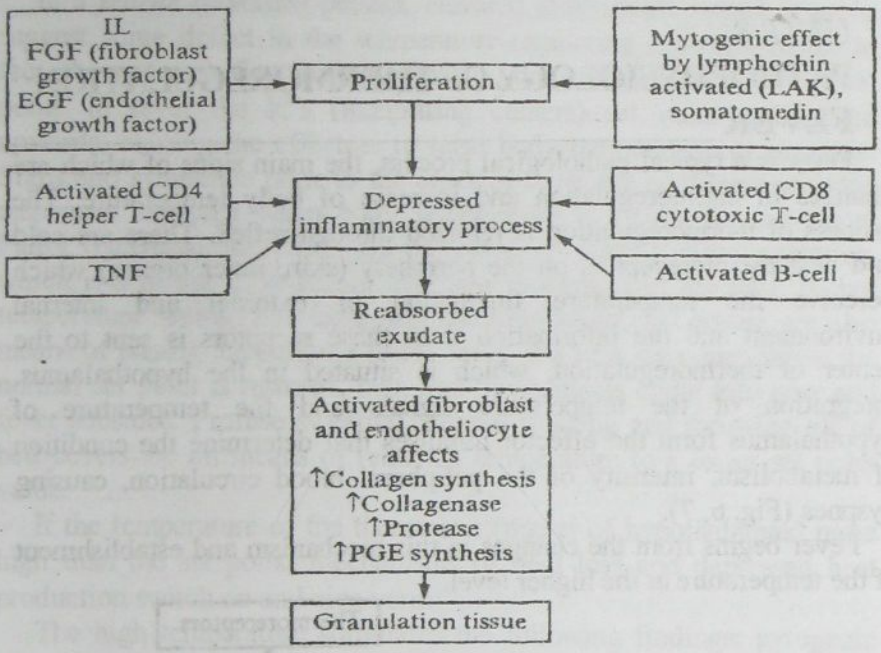

Fig. 5. Mechanism of graft rejection

COMPREHENSION CHECK

Try to answer the following questions.

1. Define inflammation.
2. Name and describe the systemic and local signs of inflammation.
3. Name exogenic and endogenic flogogenic factors.
4. Identify mechanism of alteration, microcirculation disorders in inflammatory focus.
5. Speak about mechanisms of exudate formation.
6. Name and explain the role of chemical mediators of inflammation.
7. Identify the role of mast cells, platelets, neutrophils, T-cells, B-cells, TNF, fibroblast and endotheliocyte affects in the repair under inflammation.

UNIT 8

PATHOPHYSIOLOGY OF THERMOREGULATION

FEVER

Fever is a typical pathological process, the main signs of which are changes in thermoregulation and increase of body temperature. The process of thermoregulation is realized through reflex. There are cold and heat thermoreceptors on the periphery (skin, inner organs) which perceive the temperature fluctuation of external and internal environment and the information from these receptors is sent to the center of thermoregulation, which is situated in the hypothalamus. Integration of the temperature signals and the temperature of hypothalamus form the effector impulses that determine the condition of metabolism, intensity of the peripheral blood circulation, causing dyspnea (Fig. 6, 7).

Fever begins from the changes in this mechanism and establishment of the temperature at the higher level.

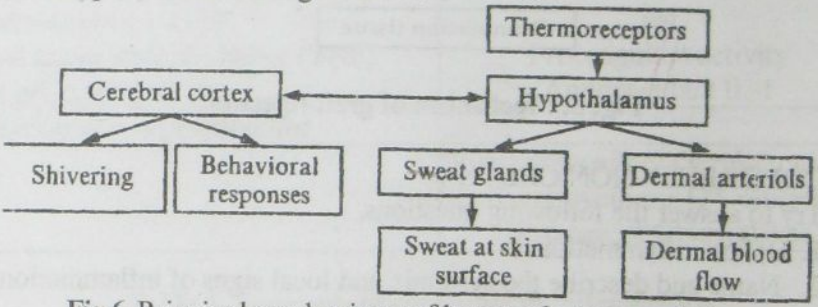

Fig 6. Principal mechanisms of human thermoregulation

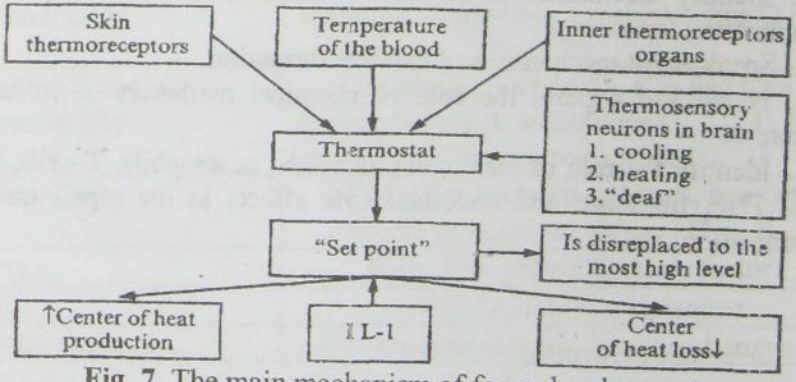

Fig. 7. The main mechanism of fever development

In a ***febrile*** (feverish) patient, elevated temperature would seem to suggest some defect in the temperature-regulating control system. In fact, the system is functioning normally, but on the basis of a new set point. In fever the IC's (integrating centers) set point is adjusted upwards, causing the effectors to raise body temperature in response. Signs and symptoms prior to the onset of fever are consistent with the responses expected when body temperature is below the set point. Pallor (paleness) and chills are the result of dermal vasoconstriction, which is a means of reducing heat loss in support of the new, higher temperature setting. Shivering and huddling under bed covers are also means of raising temperature to the level of a new set point. When the normal set point is restored, heat loss mechanisms come into play and fever subsides. Profuse sweating, dermal flushing and throwing off of bed covers are all means of reducing temperature to a lower set point value.

If the temperature of the thermostat (nuclei of hypothalamus) more high than the set point, mechanisms of heat loss and depressed heat production switch on and vice versa.

The high temperature stimulates the following findings: pyrogenic effect, doziness, leukocytosis, depressed nervous system, myalgia, decreased appetite.

Etiology of Fever

There are two causes of fever: infectious and non-infectious. In the process of evolution fever was first of all considered as a response to penetration of microorganisms and their toxins in the human body. At the same time it is well known that fever develops because of the penetration of substances which are not infectious. For example: substances that can get in to the human body at the time of blood transfusion, or paranteral feeding or proteins introduction.

Pyrogenic substances can cause fever. By their origin pyrogens are divided into exogenous (bacterial, non-bacterial) and endogenous (leukocytic).

By mechanism of action — primary and secondary.

Primary pyrogens on penetrating into the human body do not cause ***fever.*** They induce cells of the body to produce special protein substances (secondary pyrogens), which, in their turn act on the thermoregulatory mechanism, which produces fever. Primary pyrogens present bacterial toxins which penetrate into the human body together

with microorganisms, which are mostly taken from endotoxins. It stimulates chemotaxic reaction of the neutrophils, which release endotoxins. These endotoxins consist of three parts — two polysaccharide ones and a lipoid one. This lipoid part (lipoid A) can cause intoxication and fever. For example 0,0001 mcg/kg of endotoxin can cause fever in rabbits.

Pathogenesis

The main stage of pathogenesis is producing secondary pyrogens under the influence of primary pyrogens (Fig. 8). This process takes place in macrophages (both fixed and active) and neutrophilic granulocytes. Synthesis of secondary pyrogens was conducted ***in vitro.*** We add primary pyrogens to leukocytic culture, some time later we can find such substances in the cultured fluid that after injecting into the body it produces fever. Recently it was proved that interleukin-1 causes not only pyrogenic effect, but also many others. Synthesis of the secondary pyrogens is coded in a genome of leukocytes. Biosynthesis of pyrogens begins after the primary pyrogens acting on them. The primary pyrogens act with the help of receptors, which are situated on the cellular membranes or by penetration of toxin inside (phagocytosis, pinocytosis). The results of contemporary investigations show that macrophagic in flammatory protein-1-2 — is an endogenic pyrogen. This protein has an ability to be found with heparin.

Peculiarities of this pyrogen to cause fever is not connected with t ie activity of cyclooxygenase. That is why this kind of fever is not stopped by acetylsalicylic acid or other non-steroid anti-inflammatory agent, that reduce activity of cyclooxygenase (enzyme that tikes part in the formation of prostaglandins El and E2). Necrosis factor of the tumors is related to the endogenic pyrogens. It has been proved, that pyrotherapy in connection with chemo- and radiotherapy could delay the tumour growth. In 1898 Coley (a founder of American dynasty of surgeons) applied a mixture of bacterial nature. This mixture consists of enzymes of hemolytic streptococcus, i.e. streptokinase and streptodomase. After its parenteral injection, tumors begin to undergo destruction. Antigen stimulation became the reason of fever and then the formation of endogenic pyrogen was called the factor of tumor necrosis, which intensifies the cytolysis of malignant cells.

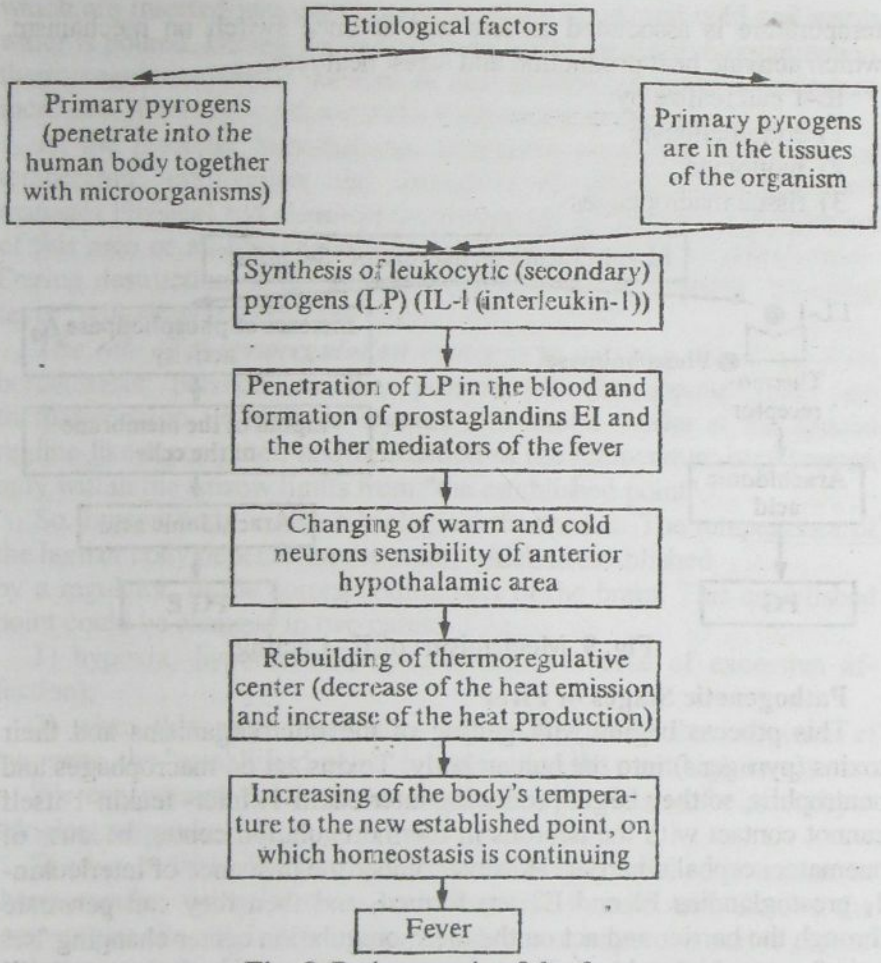

Fig. 8. Pathogenesis of the fever

Interleukin-1 is a protein with the molecular mass 14,000. It is secreted by macrophages at the time of their activation, then it influences specifically the systems of the human body. The target cells for interleukin-1 are: lymphocytes, hepatocytes, fibroblasts myocytes, sinoviocytes. It is possible, that there exist receptors for interleukin-1, located on the membranes of all those cells. So the output of interleukin-1 causes not only an increase in temperature but also engages the systems of the human body into the process (Fig. 9).

Group PG depressed sensitivity of the neurons of set point to impulses of thermostat. As result may be situation when normal

temperature is associated as less and at once switch on mechanism, which activate heat production and arrest heat loss.

IL-1 can realize by:

1) endotheliocyte
2) monocyte
3) tissue macrophages

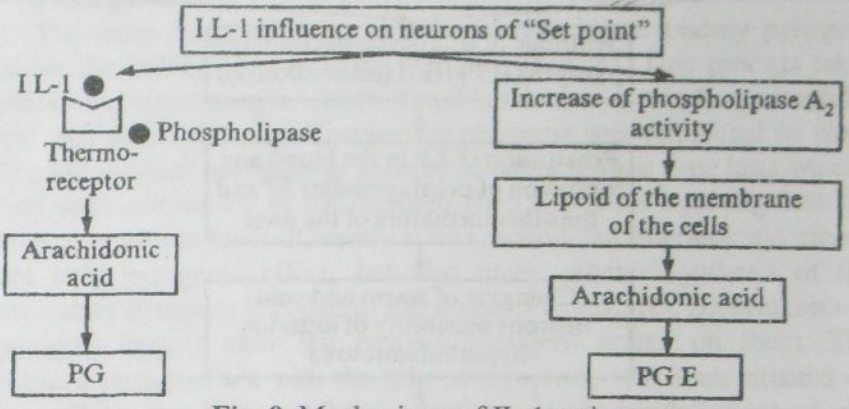

Fig. 9. Mechanisms of IL-1 acting

Pathogenetic Stages of Fiver

This process begins with getting of the microorganisms and their toxins (pyrogens) into the human body. Toxins act on macrophages and neutrophils, so they begin producing interleukin-1. Inter- leukin-1 itself cannot contact with the neurons in thermoregulation center, because of haematoencephalic barrier. However, under the influence of interleukin-1, prostoglandins El and E2 are formed, and then they can penetrate through the barrier and act on the thermoregulation center changing "set point" onto a higher level. The temperature of human body increases till interleukin-1 is synthesized.

Centers of Thermoregulation and their Part in the Development of Fever

Hypothalamic area is the most important center of thermoregulation, but the other parts of the central nervous system from segment centers of the cerebral cortex, spinal cord take part in thermoregulation. It has been established that thermosensible neurons (cold and heat) are situated before visual area of anterior hypothalamic area. The information from the peripheral (superficial and deep) thermoreceptors gets to anterior hypothalamic area. This area is very sensible to the temperature changes, this we can prove by using of special methods,

which are inserted into certain centers of the brain, and cold and warm water is poured. During the use of warm water we observe organization thermoregulation that is directed at heat generation, rectal temperature increases. If we take cold water the temperature decreases.

At the posterior hypothalamic area there occurs an integration of temperature information and formation of effective stimulus that manages physical and chemical thermoregulation. In case of destruction of this area or all hypothalamus animals become to be poikilothermal. During destruction of the anterior hypothalamic area ability "to make fever" will recover some time later.

The role of thermoregulation center is to preserve the temperature homeostasis balance in the process of thermoproduction and thermoemission. It happens because this center works at the special regime like a computer, and fluctuation of the temperature may happen only within the narrow limits from "the established point".

So, human body is like a biological thermostat. The temperature of the human body depends on the point, which is established by a regulator, in the corresponding part of the brain. This established point could be changed in two cases:

1) hypoxia, hypothermia, hyperthermia (in case of excessive affection);

2) when this mechanism does not work (under the influence of pyrogens, the "established point" is replaced to the most high level).

We can present the fever mechanism on the basis of electrophysiological researches.

There are three kinds of neurons in the hypothalamic center of thermoregulation: sensitive to heat, sensitive to cold and "deaf to the temperature change. It is possible, that the most important part is played by latter neurons. They generate signals of a standard character, which are the signal for comparing the thermosensory neurons. If the function of thermosensory neurons changes due to influence of pyrogen substances, the signal for comparing changes as well and hence the "established point" for temperature homeostasis is changed too.

This is other explanation of the established point formation. The established point is determined by the primary condition of the neurons function (cold- and heat-sensitive). With the help of special equipment it was found that due to the pyrogen influence the activity of cold-sensitive neurons increases, and heat-sensitive — decreases. So, the threshold of sensitivity of the thermoregulatory center is displaced to cold, and the normal body temperature is perceived like a decreased one.

In that case the path of thermoemission closes, the temperature of the human body increases and keeps at this level for some time.

But not only pyrogens take part in the formation of fever, but also hormones. They influence the center of thermoregulation, reorganize it the other way, increasing or decreasing its sensibility to pyrogens. Thyrotoxicosis with an infectious disease is accompanied with a higher temperature.

Glucocorticoids "brake" the development of fever. They inhibit the metabolic process in leukocytes.

Stages of Fever

There are three stages of fever. At the I stage (st. incrementi), the temperature of the body increases, the II stage (st. fastigii) it keeps at the increased level. The III stage (st. decrementi) decreases to the initial level.

The I stage: increasing of the temperature. The temperature increases because of adjusting of thermoregulation center. Heat producing is higher than heat dissipation. Heat dissipation decreases because of contraction of peripheral vessels, the decrease of blood flow to the tissues, inhibition of sweating, depression of evaporation.

Increasing of the heat producing can be achieved by activation of metabolism in the muscles (contracted thermogenesis), muscular tremor is connected with a spasm of peripheral vessels. Because of a decrease of blood flow the temperature of the skin decreases. Thermoreceptors are excited and the feeling of cold arises. At the same time with this process the non-contracted thermogenesis increases that is the heat formation in the organs like liver, lungs, bone marrow. This is the result of trophic action of nerves on the tissues due to which activation of enzymes occurs increasing consumption of oxygen and heat formation.

Heat producing takes place in muscles and visceral organs. There are two kinds of thermogenesis: contractive and non-contractive. The first one provides arbitrary muscular movement, muscular tremor and contraction of smooth muscles of the skin.

The second one provides metabolism, which depends on the action of hormones (catecholamines, triiodothyronine).

Heat dissipation is realized by:

1) heat convection (moving and mixing of the air around the body surface);
2) heat radiation;
3) heat conduction (heat emission during contact);
4) evaporation.

Heat dissipation is determined by the intensity of blood flow in the

vessels of the skin: for example, heat dissipation from the surface of the skin increases during conversion from cold to heat because of dilation of the microvessels and increase of blood flow. Evaporation has the most important part is humans. We can get convinced of high effectivity of heat dissipation in sweating from the next indices. A man may produce 10-12 l of sweat within 24 hours. In sportsmen during hard physical loading heat dissipation is realized through evaporation (75%), but 12-18% is performed by radiation and convection.

The II stage — a stable high level. After the temperature increase at the I stage it keeps at this level for some time (for hours or days). Heat dissipation is increased. The temperature does not increase. Heat dissipation occurs because of dilation of the peripheral vessels. The temperature keeps at the same high level, because of the leukocytic pyrogens. At this level the mechanism of thermoregulation is renewed. We distinguish the next kinds of fever according to the level of temperature increase.

a) subfebrile — 37-38 °C,
b) moderate — 38-39 °C;
c) high — 39-41 °C;
d) hyperpyretic — higher than 41°C.

The III stage is decreasing of the temperature. After the pyrogen action stops the thermoregulation center comes to its previous normal condition. The heat that accumulates in the body is relieved by sweating, frequent respiration and dilating of the skin vessels. Decreasing of the temperature can be lytic (few days) or critical. A critical decrease is very dangerous for the human body, it may cause a collapse. Pyrogens and fever are the stress factors and they cause activation of sympathoadrenal and hypophyseal-adrenal systems. IL-1 is one of the stress mediators, in opinion of some authors.

Activation of sympathoadrenal system and hypercatecholaminemia are significant during temperature increasing, because it causes redistribution of the blood, that helps to limit the heat dissipation (spasm of peripheral vessels).

Under the influence of pyrogens hypertrophy and hyperplasia of adrenal cortex occur because of intensive excretion of ACTH (adrenocorticotrophic) hormone and ejaculation of glucocorticoids into the blood. The level of these hormones increase earlier than we can register the temperature rise.

The Temperature Curves

The temperature curves at time of fever consists of three parts

increasing, keeping up at the high level and decreasing. But each of these parts can have their own peculiarity, which has a differential diagnostic meaning.

Biological peculiarities of the causative agent can influence the character of the temperature curve. For example cyclic development of causative agent in the blood. Biorhythms of fever depend not only on the causative agent, but also on the human body properties, possibilities of the patient's immune, nervous and endocrine, systems.

Types of Fever

1) Febris continua — morning-night fluctuation of the temperature is not higher than 1 °C (pneumonia, intestinal typhus).

2) Febris remittens — morning-night fluctuation of the temperature is 1.5-2.0 °C, but it does not get to the standard one (bacterial infection).

3) Febris intermittens — fluctuation is higher than 2.0 °C, but in the morning it gets to the standard and lower ones (lymphoma, wound infection).

4) Febris hectica — fluctuation of the temperature is from 3.0 to 6.0 °C (causative agent: sepsis, wound infection).

5) Febris reccurent — the temperature may fluctuate, from high to standard condition, and these periods of high and standard temperature can last from one to several days.

6) Febris typica is characterized by several rises and falls of the human body temperature during the day (causative agents: sepsis).

7) Febris ephemera is characterized by low increasing of the temperature for a short period of time (37.5-38.0 °C) with unstable morning-night fluctuation (chronic infectious disease).

8) The type of the temperature curve is the "established point" for diagnosis and prognosis of the disease course.

Hyperthermia and its Difference from Fever

We should distinguish hyperthermia (heat stroke) from fever. The mechanisms of these conditions are absolutely opposite. Firstly, during hyperthermia the influence of pyrogens is absent and the increase of body temperature can be the result of an external action which limits heat dissipation or primary disturbance of the hypothalamus thermoregulation center.

The compensation in hyperthermia includes two ways:

1) overcoming the difficulties of heat emission;

2) preserving the heat homeostasis.

If the temperature of the environment is over 30 the process of heat transfer cannot go on by convection and radiation and this can be

carried on by evaporation of sweat and liquid from the respiratory tract.

Fever as a complex temperature and non-temperature reaction to interleukin-1. Fever is a pathologic process which involves not only the system of thermoregulation but other systems as well. This becomes clear when one takes into consideration that fever originates as a response reaction to infections. We can say that fever, inflammation and immunity (allergy) determine the response to the action of microorganisms. When a microorganism gets into the human body it produces a toxin (pyrogen) and macrophages produce interleukin-1 (as the response to the toxin). As it is evident interleukin-1 acts on:

1) T and B-lymphocytes and stimulates them to divide and produce antibodies;

2) hepatocytes and stimulates them to synthesize and secrete different proteins — fibrinogen, ceruloplasmin, C-reactive protein;

3) fibroblasts and they react by proliferation and synthesis of collagen. But in the muscles and chondrocytes interleukin-1 acts in the other way. In the muscles it causes proteolysis and in chondrocytes it intensifies the production of collagenase, cartilaginous tissue is destroyed.

Changing in Organs and Systems During Fever

There are a lot of nontemperature changes developing during the fever, such as, disorder of metabolism, cardiovascular and respiratory systems, secretory and excretory functions. A complex of conditions arise, it is very difficult to distinguish which of them depends on the influence of the pyrogen, interleukin-1 or on disease (pneumonia, infarct, hepatitis) that cause fever. In the blood system we can observe clear changes. Increasing of the temperature by 1 °C is accompained by a change of the pulse, that becomes more frequent (by 8-10 beats).

Tachycardia during fever depends on local heating of the sinoatrial node (cardial pacemaker) that is accompanied by more frequent heart contractions, as well as increasing of the tonus of sympathic nerves is very important. Stroke and minute volume of the blood are increased. At the first stage of fever arterial pressure can increase and contraction of the skin vessels and their dilation of the internal organs happens. At the III stage of the fever during a critical decreases of the temperature a collapse may be observed because of the lowering of arterial tonus. We point out that tachycardia does not always develop (during fever). In some infectious diseases bradycardia is observed at the same time (for example, in typhoid and relapsing fever).

The heart reacts not only to high temperature but also to the action

of exogenic and endogenic substances. External respiration is slowing down at the first stage of fever, then respiration becomes more frequent (when the temperature is at maximum). Deepness of respiration is lowering, so the pulmonary ventilation does not change. Disorder of respiratory rate occurs because of an increase in brain temperature, that causes polypnea (respiration becomes frequent).

Digestive system changes too. Salivation is oppressed (coated and dry tongue). Acidity and amount of gastric juice is lowering. But all these changes depend on the character of a disease. For example, during the flu these changes are less expressed, than during the typhoid fever. P. M. Veselkin supposes that all these changes in the digestive system depend on fever to a less degree, but more often on intoxication, non-thermal influence of bacterial toxins and starvation.

Fever is accompanied by changes in the endocrine system. We can observe signs of stress during hypophyso-adrenal glands activation.

Increasing of basal metabolism occurs during infectious fever, because of intensification of thyroid gland hormones. On the part of the central nervous system we can observe changes of excitation and inhibition processes. On EEG (electroencephalogram) we can observe the a-rhythm that is typical for inhibition of cerebral cortex. Basal metabolism during fever increases. Nitrogen balance is negative. Water-electrolyte metabolism changes too.

At the I stage of fever diuresis decreasing is observed because of increasing of arterial pressure and blood flow to internal organs. At the II stage the production of aldosterone increases and sodium stays too long in tissues, so does the water. At the III stage chlorides excretion decreases, sweat and water excretion increases.

Biological Significance of Fever

During the fever, as in other typical pathologic processes there are harmful and useful factors acting in connection with each other. Such causative agents as viruses, spirochetes, cocci cannot proliferate when the temperature of human body is increased. Many microorganisms can reproduce when the temperature of human body is 40 °C, but they lose their stability to fever drugs. Fever influences positively the functions of the organism: phagocytosis is increased, production of antibodies is stimulated formation of interferon is increased. Artificial suppression of the fever causes a decrease of neutrophils and macrophagal elements in the blood.

Fever and inflammation are connected with each other. Macrophagocytes are not only absorb bacterial but; also synthetize pyrogenic substances. We can add that macrophagocytes take part in

producing antibodies together with lymphocytes. Activation of hypothalamo-hypophyso-adrenal glands is very important because of the nonspecific resistance increase of the organism. Infectious diseases are accompanied by defence reactions of the human body, and these reactions may loose their importance because of intoxication development and injuries of vital organs.

Heat lowering (decrease) therapy is used for decreasing the temperature of the body during fever, inhibiting negative effects of high temperature on the life of the body. Lowering of temperature can be acquired with the help of medicines acting on:

1) thermoregulatory center;
2) process of heat production;
3) process of heat exchange.

The widely-used analgesics are acetylsalicylic acid (aspirin), amidopyrin. They inhibit the synthesis of prostoglandins of group B. The use of preparations of quinine may lower the process of heat production.

Pyrotherapy

There exists a method of treatment by artificially increased temperature of the body, with the help of pyrogenics, e.g. pirogen. It represents a polysacharide complex, secreted from cellular membranes of the gram-negative bacteria. Pyrotherapy is used for the intensification of the reparative processes after trauma, healing of cuts, in nervous diseases. Likewise nonspecific effects of pyrotherapy are used for the treatment of the sexually transmitted diseases (STD's), e.g. gonorrhea, late stages of syphilis.

COMPREHENSION CHECK

Try to answer the following questions.

1. What does fever mean?
2. What is etiology of fever?
3. Characterize the pathogenesis of fever.
4. Describe states of fever and types of temperature curves.
5. Name changes in organs and systems during fever.
6. Identify biological significance of fever and why pyrotherapy may be used as treatment method?

UNIT 9

PATHOPHYSIOLOGY OF THE IMMUNE SYSTEM

The immune system consists of the central (the bone marrow, the thymus, Fabricio's bursa in birds and its analogue in a human) and peripheral (the spleen, lymphatic nodes, the lymphoid tissue of the digestive system and tonsils) organs. Besides it has movable immunocytes-lymphocytes, which are transported by flow of blood and lymph. The main function of this system is to maintain antigenous homeostasis in the organism. The immune system provides fixation and the destruction of both infectious and non-infectious antigens thus fulfilling the protective function. The immune reactivity represents the ability of the organism to react to the action of the antigens by the cellular and humoral responses, which are specific with respect to the antigen. This ability is conditioned by two kinds of immunocytes — T (thymus-dependable) and B-lymphocytes. T-lymphocytes react to the antigen directly and accomplish the cellular immune reaction (Fig. 10). Under the influence of the antigen B-lymphocytes turn into the plasmatic cells, which produce immunoglobulin responsible for humoral immune reactions. Thanks to combination of mechanisms providing mutation and diversity of variable parts of the antibody, their recombination and potential polyvalency of immunoglobulins, the organism is capable of reacting to a large number of various antigens. A high degree of response to the antigen is provided by simultaneous development of the cellular humoral immune reactions of different types as well as by production of 100,000 molecules of antibodies per one molecule of the antigen. This effect is explained by cooperation of macrophagocytes, T- and B-lymphocytes, reproduction of the clone cells in stimulation by the antigen. With regard to potential antigens of its own organism, the immune tolerance (as specific tolerance reactivity) develops, which may be explained by the blockade of the immunity function by these antigens. The formation of tolerance is going on during the whole life. And as a result of gene mutations new clones of T- and B-lym- phocytes are formed which are capable of reacting to their own antigens. These cells of T-lymphocytes are eliminated in the thymus. But B-lymphocytes produced in the bone marrow and other organs of the immune system do not have such an opportunity as T-lymphocytes. Suppressed clones of B-lymphocytes

intolerant to the antigens of the organism remain uninhibited or are inhibited by the type of high dose tolerance (surplus of the antigen causes the blockade of its clone). It turned out that some part of B-lymphocytes of a healthy person is not tolerant to the antigens of the organism. But the autoimmune processes do not arise, for T-lymphocytes are tolerant to their antigen in the norm and B-lymphocytes are not stimulated by the antigen without T-helpers.

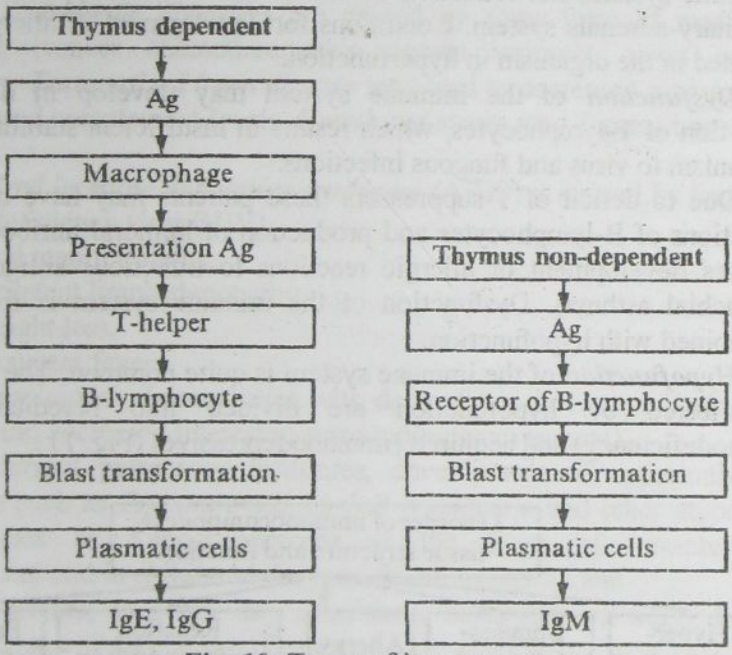

Fig. 10. Types of immune respons

COMMON REGULARITIES OF DISTURBANCES OF THE IMMUNE SYSTEM

The immune system possesses a number of peculiarities, which influence the development of pathologic processes in it.

1. High sensitivity to the effect of mutagens, cancerogens and cytostatics.

2. The cells of the immune system are specific antigens themselves, which may cause autoimmune processes.

3. Tolerance formation depends upon the contract with the antigen, the influence of which may disturb these processes, for example, induce

tolerance to the infectious antigen.

Function alteration of the immune system may be manifested as hyperfunction, dysfunction and hypofunction as well as tolerance changes to the antigens.

Hyperfunction of this system develops in overtension by the antigen, introduction of stimulators of the immune response onto the organism. Hyperfunction may be caused by inhibition reduction in the immune system, i.e. reduction of the function of the hypoth- alamus-pituitary-adrenals system. Conditions for development of allergens are created in the organism in hyperfunction.

Dysfunction of the immune system may develop in decreased function of T-lymphocytes, which results in insufficient stability of the organism to virus and fungous infections.

Due to deficit of T-suppressors these patients may have increased reactions of B-lymphocytes and production of humoral antibodies that causes development of allergic reactions to infectious antigens (e.g. bronchial asthma). Dysfunction of the immune system is frequently combined with hypofunction.

Hypofunction of the immune system is quite common. The diseases manifested by hypofunction are divided into hereditary (immunodeficiency) and acquired (immunodepressive) (Fig. 11).

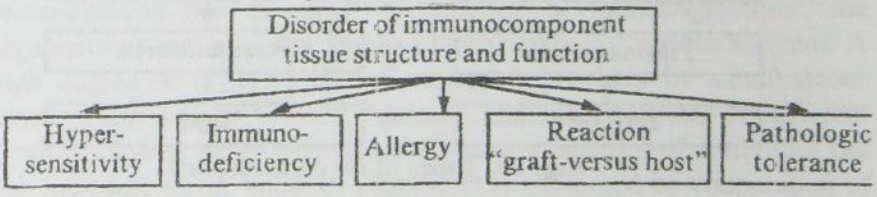

Fig. 11. Classification of the immune system pathlogy

THE MAIN IMMUNE DISORDERS SYNDROME

Inherited Forms

1. ***Primary immune deficiency*** (congenital) occurs if lymphocyte development is disturbed in the fetus or embryo or if there is a genetic anomaly.

As a result B-, T-cells lines may be partially deficient.

2. ***Severe combined immune deficiencies*** (SCID) occur when a common stem cell for all white blood cells is absent.

Therefore, T, B, phagocytic cells never develop. Most children may

die in utero or very soon after birth.

3. ***Di-George syndrome*** is a complete lack, or more commonly partial lack, of the thymus.

4. ***Bruton syndrome*** (agammaglobulinemia). The formation of all types of the plasmatic cells is blocked so that the number of IgA, IgM is 100 times reduced, B-lymphocyte and plasmatic cells are absent.

Acquired or Secondary Immune Deficiency

It is characterized by nutritional deficits in calorie, protein, vitamins and Zn. ***Yatrogenic disorders*** are caused by some form of medical treatment (cancer chemotherapeutic agents suppress blood cells formation. ***Traumatized burn disease*** may lead to decreased neutrophil function and complement levels. ***Emotional stress*** may depress immune response.

Acquired immune deficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV).

Clinical manifestations:

1. Persistent limphadenopathy.
2. Weight loss.
3. Recurrent fevers.
4. Neurological abnormalities with dementia in late stage (lack: of memory and decreased interest to surrounding environment).
5. Recurrent pulmonary infiltrates, development of opportunistic infections such as ***Pneumocystic carinii*** pneumonia and other atypical malignancies as Kaposi sarcoma at the stage of intrauterine development and in childhood. Beyond doubt, the social and hygienic factors, as every day conditions, conditions of work, food habits, etc., are of special significance.

COMPREHENSION CHECK

Try to answer the following questions.

1. Characterize immune response (humoral and cell-mediated).
2. Describe the forms of changes and disorders of immune system.
3. Characterize immunodeficiencies (congenital or primary immune deficiency).
4. Name causes and consequences of acquired or secondary immune deficiencies.
5. What is AIDS?

UNIT 10

ALLERGY

Allergy is a complex of breaches, appearing in our organism by the humoral and cellular immunological reactions. Both inflammation and allergy is a protective response against the exo- and endogenous factor.

The allergy *is the changed organism's reaction upon the antigens and non-antigens,* which leads to different disorders in the organism — the inflammation, bronchial spasm, necrosis, shock and others.

Allergens are divided into exo- and endogenous.

Exogenous:

— bacterial;
— vegetable;
— medicinal drugs;
— food;
— everyday chemical compounds (e.g. perfume and oth.);
— dust, pollens.

Endogenous are divided into natural (autoallergens) and acquired.

Autoallergens:

— gray matter of the brain;
— lens;
— thyroid glands;
— CNS myelin;
— acetylcholine receptors — peripheral nervous system;
— adrenals, testes;
— glomerular basement membraine;
— salivary glands.

Acquired endogenous allergens (antigens) are classified as follows (see fig. 12):

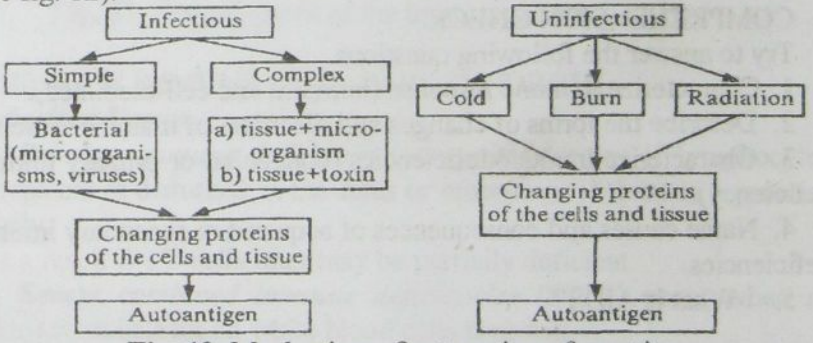

Fig. 12. Mechanism of autoantigen formation

Pathogenesis of Allergy by A. D. Ado

There are three stages of allergic reaction.

The immunological stage, when the antigen enters the organism; antibodies are forming and then organism's sensitivity increases. If such an antigen gets into the organism again, the allergic reactions will develop.

The first entrance of allergen is called sensibilizing, and the next one — resolving.

The pathochemical stage consists in the forming or activation of biologically active substances (BAS).

Complex Ag + Ab is circulating in blood and then it catches up different cells of our organism, and neutralization, precipitation, agglutination, complement fixation, lysis, immobilization, etc. take place. In this stage many various biologically active substances (BAS) are released (Fig. 13, 14, 15, 16; Table 6).

The pathophysiological stage (clinical manifestations). If immune-mediated tissue injury release of vasoactive amines, vasodilatation and edema develop. Activation of the complement and reticuloendothelial system, smooth muscle constriction, irritation of high and peripheral nervous system are determined. The pathophysiological stage is accompanied by numerous clinical manifestations as cutaneous swelling (skin allergy), nasal and conjunctival discharge (allergic rhinitis and conjunctivitis), high fever, bronchial asthma, allergic gastroenteritis (food allergy), polyarteritis nodosa, systemic lupus erythematosus, scleroderma, dermatomyositis. rheumatoid arthritis and its variants.

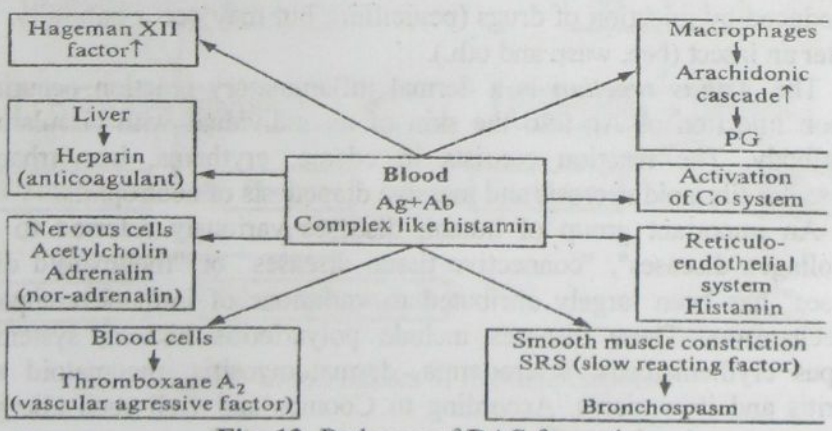

Fig. 13. Pathway of BAS formation

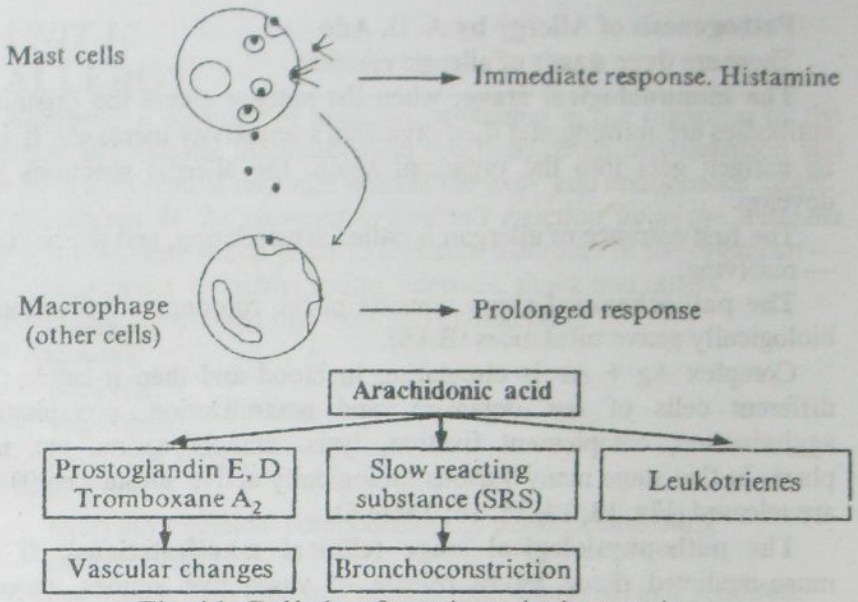

Fig. 14. Cellular functions in immunity

Anaphylactic shock may occur in atopic individual after either systemic or local exposure to allergen. *Systemic vascular dilatation is prominent, with increased permeability of small vessels, leukopenia, fall in temperature and decreased serum complement levels. Death may result from hypotension or from obstruction and edema of the upper respiratory tract.*

Acute systemic anaphylaxis in humans is usually iatrogenic, that is, produced by injection of drugs (penicillin), but may occur naturally, as after an insect (bee, wasp and oth.).

The ***Arthus reaction*** is a dermal inflammatory reaction occuring upon injection of Ag into the skin of an individual with circulating antibody. The reaction consists in edema, erythema, hemorrhage, vascular fibrinoid necrosis and massive diapedesis of neutrophils.

An important group of human diseases variously referred to as "collagen diseases", "connective tissue diseases" or "rheumatoid diseases" has been largely attributed to variations of immune complex mechanisms. These diseases include polyarteritis nodosa, systemic lupus erythematosus, scleroderma, dermatomyositis, rheumatoid arthritis and its variants. According to Coombs and Gell such allergic diseases can develop in the way, presented in Table 7.

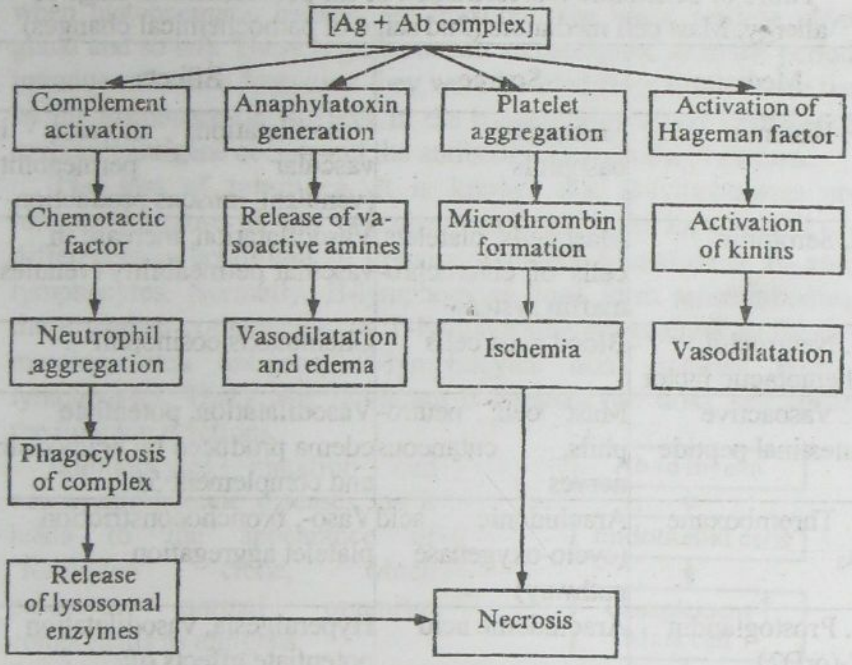

Fig. 15. Schematic representation of the pathogenesis of immune complex — mediated tissue injury

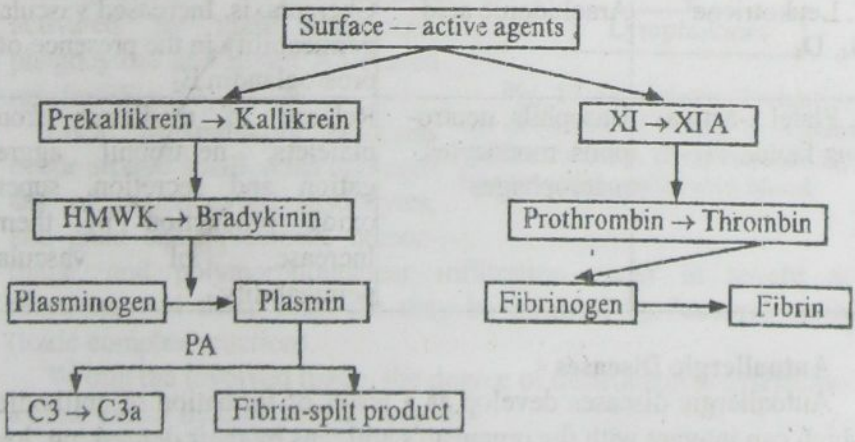

Fig. 16. Blood factors of immune response

Table 6. Schematic representation of the pathochemical stage of allergy. Mast cell mediators (2nd stage of pathochemical changes)

Mediator	Source	Effects
1. Histamin	Mast cells, basophils	Vasodilatation, increase in vascular permeability (venules), muscus production
2. Serotonin	Mast cells, platelets, cells of enterochromaffin system	Vasodilatation, increase in vascular permeability (venules)
3. Neutrophil, chemotactic factor	Blood mast cells	Chemotaxis eosinophil
4. Vasoactive intestinal peptide	Mast cell, neutrophils, cutaneous nerves	Vasodilatation, potentiate edema produced by bradykinin and complement 5a
5. Thromboxane A_2	Arachidonic acid (cyclo-oxygenase pathway)	Vaso-, bronchoconstriction, platelet aggregation
6. Prostoglandin E_2(orD2)	Arachidonic acid	Hyperalgesia, vasodilatation potentiate effects of: a) histamine b) bradykinin c) leukotriene
7. Leukotriene B_4, D_4	Arachidonic acid	Chemotaxis. Increased vascular permeability in the presence of prostoglandin E_2
8. Platelet-activating factor	Basophils, neutrophils, monocytes, macrophages	Release of mediators from platelets, neutrophil aggregation and secretion, superoxide production by them. Increase of vascular permeability

Autoallergic Diseases

Autoallergic diseases develop as a result of formation of antibodies which can interact with the organism's antigens by their demasking, loss of tolerance and somatic mutations.

Antigenous demasking is observed in highly-differentiated organs,

when histohaematic barriers are impaired (the brain, testicle, thyroid gland and so on). These organs contain autoantigens, as in the period of immune tolerance formation they were isolated from the immune tissue by the histohaematic barriers. In the barriers impairment demasking of such autoantigens occurs and the antibodies form in the organism.

The loss of tolerance. It is known, that B-lymphocytes aren't tolerant to most of the organism antigens. It is explained by the differences in conditions of immune tolerance formation of B- and T-lymphocytes. Normally, B-lymphocytes don't form autoantibodies to the organism components, as T-lymphocytes are tolerant to them. On meeting such antigens, T-lymphocytes don't interact with B-lymphocytes. That's why intolerant B-lymphocytes don't participate in the immune reactions.

Immunocytes mutation can cause autoimmune diseases, as it leads to the appearance of "forbidden" clone, which perceives normal organism components as antigens.

Sensitized lymphocytes move into white matter with myelin antigen, and release lymphocyte mediators. Macrophages, attracted and activated by these mediators, phagocytose and digest Ab-coated myelin*(Fig. 17).

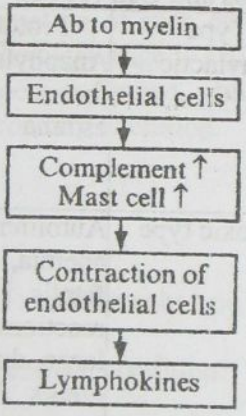

Fig. 17. Schematic illustration of the sequence of events in traumatic syndrome when encephalogenic protein (myelin) passes into blood

Local inflammatory reactions occur around small veins and consist of lymphocytes, histiocytes, and giant cells. Necrosis, hemorrhage, and polymorphonuclear infiltration occur in severe acute reactions, and these reactions may be initiated by humoral antibody (toxic complex reaction).

Within the involved tissue, the degree of destruction is determined to a great extent by blood-tissue barriers.

Antibodies and sensitized cells may act synergistically or antagonistically in the autoimmune process.

If zones of demyelination are large, fibrosis will occur and permanent loss of function will result.

The Prevention of Allergy.
Hyposensitization

The prevention of allergy can be caused by the organism isolation from potential antigen, by reproduction of specific immune tolerance or immunodepressive conditions. Immune tolerance is provoked by the injection of certain antigen to the newborn child or embryo. It is an interesting fact for the organ transplantation and for the prevention of hereditary ability to allergy to any allergen. In adults the specific immune tolerance is provided by the injection of a large dose of the dissolved antigen (Felton's paralysis).

Table 7. Mechanisms of immunologycally mediated disorders by Coombs and Gell (1968)

Type	Prototype disorder	Immune mechanism
Anaphylactic type	Anaphylaxia, some forms of bronchial asthma	Formation of IgE (cytotropic) antibody -> release of vasoactive amines and othei mediators from basophils and mast cells
Cytotoxic type	Autoimmune hemolytic anemia, erythroblastosis fetalis, cytotoxic reactions the action of large doses of Bogomglets's ACS (antireticular cytotoxic serum)	Formation of IgG, IgM -> binds to antigen on target cell surface phagocytosis of target cell or lysis by C 8,9
Immune complex disease	Arthus' reaction/serum sickness, systemic lupus erythematosus, certain forms of acute glomerulonephritis	Ag + Ab -> activated Co attracted complexes neutrophils —> release of lysosomal enzymes
Cell-mediated (delayer) hypersensivity	Tuberculosis, contact dermatitis, transplant rejection	Sensitized thymus-derived T-lymphocytes —> release of lymphokines and T-cell-mediated cytotoxicity
Stimulating allergic reactions via BAS, hormones, mediators	Collagen diseases, connective tissue diseases, rheumatoid arthritis and others	The cells, containing Ag, begin to function intensively under the influence of Ab. Then cells secrete hormones or mediators

Immunodepressive conditions can be caused by the depression of ability to form antibodies to many antigens. There are 3 methods of depression: irradiation, immunodepressors, which inhibit protein synthesis and cell division, and the specific antilymphocytic antibodies.

The essence of hyposensitization is that we choose a little dose of antigen for the repeated introduction, so that the formed BAS are inactivated by the organism itself. Antibodies will be connected with antigen without allergy.

Allergy and Inflammation

The complex antigen-antibody is a flogogenous agent. This complex becomes the cause of primary alteration — the initial stage of inflammation — when antibodies or cells-killers interact immediately with the organism cell antigens (for example in cytotoxic reactions or in allergic reactions of delayed type). If the formation of such complex doesn't lead to the direct cell damage, the biochemical stage is activated 100. As a result the biologically active substances are formed, which are mediators of inflammation and the cause of secondary alteration.

COMPREHENSION CHECK

Try to answer the following questions.

1. Define allergy and allergens.
2. Explain pathogenesis of allergy by A. Ado and Coombs arid Gell.
3. Characterize autoallergic diseases.
4. What is immune tolerance or immunodepressive condition?

UNIT 11

NEOPLASIA

Neoplasia is a widespread and potentially grave growth abnormality (dystrophic proliferation), which results in cancer as the most serious form.

Cancer is a disease of growth, division and cell differentiation, it is the result of mutation of genes controlling these processes.

Tumor is a typical pathologic process characterized by irregulated limitless growth of the tissue, which is not connected with the general structure of the impaired organ and its functions.

Tumor is formed in the organism as a result of transformation of the normal cells into the tumor ones where the regulation of division is disturbed.

Such cells have no or insufficiently effective inhibition of cells division, or they have self-supporting stimulation of division (autoimmune mechanism of cells division is stimulated by the factor produced by itself).

Tumor is growing from itself, i.e. it grows as a result of reproduction of even one malignant cell.

The tissue of tumors differs from the original one by structure, physical and chemical, biochemical, functional and other signs. It is called ***atypism.***

These changes indicate anaplasia that is returning of the cell to its embryonic state and also metaplasia — acquisition of properties of other tissue.

ETIOLOGY

All factors causing tumors are called ***carcinogenic*** or ***blastomogenic.*** Agents, intensifying the effect of carcinogens, but not causing tumors themselves are called ***cocarcinogens.*** Carcinogens acting in combination are called ***syncarcinogens.***

Chemical, physical and biological carcinogenic substances are related to exogenic carcinogens.

Chemical carcinogens are polycyclic aromatic hydrocarbons (PAH). 3,4-benzpyren, 9,10-dimethyl-1,2-benzantrazen are related to them. When put on the skin they cause cancer, in subcutaneous introduction they cause sarcoma. They may cause tumor in the organs where they accumulate: mammary gland tumor is formed in their excretion with

milk and kidney tumors in excretion with urine. PAH are widely spread in nature: water, air and ground. They are products of incomplete burning and are formed at 400-500 °C (temperature of tobacco burning in the cigarette), they are in the smoke, overroasted butter, exhaust gases, smoked foods, oil and coal.

Carcinogenic aminonitrocompounds and amines possess organotrophy. Dimethylaminoasobensol causes cancer of the liver in 80% of cases regardless the place of introduction. P-naphthilamin causes cancer of the bladder. Nitrozamines also posses organotrophy. Diethylnitrosamin causes cancer of the liver and esophagus. Methylnitrosurea causes tumor of the brain.

Non-organic carcinogenic substances are chromium, arsenic, cobalt, lead, nickel, etc. The fungus Aspregillus flavum synthesizes aphlotoxin — a substance causing tumors of the liver. This fungus is well reproduced in the most environment. It may affect rice, peanut, milk in powder, eggs and corn.

Biological Carcinogens

They are oncoviruses (that is virus causing tumor). Depending on the type of nucleic acid, which they contain, oncoviruses are divided into the following groups:

1. ***RNA-genome viruses*** (or oncornaviruses). Retroviruses have reverse transcriptase (or RNA-depend DNA-polymerase), which helps to synthesize DNA-copies in RNA-genes of virus.

2. DNA-genome viruses. They are:

a) viruses of **papova** (Shoup's papilloma of rabbits, polioma of mice, vacuolizing cancer of apes) group;

b) Lucket's virus causing adenocarcinoma of the kidneys in frogs:

c) Epshtein-Barr's virus causing Berkitt's lymphoma.

The human tumors supposed to be caused by oncoviruses are:

1. Berkitt's lymphoma. This tumor is spread as epidemic among children in the countries of the Central Africa.

2. T-cellular lympholeukosis of the aduits. The patients are revealed to have antibodies against proteins of the virus.

3. Tumors in AIDS are supposed to be caused by virus HTLV- III. The proofs are:

a) tumors (Kaposhi sarcoma) are concomitant with AIDS;

b) it is spread with AIDS.

Physical Carcinogens

They are sun and ultra-violet radiation and ionizing radiation

consisting of X-ray radiation; a-radiation; j3-radiation; y-radiation.

They are all possess a high penetrative ability. X-ray may be the cause of the professional cancer and iatrogenic ***cancer (it*** occurs in people exposed to X-ray treatment). Radioactive substances such as phosphorus, iodine and radium, etc. may also cause a number of tumors in people and animals.

Endogenic Carcinogens

They are some hormones, for example, folliculin; derivatives of the aminoacid thryptofan — indol; bile acids and cholesterol (from bile acids); free radicals and peroxide.

PATHOGENESIS
(MECHANISM OF CANCEROGENESIS)

Till nowadays all theories were based on supposition that transformation of the normal cell into tumor results from stable changes in the cell genome.

It was shown that DNA of the normal animal cell had an area, which was homological, by nucleotide composition to virus oncogen (for each of 20 known retrovirus oncogens). In the normal cells the analogue of virus ***oncogen is inactive and it is*** called ***prolooncogen*** and in tumor cells it is active and called ***active cellular oncogen.*** The transfer of protooncogenes into active cellular oncogenes takes place under the influence of different carcinogenic factors.

There are several general stages of tumor pathogenesis:

1. Conversion of proto oncogenes into active cellular oncogens. The mechanisms of conversion:

a) mutation;

c) *participation of promo tor* (i.e. the area of DNA if it is near to protooncogen). The role of promotor for proto oncogenes may be played by DNA-copies of oncoviruses as well as "jumping" mobile genes which are able to enter different areas of genome;

c) ***amplification*** (i.e. increase of protooncogenes amount, as a result, their general activity in the cell increases that may lead to tumor transformation of the cell);

d) ***protooncogen transformation*** (i.e. protooncogenes shift to functioning promotor).

2. Expression of active cellular oncogenes is the increased synthesis of oncoproteins or synthesis of structurally changed oncoproteins. Oncoproteins are tumor proteins. Their synthesis in large quantities is

programmed by active cellular oncogens. With their help tumor genetic program is conversed into tumor with its specific signs. Oncoproteins are also formed in the normal cells (in small amount) where they function as regulators of sensitivity of their receptors to growth factors. The total amount of the known oncoproteins is over 20.

3. Transformation of the normal cell into the tumor one takes place in two stages: the early stage is characterized by immortalization of the cells; later on the ability of cells to tumor growth is formed.

The supposed mechanisms are:

a) oncoproteins joint to the receptors for growth and generate signals for cell division;

b) oncoproteins increase receptors sensitivity to growth factors or decrease sensitivity to growth inhibitors;

c) oncoproteins act as growth factors.

Transformation may take place in two ways: mutagenic and epigenomic.

According to modern hypothesis gene regulation of the; cell is fulfilled by the system consisting of three regulator) genes (Fig. 18).

In the norm there is no excessive division in the cells as. genes-regulators provide inhibition of gene activity which codes division in switching on of the gene of the initiator of eel division suppresses the function of repressor 2 and thus synthesis of repressor which suppress the function of the gene of the initiator of cell division (arrows in the scheme indicate the direction of the suppressing influence).

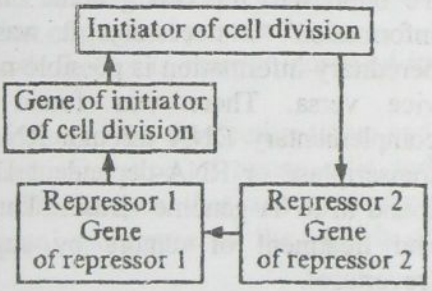

Fig. 18. System of genes regulating cell division

To reproduct the cell needs the factor in its genome that causes activation of repressor 2 by the initiator of cell division or activation of the gene of the initiator or cell division by repressor 1. If there is no such factor, the system of regulatory genes "switches off the gene of the initiator. Reproduction of the cell is stopped.

Mutation carcinogenesis is connected with mutagenic factors that cause disorders in repressor 1 and its not synthesized. In this case gene-

indicator of cell division is uninhibited and replication of DNA begins. The formed cells do not possess repressor therefore the cells go on DNA replication and form the family of cells capable of limitless uncontrolled division of cells.

Epigenome carcinogenesis may be formed under the influence of the virus, which infects the cells and gets into each new one in mitosis. It is assumed that there is a gene of the type of cell repressor 2 in virus genome. In appearance of virus in the cell, synthesis of virus repressor 2 begins which inhibits work of repressor 1. As a result, gene-initiator of cell division becomes activated and the initiator of cell division is synthesized. The appearance of initiator of cell division leads to the beginning of DNA replication, that is cell division.

The initiator of division inhibits work of repressor 2 of the cell, but can't switch off work of repressor 2 of the virus. The cell goes on reproduction.

The Role of Viruses in Carcinogenesis

In 1945 professor A. A. Zilber suggested the virus-genetic theory of a tumor origin according to which virus genome invades cell genome. To build into the cell genome "the reverse transmission of genetic information" is necessary. It was established that transmission of hereditary information is possible not only from DNA to RNA but also vice versa. There was found an enzyme, which synthesizes complementary DNA through RNA. The enzyme was called reverse transcriptase or RNA-dependent DNA polymerase. The enzyme was found in RNA-genome viruses. Thus, there was an idea of prophylaxis and treatment of tumors by suppression of reverse transcriptase (revertase).

Pathogenesis

There are 3 stages of pathogenesis:

I. Transformation (initiation stage)

II. Promotion

III. Progression

Transformation is characterized by the ability to transform healthy cells into cells with endless growth. Such ability can be the result of mutation or genome changes as a consequence of disregulatory processes. If in cells a gene appears, which depressed the initiator of cell division, can destroy or damage the mechanism of this gene switching on or off, which leads to uncontrolled growth.

Promotion is the second stage in the mechanism of carcinogenesis.

The transformed cells may remain in the tissue in inactive form for a long time. Additional influence of cocarcinogenic factor stimulates cell reproduction and formation of tumor node.

Progression is the third stage of the mechanism of carcinogenesis. Progression is realized as stable qualitative changes of tumor properties towards malignization. These changes arise under the influence of several factors:

1. Not one but several cells become involved into primary carcinogenic that promotes formation of law sublines of cells in the growing tumor. A constant selection of the most viable cells goes on in the growing tumor under the influence of the changing conditions of its growth (nutrition, blood supply and innervation).

2. Change of genotype and phenotype of the cells resulting in progression may be connected with continuation of the effect of carcinogenic factors on the genome of tumor cells.

3. Acquisition of new properties by tumor cells, which is connected with superinfection by tumor and non-tumor viruses.

Due to heterogeneity of tumor cells in chemotherapy of tumor there is a selection of cells stable to the action of medical preparations.

1. Synthesis of receptors for growth factors is sharply increased in tumor cells.

2. Enzymes regulating the components of the connective tissue and vessels are synthesized that conditions migration of tumor cells and metastases. These are the enzyme plasminogen that activates other enzymes; collagenase of IV type (basal membrane of the vessels of collagen of V type).

3. Cytoskeleton in tumor cells is changed. There is phosphorylation of cytoskeleton proteins — vinculin, change of this protein function. The number of intracellular contacts is sharply decreased and owning to this metastatic spreading is facilitated.

4. Factor promoting synthesis of collagens of different types for growth of the vessels and stroma are formed in tumor cells. Owing to these factors tumoral metastases fix and grow in other organs.

Biological Peculiarities of Tumors

Malignant tumor is characterized by different forms of anaplasia. There are benign and malignant forms of neoplasia — the uncontrolled disorderly proliferation of cells (Table 8).

1. The morphological type.

a) Polymorphism (size).

b) Large nucleus with multiple vacuoles nuclear chromatin.

2. Reproduction atypism.

a) Unregulated reproduction of the cells — loss of contact inhibition poor cellular cohesiveness by tumor cells predispose to their moving — metastasis.

b) Loss of upper limit of a number of cell division — Heiflik's limit, absent (in norm maximal limit of cell division is 30-50 divisions ***in vitro***, after that cells die). Tumor cells acquire an ability of limitless division that leads to "immortality".

3. ***Atypism of differentiation*** consists of partial or complete inhibition of cells maturation.

4. Metabolic and energy anaplasia (atypism).

a) Intensive synthesis of oncoproteins (tumoral proteins) from protooncogenes — inactive predecessors in all normal cells.

Table 8. Comparative characteristics of tumors

Kind	Benign	Malignant
Growth rate	Slow	Rapid
Mitosis	Few	Many
Nuclear chromatin	Normal	Increased
Differentiation	Good	Poor
Local growth	Expansive	Invasive
Encapsulation	Present	Absent
Vessel invasion	None	Frequent
Metastasis	None	Frequent
Effect of host	Often insignificant	Significant cachexia, death

b) Synthesis and contens of histones are decreased. Histones — are the proteins suppressors of DNA synthesis. Without histones proteins synthesis changes qualitatively and quantitatively.

c) Reamination and desamination of amino acids are reduced.

d) Formation of embryonic proteins ***α-phetoprotein*** is synthesized by fetus hepatocytes and never produced by mature hepatocytes. That's why the organism doesn't form Ab against these α-phetoprotein (as own protein).

e) Intensification of glycolysis — anaerobic and aerobic phases due to which amount of ATP increase. There are negative ***Pasteur effect*** —

in tumor cells intensive anaerobic glycolysis doesn't not decrease in change of anaerobic conditions into aerobic ones but persists.

f) The phenomenon of substrate "traps" for glucose, nitrogen and cholesterol — all substrates are used for energy. C-AMP reduces due to division activation of the cells because in the norm C-AMP depresses division. C-GMP elevates due to increasing of proliferation.

5. ***Physico-chemical atypism*** is manifested by increased contents of water and potassium ions in the tumor cells and decrease of calcium and magnesium in them.

a) It stimulates diffusion of metabolic substances into the cells and its products outside.

b) The increased amount of K^+ is accompanied by the development of intracellular acidosis due to intensification of glycolysis and accumulation of lactic acid. But in blood alkalosis due to switch on compensatory mechanisms.

c) The decreased amount of Ca^{2+} reduced intracellular adhesion due to they move into surrounding normal tissue in ***invasive growth.***

6. Functional atypism is marked by:

a) Dysfunction of diseased organ, for example

— decreased secretion of the gastric juice in stomach cancer;

— reduction of bile formation in cancer of the liver;

— tumor from the cells of pancreas causes hyperglycemic condition and even coma.

b) "***Perversion*** " of functions. For example, synthesis of the hormone of the thyroid gland — calcitonine in breast cancer; hormones of pituitary gland (ADH, ACTG) are synthesized in lung cancer.

7. ***Antigenic atypism*** consists of changes of antigenic composition of tumor cells in different directions — antigenic simplification or appearance of new antigenes. Antigenic simplification is loss of antigens by the tumor cells in the initially normal cells. For example, (1) cancerous hepatocytes lose organospecific antigen of the liver-human- antigen; (2) tumors may have antigens specific for embryonic tissues: fetal a-protein is found in hepatoma (liver tumor). Tumor of the liver may be diagnosed by presence of this protein in the blood before its clinical manifestation.

Appearance of the tumor cells in the organism does not obligatory result in development of tumor process. Clones of tumor cells are controlled by the immune tissue and the clone with any antigenic differences is eliminated as a result of immunologic reactions. Thus, the

growth of the tumor tissue is observed due to escape of tumor cell from immunologic control.

Mechanism of such escape from immunologic control is the following:

1) Antigenic simplification of the tumor tissue that promotes survival of tumor cells. It reaches the degree when tissue specific and individual antigens are lost completely. Only specific species antigens remain for which there is tolerance in the organism of definite species.

2) Appearence of fetal antigens in the tumor tissue does not cause immunologic reactions as there is immunologic tolerance for these antigens.

3) Masking of antigens. For example, cells of chorionepithelioma gave neutral polysaccharide capsule.

4) In some tumors there are some antigene determinants, which stimulate T-suppressors.

8. ***Morphological atypism*** is divided into tissue and cellular.

Tissue atypism is characteristic of benign tumor.

Cellular atypism is characteristic of malignant tumor. It is manifested by polymorphism — different shape and size of cells and nuclei; hyperchromia of nuclei; increased amount of nucleoli in the nuclei; increased number of mitosis; appearance of mitochondrias different in size and shape.

Spreading of metastases consists of the following stages: tearing off of the tumor cells from the adjacent cells, movement in the tissue, the components of the connective tissue and vascular wall are melted, spreading by the blood and lymph, adhesion to the vascular wall at a new place, growing into the connective tissue and vessels of the newly formed tumor tissue.

1. The initial stage is cessation of intercellular contacts formation, change of membrane receptors, acquisition of mobility due to change of cytoskeleton proteins.

2. The next stage is synthesis of plasminogen activator, the enzyme which destruct the connective tissue and vessels. Collagenases, which destruct different types of the vascular wall collagen are formed. Tumor cells produce the factor attracting monocytes and basophils, whose enzymes (seric protease) promote matrix splitting ind heparin intensifies angiogenin effect and growing of the vessels into the tumor tissue.

3. Angiogenin and other growth factors of the vessels are synthesized by tumor providing blood of the tumor tissue.

4. Radicals of neuramin acid and glycoproteids remain open in the membranes of tumor cells providing decrease of contact inhibition and promoting infiltrate growth and formation of metastases.

COMPREHENSION CHECK

Try to answer the following questions.

1. Define neoplasia.
2. Classify carcinogenesis.
3. What is the role of protooncogene?
4. Describe carcinogenesis.
5. Summarize biological peculiarities of cancer.
6. Characterize neoplasms outcomes.

UNIT 12

HYPOXIA

Hypoxia — is a typical pathologic process, developing as a result of insufficient tissue supply by oxygen or its disturbed use.

THE TYPES OF HYPOXIA

As to the mechanisms of development there are hypoxic, respiratory, haemic, circulatory, tissue and combined hypoxia.

Hypoxic or exogenous hypoxia develops under conditions of the decreased partial pressure of oxygen. The most typical example of it — is a mountain disease.

Respiratory hypoxia occurs as a result of disturbed external breathing: the disturbance of lung ventilation, lung blood supply or diffusion.

Haemic hypoxia develops in connection with blood disturbances and in particular with the decrease of its oxygen capacity.

It's subdivided into anemic hypoxia and the hypoxia, caused by haemoglobin inactivation.

In pathologic conditions such haemoglobin compounds are formed, which are not able to realize respiratory function. It is carboxyhaemoglobin, formed from haemoglobin and carbon monoxide. Haemoglobin can't transfer oxygen in such compounds. The iron containing enzymes are inactivated too. Methemoglobin is forming during the poisoning by nitrates.

Circulatory hypoxia develops in different disturbances of blood circulation. There are ischemic and congestive forms.

If the disturbances occur in systemic circulation, blood oxygenation can be unchanged, but there are some disturbances in oxygen transfer to the tissues. If the changes are in pulmonary circulation the oxygenation of arterial blood is disturbed.

Circulatory hypoxia can be provoked by both the absolute insufficiency of blood circulation and the relative one. This condition can appear in cardiac muscle during emotional exertion.

Microcirculatory disturbances also lead to the hypoxia of the same type.

Tissue hypoxia is a disturbance of oxygen utilization. Tissue supply by oxygen is sufficient, but its biological oxidation is disturbed. The causes are the decreased number and activity of respiratory enzymes, the disconnection of oxidation and phosphorylation. A classical

example is poisoning by cyanides. Large doses of alcohol and some drugs inhibit dehydrogenases. Avitaminosis also provokes the inhibition of synthesis of some respiratory enzymes.

The disconnection of oxidation and phosphorylation leads to less effectiveness of biological oxidation, energy becomes dispersed as free heat, the resynthesis of macroergs. Peroxide lipid oxidation provokes the destabilization of mitochondrial and lysosomal membranes. All these things lead to hypoxia. The causes are: ionizing radiation, hypoxia, the deficit of natural antioxydants, which reduce free radicals and destroy hydrogen peroxide. These are: ascorbinic acid, katalase, cholesterol, some steroid hormones, serotonin and others.

Usually, we meat combined forms of hypoxia. So, on this ground the sixth type of hypoxia — combined hypoxia was distinguished.

Sometimes, we distinguish hypoxia of load, which develops on the background of sufficient or even surplus tissue supply by oxygen. But, the increased functional requests of the organ lead to the inadequate oxygen supply and metabolic disturbances, typical for the true oxygen insufficiency.

PATHOGENESIS

There are two stages of hypoxia — compensation and decompensation. Due to the compensatory-adaptative reactions, the normal tissue supply by oxygen is maintained. The stage of decompensation develops when adaptation is exhausted.

Compensatory-adaptative reactions develop in the system of transport and utilization of oxygen.

The increase of lung ventilation is realized in the expense of reflex excitation of the respiratory center by impulses from the vascular chemoreceptors. These receptors react upon the changes in blood chemical composition, in particular the accumulation of $C0_2$.

In hypoxic hypoxia, chemoreceptors react upon the decrease of oxygen content in blood. Lung hyperventilation is a positive organism reaction upon the height. But it has some negative consequences: the development of hypocapnia and alkalosis as a result of carbonic acid loss in the organism. Carbonic acid has a significant influence upon the cerebral and coronary blood circulation, the regulation of respiratory and vasomotor centers tension, haemoglobin dissociation. All these functions can be disturbed by the deficiency of carbon dioxide.

The increase of blood circulation is intended to mobilize the means

of oxygen transfer (heart hyperfunction, the increase of blood speed). Blood is redistributed to supply the most important organs: the lungs, heart, brain and the expense of decreased blood circulation in the skin, spleen, muscles, and intestines. The changes are regulated by the reflex and humoral mechanisms and by the products of tissue decay, which can dilate the vessels.

The increase of erythrocytes and haemoglobin extends oxygen capacity of blood. The ejection of blood from depots provides short adaptation to hypoxia. During prolonged hypoxia, the production of erythrocytes is increased in the bone marrow under the influence of renal erythropoietins and the products of erythrocytes destruction.

The changes of oxyhaemoglobin dissociation curve. In hypoxia, the ability of haemoglobin A to add oxygen to the lungs and to give it to the tissues is increased. The curve displacement to the left of higher inflexion testifies to the increased ability of Hb to absorb oxygen in low partial pressure in the air. So, the arterial blood is saturated with oxygen better than usually. Right declination of lower inflexion testifies to the decrease of Hb affinity with oxygen in tissues. So, tissues get more oxygen.

THE MECHANISMS OF LONG-TERM ADAPTATION TO HYPOXIA

Emergency hyperfunction of the external breathing and blood circulation cannot provide steady and long adaptation to hypoxia, as it requires the increased use of oxygen. It is accompanied by the increased functioning of the structures and the extended albuminolysis. Emergency hyperfunction requires energy and structural support to realize active physical and mental work in long-term hypoxia.

The subject of investigation are mountain and diving animals, the inhabitants of mountain regions and experimental animals adapted to hypoxia, during some generations. It's established, that the system responsible for the oxygen transfer is the subject to hypertrophy and hypoplasia. The weight of respiratory muscles, lung alveoli, myocardium, and respiratory neurons is increased. These organs become better supplied with blood at the expense of the increased number of capillaries and their hypertrophy. The functioning of structures is normalized.

During long acclimatization to mountain hypoxia, oxygen diffusion from the alveolar air to blood improves at the expense of increased

capillary permeability. Myoglobin content is increased. It's an additional oxygen capacity and a stimulator of oxygen diffusion to the tissue.

The changes in oxygen utilization are the following:

1. Tissue ferments utilize oxygen better, support a high level of oxidizing processes and realize normal synthesis of ATP in spite of hypoxemia.

2. The most effective use of the energy got during the oxidizing processes.

3. The increase of energy output during glycolysis.

There is supposition, that the final enzyme of the respiratory chain — cytochromoxidase — is changed during long adaptation to hypoxia.

The other mechanism of adaptation is an increase of the respiratory enzymes and mitochondria.

The initial link is an inhibition of oxidation and oxidizing resynthesis of ATP in the deficiency of oxygen. As a result, the number of tissue macroergs is reduced and the products of tissue decay are accumulated. The correlation ADP · Ph = ATP, marked as a phosphorylation potential, is increased. It is a stimulus for the cellular genetic apparatus. It leads to the increased synthesis of nucleic acids and proteins in mitochondria. Mitochondrial weight increases. Thus, the cells can produce in spite of oxygen deficiency in blood.

The described processes mainly proceed in the organs, responsible for the oxygen transfer (the lungs, heart, respiratory muscles, bone marrow) and in the organs, which suffer from oxygen insufficiency (the brain cortex, respiratory neurons). Synthesis of structural proteins is increased in these organs, it leads to their hyperplasia and hypertrophy. So, the prolonged hyperfunction of transport and utilizating systems gets a plastic and energy provision. The stable and economical adaptation develops.

The changes in the endocrine system and the production of some hormones (glycocorticoids) promote tissue stability to hypoxia.

But in different types of hypoxia, the correlation between the described adaptive reactions is different.

THE PATHOLOGICAL DISORDERS IN HYPOXIA

The disturbances develop as a result of insufficiency of exhaustion of adaptative mechanisms.

Energy got during redox processes is preserved in phosphorus compounds, containing macroergic bonds. In hypoxia, the number of

this compounds is decreased. Thus, the deficiency of oxygen leads to energy deprivation of tissues. All disturbances are based on it.

In oxygen insufficiency, metabolism is disturbed and toxic products of incomplete oxidation are accumulated. For example, glycogen content in the liver and muscles is reduced, glucose isn't oxidized completely. The accumulated lactic acid leads to acidosis. The appearance of products of lipid peroxide oxidation is an important factor of hypoxic injury of the cell.

The intermediate products of albuminous metabolism are accumulated. The ammonia increases, glutamine decreases. Phosphoproteid and phospholipid metabolism becomes disturbed. The negative nitrogenous balance is formed. The synthesis is reduced. The active transport of ions through the biological membranes is disturbed. The content of intracellular potassium is decreased. The accumulation of calcium in cytoplasm is one of the basic links of hypoxic damage of the cell. The synthesis of the nervous mediators is reduced too.

The described biochemical reactions cause structural disturbances in the cell. So, the increased acidity and other disturbances lead to the damage of lysosomal membrane. The active proteolytic enzymes release and damage cellular structure. The ultrastructure disturbances are marked as hyperchromatosis, the decomposition of nucleus, swelling and dehydratation of mitochondria.

It was mentioned that the basis of the prolonged adaptation to hypoxia was a structurally supported hyperfunction of systems of oxygen utilization and transfer. Its conditioned by the activation of genetic apparatus. In differentiated cells (the brain cortex), this process can result in exhaustion.

The sensitivity of different tissues to the deficiency of oxygen depends on the following factors:

1) The intensity of metabolism.

2) The capacity of tissue glycolytic system.

3) Energy stocks and macroergic compounds.

4) The ability of genetic apparatus to provide the plastic consolidation of hyperfunction.

The nervous system is in the most unfavorable conditions.

The Disturbances in the Organs and Physiological Systems

The first signs of oxygen deprivations are the ***disturbances in the nervous system.*** First, euphoria occurs. It is characterized by the

emotional and motion excitation, the feeling of one's own power or, on the contrary, the lost of interest to the surroundings, inadequate behavior. The cause is the disturbance of the internal inhibition.

In prolonged hypoxia the metabolic and functional changes in the nervous system are more severe. Inhibition develops. The reflex activity is disturbed, the regulation of breathing and blood circulation is impaired too. Loss of consciousness and convulsions are the symptoms of oxygen deprivation.

The disturbances in other organs are interconnected with the disturbed nervous regulation, energy deprivation and the accumulation of toxic metabolic products.

As to sensitivity to oxygen deprivation, the ***cardiac muscle*** takes the second place after the nervous system. The conductive system is more stable than the contractive one. The clinical manifestations of the disturbed excitability, conduction and contraction of the myocardium are tachycardia and arrhythmia. Cardiac insufficiency and the reduced vascular tension lead to hypotension and general disturbance of blood circulation. The latter complicates the course of the pathologic process.

The disturbance of the ***external breathing*** consists of the disturbance of the lung ventilation. The periodical Chein — Stocks' breathing appears. The development of congestive processes in the lungs leads to decreased diffusion of oxygen from the alveolar air to blood.

In the alimentary system the following pathologic conditions are observed: inhibition of peristalsis and secretion in the stomach, intestines and pancreas, polyuria, followed by disturbance of renal filtration, the decrease of temperature, the exhaustion of the adrenal cortex.

But, pathologic conditions at the same time can be considered as adaptive ones. So, the nervous system is very sensitive to oxygen deprivation. In hypoxia, the protective inhibition develops. As a result, the nervous system becomes less sensitive to oxygen deprivation.

In hypoxia, the impairment and protection are closely interconnected. But, it is an injury that is the initial link of compensatory adaptation. So, the decrease of pO_2 in blood provokes the stimulation of chemoreceptors and mobilization of the external breathing and blood circulation.

The stability for hypoxia depends on several causes, in particular the age. The automatic activity of the respiratory center in hypoxia can be supported by the primitive form of metabolism — anaerobic decomposition of carbohydrates in newborns. The blood of newborns

contains fetal haemoglobin, which can realize the respiratory function in the law partial pressure of oxygen in blood. But the most important facts is a poor development in the newborns' central nervous system.

There are some individual differences in the sensitivity to hypoxia. It depends on many factors, in particular, the production of such antioxidizing erythrocytic enzyme as superoxide dismutase, which has different activity in many individuals.

Some conditions, characterized by deep inhibition of the central nervous system and metabolism (sleep, narcosis, hypotermia), promote the reduction of organism sensitivity to hypoxia.

We can raise the stability for hypoxia by the decrease of organism requests in oxygen and by the improving of adaptive reactions in the conditions of altitude chamber. At the same time, the organisms adapt to other unfavorable factors, in particular, physical load, the change of temperature, infection, poisoning, ionizing radiation.

If the utilization of oxygen is disturbed, we can introduce it. In some diseases, we used oxygen under the increased pressure. It creates oxygen stocks in blood and tissues. We use it during poisoning by carbon monoxide, congenital cardiac failure, operations on the dry heart (without blood supply).

We can correct metabolic disorders with the help of the specific antihypoxic preparations. They stimulate the transfer of electrons in the respiratory chain (cytochrome C-like preparations), and inhibit free radical oxidation (antioxidators).

The following preparations are used — phosphorylated carbohydrates, blockers of calcium canals and substances, increasing glycolysis and reducing organism requirements in oxygen.

COMPREHENSION CHECK

Try to answer the following questions.

1. Define hypoxia and characterize its types.
2. Explain mechanisms of long term adaptation to hypoxia.
3. What disturbances occur in the organs and systems under hypoxia?
4. How to correct hypoxia?

UNIT 13

THE DISTURBANCE OF ENERGY, PROTEIN AND BASAL METABOLISM. STARVATION

Metabolism in the organism is determined by hereditary factors and regulated by the nervous and endocrine systems. Therefore these disturbances of metabolism may have a hereditary nature or appear in the process of the life as a result of disturbance of the regulatory systems. The disturbances of metabolism can be manifested on all levels of biological organization from the cellulomolecular level to the organism. The leading role in carrying out self-regulation belongs to genetic information at the cellular level. Majority of hereditary defects of metabolism are stimulated by mutation of the genes encoding the synthesis of ferments — hereditary enzymopathies. The essence of enzymopathy is that fermental protein isn't synthesized or synthesized with the changed structure that alter its activity. Accumulation of unmetabolized substrate or falling out of intermediate product of metabolism are possible in fermental activity changing. Increase of fermental activity leads to accumulation of final products of metabolism. The constant influx of information, which is carried out by the nervous system mediators and hormones, is necessary for coordination of metabolism in the cells. There are specific receptors on the membrane in the cell for perception of this information. Pathology of the receptors can be one of mechanisms of pathologic process development, for example, in diabetes mellitus and diabetes insipidus. Together with intracellular mechanisms of selfregulation the organism has got the more complicated mechanisms — neurohumoral mechanisms of regulation. The nervous system controls the tissue metabolism with the help of mediators; the neurodystrophic process develops in disturbance of this function.

Disturbance of metabolism on higher level of organization — organ and organism — depends on the state of the neuroendocrine regulation to a greater degree. So the emotional stimulation is accompanied by change of the cortical regulation of heat production, carbohydrate metabolism, ect. Many disturbances of metabolism are stimulated by lesion of the diencephalons. The role of hypothalamus is especially important, which exerts influence of metabolism with the help of releasing-factors through the pituitary body. Disturbances of the

vegetative nervous system also provoke the changes of metabolism. Thus there is close connection between intracellular mechanisms of selfregulation connected with genetic information and neurohumoral regulation of the metabolism. And the disturbance of any of them is accompanied by development of pathology.

THE DISTURBANCE OF ENERGY METABOLISM

The disturbance of energy metabolism is the basis of majority of functional and organic disturbances of organs and tissues. They can arise of all stages of energy transformations as a result of absence or deficiency of a substrate, change of ferment activity, due. to genetic defects, action of inhibitors of ferments, insufficient entrance of indispensable amino acids, fat acids, vitamins, trace elements and other substances, which are necessary for carrying out metabolic processes or as a result of damage of the regulatory systems. Normal course of metabolism is stimulated by dynamic cooperation of catabolism and anabolism processes at the molecular level.

Oxidation of metabolic products in the Krebs cycle is the most effective in energy respect; 0-oxidation and glycolysis are less effective. Degree of conjugation of respiration and phosphorylation in the cells is a regulated process, which is connected with the state of mitochondria. In some conditions, which are connected with the necessity to maintain its own temperature under the influence of cold, the organism is in need of urgent mobilization of heat, which: happens by estrangement of oxidative phosphorylation and increase of free oxidation. Parathyrine, progesterone, growth hormone, and vasopressin are related to the estranged factors. Oxidative phosphorylation is essentially disturbed in avitaminosis, especially of B group, as many vitamins of this group are present in composition of Krebs cycle coferements. Deep disturbance appear in diabetes mellitus, when the production of macroergic compounds is decreased due to the disturbance of inhibitors of ferments, insufficient respiratory chain, stipulated by limitation of capacity of the Krebs cycle.

THE DISTURBANCE OF BASAL METABOLISM

Basal metabolism is a quantity of energy secreting by the organism is standard conditions (at rest, on an empty stomach, temperature is 18

°C). The nervous and endocrine systems participate in regulation of the basal metabolism.

Thyroxin is one of the basic regulators, it increases the permeability of mitochondria, influences on the oxidation and phosphorylation processes and intensity of energy processes. Increase of the basal metabolism by 20% and more is a diagnostic sign of thyrotoxicosis, and its decrease indicates on hypofunction of the thyroid gland.

The hormone of the pituitary body — **somatotropin** — stimulates free oxidation and due to this increase the heat production. That's why the intensification of energy processes occurs in tumors of the pituitary body.

Adrenaline stimulates the basal metabolism, especially in cold conditions.

Insulin has the opposite influence; it reduces muscular trembling and heat production increasing the estrangement of oxidation and phosphorylation.

Sex hormones — **testosterone** and **progesterone** — activate free oxidation and promote energy release.

THE DISTURBANCES OF PROTEIN METABOLISM

The proteins occupy a central place in carrying out vital function processes of the organism, and therefore the disturbance of protein metabolism is an important component of all pathologic processes without exception. The depot of proteins is practically absent in the organism and the food is the source of amino acids. Not only amino acids but also the normal functioning of the system of synthesis and its encoding genetic structures are necessary for the normal synthesis of amino acids. The disturbance of protein production can be acquired and hereditary. It is expressed in change of quantity of synthesized molecules or appearance of molecules with changed structure.

The Disturbance of Transamination and Oxidative Desamination

Transamination leads to the formation of amino acids, desamination — to their destruction. The disturbances of transamination can arise in insufficiency of pyridoxine (pregnancy, suppression of the intestinal flora by sulfamide preparations). Decrease of transaminase activity takes place in limitation of protein synthesis (starvation, diseases of the liver).

The tissue transaminases enter blood in destruction of cells (my-

ocardial infarction, pancreatitis, hepatitis, ect.). And the increase of their activity in this pathology is one of the diagnostic criteria. The disturbance of correlation between substrates of reaction, and also hormones, especially of glucocorticoids and hormones of the thyroid gland stimulating this process, is important in change of transamination reaction rate.

Suppression of oxidative desamination may provoke an increase of amino acids concentration in blood — hyperaminoacidemia and aminoaciduria.

The Disturbance of Decarboxilation

Decarboxilation is carried out with formation of $C0_2$ and biogenic amines. Some amino acids are exposed to this process: histidin — with formation of histamine, glutaminic acid — γ-aminobutyric acid, 5-hydraoxytryptophan — serotonin. Biogenic amines, have a specific biological activity and increase of their quantity can cause a number of pathologic changes in the organism. Appearance of great quantity of biogenic amines in tissues (especially histamine and serotonin) can provoke the considerable disturbances of local blood circulation, increase of the vascular permeability, damage of nervous apparatus.

Hereditary disturbances of metabolism of some amino acids. Hereditary disturbances of ferment synthesis lead to the fact, that proper amino acids don't participate in metabolism, and accumulate in the organism, appearing in biological media: urina, sweat, cerebral fluid. The clinical picture is manifested at first by appearance of great quantity of the substance, which must be metabolized in participation of the blocked ferment, and secondly be deficiency of the substance, which must be formed. There are many such disturbances of amino acids metabolism. All of them are inherited recessively.

STARVATION

Starvation is a stage appeared in those cases, when the organism doesn't receive food at all or receive them in insufficient quantity, or when the organism doesn't assimilate it due to the disease.

Now starvation is considered as a state of prolonged stress connected with an adaptive activization of biosynthesis of the adrenal glands hormones. These hormones exert the direct (activated) and indirect (saving) influence on vitally important fermental systems of the organism.

Starvation can be physiological and pathological by its origin. Hibernation of some mammals is an example of physiological star-

vation. There are distinguished the following types of starvation: complete, incomplete (quantitative and qualitative). Complete starvation can be without water (absolute starvation).

The Complete Starvation

Causes of complete starvation as well as of other its types, can be external and internal. The ***external cause*** is absence of the food. ***Internal causes*** are the children's developmental defects, diseases of the digestive system organs, infectious processes, anorexia. Duration of starvation in small mammals is less than in big ones. 65-70 days are the time limit of complete starvation for a human. Small size of the body and less perfect regulation of metabolism and heat exchange explain the quick death of newborns in starvation.

Age decrease of the level of basal metabolism determines greater duration of starvation in old humans and animals. Besides all this factors, the duration of starvation is determined by individual peculiarities, connected with the character of the neurohumoral regulation and reactivity of the individual.

The Periods of Starvation

Complete starvation can be divided into four periods by clinical manifestations: indifference, excitement, suppression, paralyses and death of animal.

The deeper notion about peculiarities of different periods of the starvation gives the pathophysiological description taking into account the state of metabolism and exchange of energy. Starvation can be divided into three periods on the ground of this description: uneconomical energy expenditure; maximum adaptation, tissue decay, intoxication and death (terminal period). Duration of each period is various depending on species of the animal. Duration of the first period of a human is 2-4 days. The second period determines practically the period of starvation and can continue 40-50 days, the third one — 3-5 days.

Basic Manifestations of Starvation

One of the earliest and more serious manifestations of starvation is a sensation of hunger stipulated by excitation of food centre. Sensation of hunger in complete starvation can disappear in some days after the beginning of starvation. And the following suppression of food centre can be so deep that the special measures are necessary for its excitation. In incomplete starvation the excitation of food centre is maintained all the time and the sensation of hunger is renewed periodically.

The mass of different organs is decreased unequally. The adipose

tissue loses mass the most intensively (97%), and less intensively — the heart (3.6%) and the nervous tissue (3.9%). A little loss of mass of the brain and heart is evidence of the fact that in the starving organism the complex regulation of intermediate metabolism and processes between organs continue carrying out. It provides first of all the vitally important constantly working organs with plastic and energy materials. The quantity of the nitrous substances — albumins and globulins is increased in a gastric juice on the 6th-8th day of starvation. Proteins are absorbed in blood after splitting, and go on construction of the vitally inportant organs. This process is a result of the engaging of adaptation mechanisms providing the repeated usage of proteins of the synthetic processes.

Other processes, characterising the adaptation of the organism to the unusual conditions of life and transition to the endogenous nourishment are observed in starvation. So at an early stages of starvation there are changes of activity of ferments and isofermental systems. These systems occupy a key position in the pentosesphosphate cycle.

Metabolism in Starvation

The first period of starvation is characterised by increased expenditure of carbohydrates, hence the respiratory coefficient increases.

The glucose level in blood (less than 3 mmol/l), and secretion of insulin decrease, activity of α-cells increases, and glucagone excretes. The glycocorticoidal function of the cortex of the adrenal glands is stimulated and metabolism of proteins and glyconeogenesis increase. The content of glycogene (in the liver) decreases quickly but it does not disappear, it is formed as a result of the glyconeogenesis processes. The effectiveness of the Krebs cycle weakens as a result of depression of insulin secretion. The level of oxygenate phosphorylation decreases and such a result we can see in energy metabolism of the cells. The inhibition of the rate of hexokinase reaction by glucocorticoids decreases the assimilation of glucose by the liver cells.

At the beginning of the ***first*** period the basal metabolism can increase a little, by the end, in transition to economical energy expenditure, it decreases by 10-20% and remains on this level in the second period increasing a little in the third one. Decrease of the basal metabolism in starvation reflects a deep reorganisation of metabolic processes directed at economical expenditure of energy resources. Suppression of the thyroid gland function plays a definite role in it.

The nitrogen excretion with urine decreases on the 2nd-3rd day of

starvation (from 12-14 g to 10 g daily). Then the switching over of metabolism to fats occurs on the 5th-6th day and reserves of carbohydrates are exhausted.

The momentary increase of nitrogen excertion with urine is observed, afterwords it decreases to 7-4 g reflecting an economical expenditure of proteins.

In the ***second,*** the longest ***period of starvation*** the respiratory coefficient decreases to 0.7 that reflects the primary oxidation of fats. About 80% of energy the organism receives as a result of oxidation of fats, 3% — by oxidation of glucose, 13% — by oxidation of proteins, all reserve of glycogen is used for energy needs of the organism during no more than 6 hours of starvation. Then the activation of metabolism is registered in the adipose tissue.

As a result of low level of insulin the transport of glucose to the lipocytes decreases and deficiency of glycerine for synthesis of triglycerides occur. The dominant action of glucagone and catecholamines activates the adenylate cyclase system and makes the lipolysis stronger. The free fat acids come into the blood (lipemia) and other organs. The decrease of entering of glucose occurs in the tissues where the transport of glucose through the cellular membranes depends on insulin. The level of free fat acids increases in the liver and muscles, and their transport is stimulated through the mitochondrial membranes to the places of oxygenation. The lipogenesis and synthesis of fat acids in the liver is inhibited, but the retention of the triglycerides in the liver and development of fat infiltration occurs in deficiency of proteins and insufficiant formation of lipoproteids. In exhaustion of glycogene and decrease of entering of acetyl-KoA from glycolytic way and decrease of the level of melanin-KoA, the production of ketone bodies begins. During 12-24 h of starvation the intensification of the processes of (3-oxygenation is marked in the increased concentration of the ketone bodies in blood from 0.2 to 0.3 mM. In 48-72 h of starvation the level of ketone bodies is 3 mM. The increase of ketogenesis can lead to the ketoacidosis and the regulator mechanisms join this process. They inhibit production of ketone bodies. The increase of the level of ketone bodies in blood under principle of back connection makes the antilipolitic influence of lipoid tissue.

Catabolism of endogenous energy reserves is directed at providing the basal metabolism, functions of the vitally important organs, especially of the brain, which needs 1,600-1,800 k/day that is provided

by decay of 100-150 g of glucose.

An intensive glyconeogenesis is registered in the kidneys. 80 g of glucose is produced every day and a half of this quantity is formed owing to amino acids (protein catabolism) and glycerin (catabolism of fats). Ammonia released by desamination is expended on binding of ketone bodies, which are formed as a result of underoxidation of fats and proteins. Ungas acidosis develops as a result of this, excertion of ammoniacal salts with urine increases. The basal metabolism is decreased in this period, nitrous balance is negative. At the same time, the possibility of synthesis of another vitally important proteins preserved.

The ***third (terminal) period*** of starvation is characterized by sharp increased lysis of vitally important organ proteins using as the energy material. Respiratory coefficient is equal to 0.8. Excretion of nitrogen, potassium, sulphur, phosphorus with urine increases; ratio of nitrogen, potassium and phosphorus in urine is the same as in protoplasma of the muscular fibers. Destructive changes in mitochondria appear. Due to accumulation of chlorides and increase of the tissue osmotic concentration and also as a result of decrease of the oncotic blood pressure the retention of water occurs (cachetic oedema). The immediate cause, which provokes the disturbances of metabolism in starvation is a disorder of fermental systems connected with the difficulty of restoration of proteins — ferments, which are destructed in the process of starvation.

Organs and Systems in Starvation

Heat production is maintained during all the period of starvation on a minimum level and decreased by the end of the third period. Heat emission is somewhat reduced.

Other functions of the organism are kept within physiological limits during the first and the second period of starvation. The special disturbances are absent in the system of blood circulation and respiration. Activity of the digestive system is inhibited.

At the beginning of starvation the function of the thyroid gland and hypophysis increases. The secretion of corticotropine increases and the adrenal glands are stimulated. At the second period of starvation the function of general part of the endocrine glands is decreased. The deficiency of the non-exchange amine acids and vitamins leads to development of the symptoms which are characteristic for pellagra and beriberi.

Fattening restores all functions of the organism totally even at the beginning of the last period of starvation. It is evident that complete

starvation doesn't provoke irreversible changes. Restoration occurs during 2 weeks in loss of 40-59% of body mass during 1 month. Appetite appears, oxidative processes are intensified, process of assimilation is stimulated, and positive nitrous balance is established. However, taking into account the states of the digestive system, in starvation, it is necessary to carry out fattening carefully. Restorative possibilities of the organism become weak in repeated starvation and the moment may come, when fattening is uneffective. And the animal dies even in the presence of adipose deposits under the skin and in the omentum.

The complete starvation without water has the same course as starvation with water, but it is more severe and shorter. If water isn't introduced from without, then it is drawn from the tissues. It is the oxidative water. Many products of metabolism are formed by this, which require still more water for their excretion and the vicious circle is formed, which hastens the death of the animal.

Incomplete starvation may be **quantitative** and **qualitative.**

Quantitative starvation is registered more frequently than complete one. Many pathologic states, especially connected with disturbance of functions of the digestive organs, are accompanied by starvation of one or another degree.

Quantitative starvation appears when the organism doesn't chronically receive the necessary quantity of energy with food for energy expenditures. As this starvation is prolonged, the adaptation mechanisms begin to develop, the basal metabolism is decreased considerably. Body mass decreases slowly, that sometimes is masked by retention of water. At the same time the processes of a degenerative character develop in the tissues. These changes are more serious in incomplete starvation than in complete one, as they proceed longer. Death will come in loss about 40% of the body mass.

Qualitative starvation can be carbohydratic in deficiency of carbohydrates in food, fatty and albuminous. Albuminous starvation is the most serious. Prolonged malnutrition with primary deficiency of proteins in food leads to protein-calorie insufficiency. Such pathologic processes cause alimentary dropsy. In children it develops quicker than in adults as they have an increased need in proteins, it often leads to their death. Such starvation influences ruinously on development of nervous system of children at the age of 6 months-3 years old, when the nervous cells grow intensively. **Albuminous** insufficiency of children under condition of sufficient calorie content of food leads to the disease,

which is called Kwashiorkor's ("red boy").

The long protein insufficiency is accompanied by depression of synthesis of nucleoproteids, proteins and decrease of activity of the enzymes. The number of the cells in the organs decreases and atrophic processes develop in the marrow and in the organs of the digestive tract. The growth and development of the bones decrease. The function of the vitamins and iron is disturbed. There are conditions for development of anemia. The general metabolism decreases.

The disturbance of keratization of the skin epidermis and intensive desquamation of the skin gave rise to the name "red boy'. Development of the adipose hepatic infiltration occurs. The pancreas undergo hyalinosis and fibrosis. Spreading of dystrophic
changes to the heart and kidneys takes place. Only rational nourishment can save the child. Vitamin insufficiency is one of the forms of qualitative starvation. It can be exogenous (as a result of absence or low contents of vitamins in food) or endogenous.

Medicinal Starvation (fasting)

Now fasting is used as a non-specific method of treatment of some diseases including allergic, cardiovascular, cutaneous, diseases of the joints, obesities. Dosed starvation increases the processes of disassimilation and promotes excretion of any excessive products and "slags". It is related first of all to pathological adipose deposit, salts, products of metabolism. Transferring the endogenous nourishment the organism expends its own fats, carbohydrates and proteins. At the same time restorative processes increase, that leads to renovation, as though rejuvenation of the organism. The medicinal starvation has the same division into periods as the pathologic one, however the last period of the medicinal starvation is a period of compensation, when the general condition improves, the weakness disappears, appetite appears. Such difference from the pathologic starvation is connected with measures, carried out during the medicinal starvation for the struggle with acidosis and excretion of "slags", which increase the pathologic manifestations in a usual starvation.

COMPREHENSION CHECK

Try to answer the following questions.

1. What are the characteristics of basal metabolism?
2. Classify the types of starvation.
3. How does the basal metabolism change in starvation?
4. Characterize pathogenesis of nutritional deficiency diseases.

UNIT 14

PATHOLOGY OF THE CARBOHYDRATE METABOLISM. DIABETES MELLITUS

Pathology of carbohydrate metabolism may be presented as a complex of disturbances of both catabolic and anabolic transformations of carbohydrates. These disturbances may result from the following causes:

Disturbances of digestion and absorption of carbohydrates consist in insufficiency of amylolytic enzymes of the alimentary tract when di- and polysaccharides do not split into monosaccharides and are not absorbed. Glucose absorption is reduced, there is disturbance of its phosphorylation in the intestines. It's based on deficit in the enzyme hexokinase arising in poisoning and inflammatory process in the intestines.

In the infants of the first year of life the enzymes hexokinase and phosphatase are not quite formed or there is congenital deficiency of the enzyme lactose.

Disturbance of splitting and synthesis of glycogen. Acceleration of glycolysis in the liver results from severe excitation of the central nervous system (CNS) and is connected with intensification of sympathetic innervation (adrenalin mediator). Due to this glycogenosis (splitting of glycogen into glucose) is activated. Intensification of glycogenolysis also occurs in the increased production of hormones (Somatotropic hormone [STH], adrenalin, glucagon, thyroxin).

Reduction of glycogen synthesis occurs in severe damage of the hepatic cells (hepatitis, phosphorus poisoning, hypoxia). In glycogen deficiency the tissue energy is based on lipid and protein metabolism. In this case energy formation requires a lot of oxygen at the expense of fat oxidation. The lack of sufficient amount of oxygen leads to tissue hypoxia, accumulation of ketone bodies and development of intoxication.

12 types of glycogenoses are known, but four types are more often met. Glycogenosis of the Ist type is hepatonephromegaly or Gierke's disease. It is based on congenital deficiency of the enzyme glucose-6-phosphatase in the liver and kidneys. This enzyme splits the free glucose from glucose-6-phosphatase that promotes its trans-membraneous transfer from the cells of the liver and kidneys into blood. In its deficiency glycogen is accumulated in the cells of the liver and

kidneys, that results in their increased volume. Hypoglycemia develops and sensitivity to insulin increases. Patients have meal more often. The contents of the lactic acid from glucose-6-phosphatase are increased in blood (due to enzyme deficiency) and metabolic acidosis is broken.

Glycogenolysis of the 2nd type — Pompe's disease develops in congenital deficiency of acid a-1.4-glucosidase. This enzyme splits the glucose residues from glycogen molecules and maltose. Lysosomas contain this enzyme and it is separated from phosphorylase of cytoplasm. Glycogen is accumulated in lysosome, fills it and destroys it. As a result of glycogen oxidation in the heart, it becomes enlarged. Children die from cardiac insufficiency.

There may be disturbances of intermediate carbohydrate metabolism.

a) Hypoxia conditions (insufficiency of respiration and circulation, anemias) when lactic, and pyrotartaric acids are accumulated.

b) Dysfunction of the liver where some part of the lactic acid is re-synthesized into glucose and glycogen in the norm. Acidosis develops.

c) Hypovitaminosis of vitamin B_1 (thiamin). Decarboxilation of γ-ketoacid is disturbed in vitamin B_1 deficiency and lack of cocarboxylase results in synthesis disturbance of acetyl-CoA from pyruvate. It damages the nervous endings (acetylcholine is not synthesized and transmission of the nervous impulses is absent).

The ***frequent cause*** of disturbance of carbohydrate metabolism is change of the neurohormonal regulation that leads to hypo- and hyperglycemia.

The consequences of the nervous regulation disturbance were demonstrated by Claude Bernardt (1865) who showed that the prick into the fundus of the 4th ventricle led to hyperglycemia. Hyperglycemia may be caused by stimulation of the ashen tuber of the hypothalamus, lentiform nucleus, striate body, as well as mental overstrain, emotions, pain and attacks of epilepsy. There is a second way of the central influence of the nervous system, which goes to pancreatic islets by the parasympathetic fibers.

Disturbance of carbohydrate metabolism may be connected with disturbance of peripheral mechanisms of hormonal effect. The leading factor of disturbance is change of correlation between insulin activity and contra-insulin hormones. Insulin deficiency and prevalence of contra-insulin hormones are accompanied by hyperglycemia: its origin is explained by reduction of insulin allosteric effect that results in decrease of the cell permeability for glucose, slowing down of

hexokinase reaction and formation of glucose-6-phosphate and hence further metabolism of glucose, intensification of process of glyconeogenesis. Hyperglycemia is observed in excessive amount of such contra-insulin hormones as glucagon, adrenalin, glucocorticoids, corticotropin, somatotropin, thyroxin.

Adrenalin hyperglycemia is a result of the increased glycogenosis (splitting of glycogen into glucose) in the liver.

Glucocorticoids — hormones of zone fasciculata of the adrenal cortex increase glucose level in the blood by activation of glyconeogenesis (glucose synthesis from amino and fatty acids). They also decrease permeability of the cell membranes for glucose, slow down hexokinase reaction and formation of hexoso-6-phosphate.

Corticotropin has a similar action as glucocorticoids, for it stimulates their excretion, intensifies glyconeogenesis and inhibits activity of hexokinase.

Somatotropin (hormone of growth) is produced in adenopituitary. It may cause hyperplasia of α-cells of the pancreatic islet» and increases glucagon secretion, reduces hexokinase activity and stimulates activity of the liver insulinase.

Thyroxin is a hormone of the thyroid which stimulates absorption of glucose in the intestines, intensifies activity of the liver **Phos**phorylase. Its hyperfunction is characterized by decrease of the organism tolerance for carbohydrates.

Hyperglycemia may be alimentary, i.e. it develops after large intake of easily digestive carbohydrates. Glucose is quickly absorbed from the intestines exceeding the ability of the liver, muscles and other organs to assimilate it. Excessive carbohydrates influence on the receptors of the gastro-intestinal tract cause acceleration of glycogenolysis in the liver by reflex. If the contents of glucose in the blood exceed 8.8 mmol/1, glucose appears in the urine (glucosuria).

Alimentary hyperglycemia is used as a test for evaluation of carbohydrate metabolism (sugar loading or glucose-tolerant test).

Tolerance for carbohydrates determines the maximal quantity of glucose, which can be digested by the organism without glucosuria. It is 160-180 g of glucose taken on an empty stomach in a human. In the decreased tolerance for carbohydrates glucosuria develops in less amount of glucose, i.e. when its level in the blood exceeds the renal threshold — 8.8 mmol/1. In large concentration of glucose in the blood the enzyme systems responsible for glucose reabsorption in the tubules

of the kidneys (hexokinase and glucose- 6-phosphatase) do not provide phosporylation of all glucose and come of it is excreted with urine. In some cases glucosuria may develop without hyperglycemia, i.e. when the enzyme processes in the kidneys are disturbed. They are the basis of glucose reabsorption. Renal diabetes arises in introduction of phlorizin or in hereditary fermentative defects in the distal tubules of the kidneys.

Hypoglycemia is reduction of glucose in the blood below 4.4 mmol/1. It develops as a result of insufficient coming of sugar into the blood, its accelerated excretion from the blood or due to combination of these factors. The causes of hypoglycemia are different. They are:

1) Overdosage of insulin in treatment of diabetes mellitus.

2) Increased production of insulin in hyperfunction of the insular apparatus of the pancreas (hyperplasia, insulinoma).

3) Insufficient production of hormones promoting catabolism of carbohydrates: thyroxin, adrenalin, glucocorticoids.

4) Glycogenolysis insufficiency in glycogenosis (Gierke's disease).

5) Damage of the hepatic cells (acute and chronic hepatitis).

6) Carbohydrate fasting (alimentary hypoglycemia).

7) Melabsorption of carbohydrates in the intestines.

8) Renal diabetes in intoxication by poisons blocking hexokinase.

9) In newborns due to insufficiency of mechanisms of carbohydrate metabolism regulation.

The central nervous system is especially sensitive to glucose deficiency, for it is the only source of energy. That's why oxygen consumption by the brain is sharply decreased in hypoglycemia. Irreversible changes take place in the nervous cells in prolonged hypoglycemias.

At the level of sugar of 4-3 mmol/l there are tachycardia due to adrenalin hyperproduction, feeling of hunger (excitation of the venterolateral nuclei of the hypothalamus by low level of blood glucose), symptoms of impairment of the central nervous system — and tremor, weakness, irritability, feeling of fear. At the level of glucose below 3-2.5 mmol/l hypoglycemia coma develops with sharp inhibition of the central nervous system.

Epileptic-like convulsions occur. They have a compensatory character, for they contribute to splitting of muscular glycogen. Glucose is synthesized in the liver from the formed lactic acid and sugar level in the blood increases.

DIABETES MELLITUS

Diabetes mellitus is a disease resulting from absolute or relative insulin insufficiency and accompanying by disturbance of metabolism, mainly, carbohydrate one. The main manifestation of diabetes mellitus is hyperglycemia, sometimes reaching 25 mmol/1, glucosuria with glucose in urine up to 555-666 mmol/1 (100-200 g/day), polyuria (to 10-12 1 of urine per day), polyphagia and polydipsia. It is also characterized by the increased level of lactic acid (lactocydemia) — over 0.8 mmol/1 (N — 0.033-0.078 mmol/1); lipemia — 50-100 g/1 (N — 3.5-8 g/1), sometimes ketonemia (by determination of acetone) with the increased level of ketone bodies to 5200 mcmol/1 (N < 517 mcmol/1).

Etiology

The cause of diabetes mellitus is insulin insufficiency. According to mechanism of arising, insulin insufficiency may be pancreatic, i.e. connected with disturbance of biosynthesis and production of insulin or relative extrapancreatic in normal production of insulin by the pancreatic islands.

The main cause of pancreas alteration:

1. Hereditary predisposition.
2. Emotional overstrain.
3. Trauma, tumor.
4. Inflammatory process under the influence of infection/viruses.
5. Autoimmune conflict.
6. Hypoxia.
7. Overeating.

Classification

According to causes and degree of insulin insufficiency diabetes mellitus may be primary and secondary (sympathetic). Two types are distinguished in primary diabetes mellitus:

— I type — insulin-dependent diabetes mellitus (IDDM);

— II type — insulin-independent diabetes mellitus (IIDM) (Fig. 19, 20).

Insulin-dependent diabetes mellitus is characterized by insulinopenia, i.e. absolute insulin insufficiency, sharp metabolic disturbances and ketoacidosis. This form of diabetes develops in youth, genetic predisposition is combined with antigens of HLA system of the main histologic compatibility which are located in the 6th chromosome.

There are data indicating autoimmune origin of diabetes of this type. They are:

1. Combination with other autoimmune diseases (insulinitis, thyroiditis).

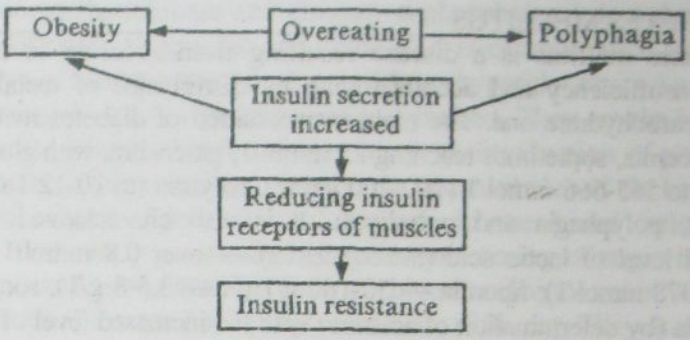

Fig. 19. Hyperinsulinemic pathogenesis of type II DM with obesity

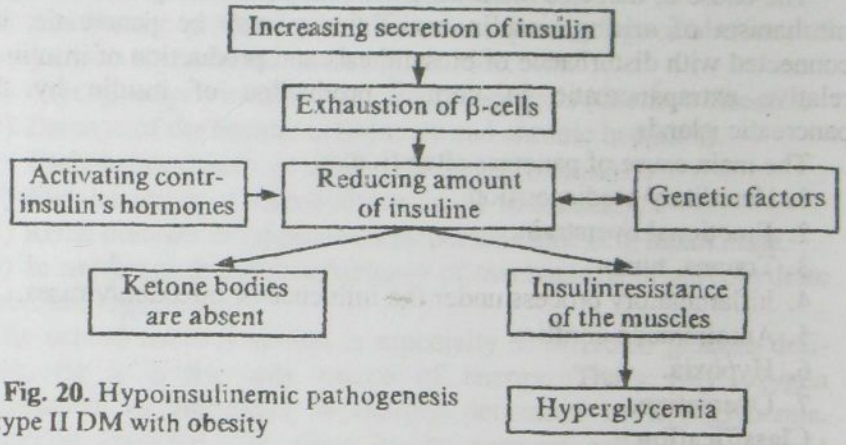

Fig. 20. Hypoinsulinemic pathogenesis of type II DM with obesity

2. Antibodies to insulin, β-cells.

3. The disease may be connected with the preceded viral infection (measles, rubella, hepatitis).

Viruses possessing increased β-tropism may be external factor promoting realization of the hereditary predisposition to diabetes mellitus. They destroy β-cells and start the development of autoimmune process (Fig. 21).

Insulin-independent diabetes mellitus is characterized by minimal metabolic disturbances. It is based on relative insulin insufficiency arising in constant overeating, obesity, the decreased number of receptors to insulin. There are no antibodies to insulin in P-cells. Diabetes is manifested after 40 and has more marked hereditary tendency than I type diabetes.

Pathogenesis

Insulin insufficiency in diabetes mellitus is accompanied by disturbance of all kinds of metabolism: carbohydrate, protein and fat.

Disturbances of carbohydrate metabolism is characterized by the following peculiarities: the speed of hexokinase reaction is slowed down. It is connected with the decreased permeability of the cellular membranes for glucose and its transportation into the cells as well as the decreased activity of hexokinase in the cells of the tissues and liver. This results in slowing down the formation of glucose-6-phosphate and its further use for glucagon synthesis, pentosophosphate cycle and glycolysis.

Glucose-6-phosphate is formed in the liver only during the process of glycogenesis. The activity of Phosphorylase and glucose-6-phosphatase increases due to insulin deficiency in the liver that promotes intensified glycogenolysis and formation of glucose.

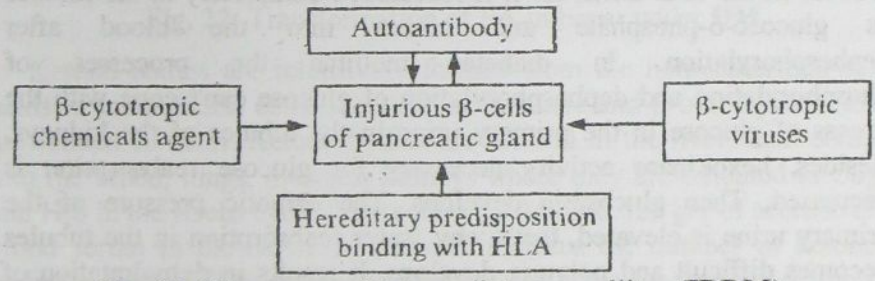

Fig. 21. The causes of **1** type diabetes mellitus **(IDDM)**

Glyconeogenesis, that is formation of glucose from aminoacids, fat acids, lactate and pyruvate, is sharply increased.

The effect of glucose-6-phosphatase and phosphoenolpyruvate-carboxilase is also activated. This reaction can be explained by the effect of glycocorticoids.

It is proved that hyperglycemia in diabetes mellitus is of compensatory character because at the high level of glucose in the blood its consumption by the tissues is improved. At the same time hyperglycemia has a negative effect being a factor of diabetic angiopathies as well as damage for organs and tissues.

Angiopathies are manifested as atherosclerosis, obliteration and other impairments of the blood vessels. In hyperglycemia the possibility of phosphorylation of excessive glucose in the cells of insulin-

independent tissues increases. These tissues are the lens, hepatic cells, basophilic insulocytes, nervous tissue, erythrocytes, aorta wall. The process of glucose transformation into sorbitol and fructose is accelerated. They are osmotically active substances leading to disturbance of metabolism in these tissues and their damage. Hyperglycemia is accompanied by increased concentration of gluco- and mucoproteids, which fall out easily in the connective tissue promoting the formation of hyalin and damage of the vascular wall. Therefore early atherosclerosis is characteristic for diabetes mellitus. Atherosclerotic process develops in the coronary vessels of the heart and renal vessels. Diabetes mellitus is often combined with hypertension in elderly people. Hypercholesterolemia in diabetes mellitus is also an important factor of damage of the vascular wall.

Glucosuria

In the norm glucose is present in the primary urine. There is no glucose in the final urine, for it is reabsorbed completely in the tubules as glucoso-6-phosphate and comes into the blood after dephosphorylation. In diabetes mellitus the processes of phosphorylation and dephosphorylation of glucose can't cope with the excess of glucose in the primary urine in the tubules of the kidneys. Besides, hexokinase activity necessary for glucose reabsorption is decreased. Then glucosuria develops. The osmotic pressure of the primary urine is elevated, that's why water reabsorption in the tubules becomes difficult and polyuria develops. It results in dehydratation of the organism that leads to intensified thirst (polydipsia).

Disturbance of Fat Metabolism

Insulin insufficiency results in reduction of glucose coming into the fat tissue and formation of fat from carbohydrates, and reduction of resynthesis of tryglicerides from fat acids. In scanty glycogen in the liver, lipolysis and mobilization of fat acids from the fatty tissue are increased. It is connected with intensification of lipolytic effect of somatotropin (in the norm it is inhibited by insulin). The increased quantity of fatty acids comes into the liver, some of them are synthesized to triglycerides which is a precondition for the liver obesity. Other part is split (3-oxidation) and a great number of acetyl-CoA is formed (Fig. 22).

There may be no fat infiltration in the liver, if the pancreas produces lipocaine stimulating the action of lipotropic substances rich in

methionine (curds, mutton). Methionine is a donor of methyl group for choline, which stimulates the release of fat from the liver. There is no obesity of the liver in this case.

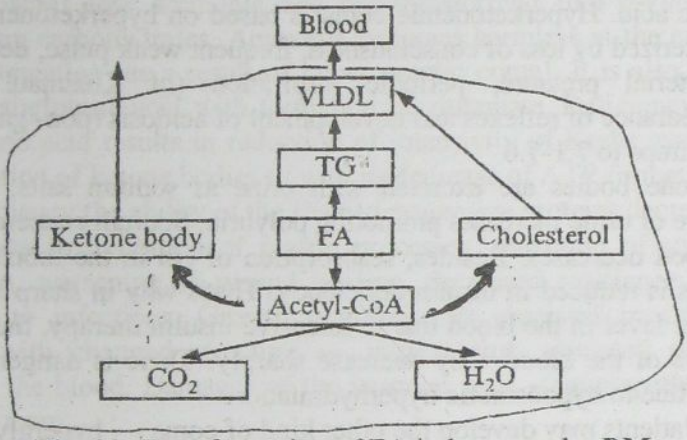

Fig. 22. Transformation of FA in hepar under **DM**

Ketone bodies are intensively formed from the non-estherified fat acids in mitchondria cells. Acetone, acetoacetic and β-oxibutyric acids are related to them. Ketone bodies are formed in the liver, then come into the blood, lungs, muscles, kidneys where they are oxidated to $C0_2$ and H_20 in the Krebs cycle. There must be 0.002-0.025 g/l of acetone in blood serum in the norm. In diabetes mellitus the number of ketone bodies increases. The following factors are in the mechanism of their accumulation:

1) Intensified decomposition of fatty acids from fat depot and their accelerated oxidation to acetyl-CoA.

2) Reduced activity of the Krebs cycle, hence there is disturbance of transformation of acetyl-CoA into citrate and its burning in the Krebs cycle.

3) Delay of resynthesis of fatty acids from acetyl-CoA in the liver and fat tissue as a result of $NADPH_2$ deficiency (reduced speed of pentosophosphate cycle).

4) There is decreased activity of the enzyme acetyl-CoA carboxilase, which participates in the synthesis of fatty acids through malonil-CoA. Therefore, acetyl-CoA is a source of ketogenesis as well as synthesis of cholesterol from acetoacetic acid being unused in the synthesis of fatty acids and uninvolved in the Krebs cycle.

Ketone bodies being in toxic concentration inactivate insulin, ag-

gravating insulin insufficiency. The concentration of acetone is the highest. It injures the cells, dissolving the lipid layer of the cells, inhibits sharply the central nervous system. The most toxic is acetoacetic acid. Hyperketonemic coma is based on hyperketonemia. It is characterized by loss of consciousness, frequent weak pulse, decrease of the arterial pressure, periodic respiration (of Kussmaul's type), disappearance of reflexes and development of acidosis (non- gas), pH of blood drops to 7.1-7.0.

Ketone bodies are excreted with urine as sodium salts. Osmotic pressure of urine increases promoting polyuria. Sodium concentration in the blood decreases. Besides, reabsorption of Na in the tubules of the kidneys is reduced in insulin deficiency. That's why in sharp reduction of sugar level in the blood due to intensive insulin therapy, the osmotic pressure of the blood, may decrease sharply. There is danger of brain edema due to hypoosmotic hyperhydratation.

Patients may develop the other kind of coma — hyperglycemic. It may develop in absence of ketonic bodies but high hyperglycemia (50 mmol/l and higher), increased amount of sodium, chlorine and urea in the blood (as a result of damages of the tubules of the kidneys). These lead to hyperosmia and total dehydration. This kind of coma is also called hyperosmotic (Fig. 23).

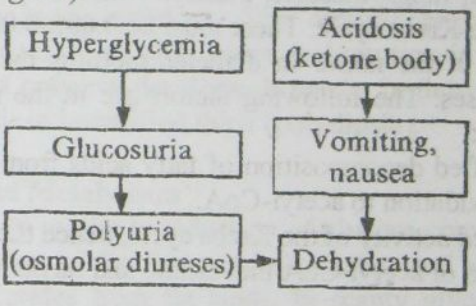

Fig. 23. Dehydration mechanisms under DM

Disturbances of Protein Metabolism

Protein synthesis in diabetes mellitus decreases. It falls out or stimulating influence of insulin on enzyme systems of this synthesis is weakened. The level of energy metabolism providing protein synthesis in the liver is decreased. Conduction of aminoacids through cell membranes is disturbed.

Thus, insulin deficiency leads to intensified activity of glyconeogenesis enzymes (glucose from aminoacids and fat is intensively formed).

Aminoacids lose ammonia and are transformed into α-ketoacids, which form carbohydrates. Ammonia becomes harmless at the expense of urea formation (as a result of hyperosmotic coma). It is also bound with α-ketoglutaric acid with formation of glutamate. Deficiency of α-ketoglutaric acid results in reduction of intensivity of Krebs cycle and accumulation of ketone bodies as well as decrease of ATP formation. In ATP deficiency the ability of the liver to synthesize proteins decreases.

It results in inhibition of plastic processes, reduction of antibody production, worsening of wound healing, decreased resistance of the organism to infections. Growth retardation is observed in children. Proteins with changed structure — paraproteins, glycozed proteins appear in the blood. Damages of the vascular wall — angiopathies are related to them.

COMPREHENSION CHECK

Try to answer the following questions.

1. Describe the main cause of pathology of carbohydrate metabolism.
2. Note the classification of diabetes and glucose intolerance, their mechanisms.
3. Identify acute and chronic complications of diabetes melli tus.

UNIT 15

PATHOLOGY OF LIPID METABOLISM. ATHEROSCLEROSIS

Fat plays a very important role in the organism.

1. Fat is a source of reserve energy, its supply are 10%.
2. Fat is a source of endogenous metabolic water.
3. Fat participates in heat production.
4. Cholesterol participates in:

a) construction of the cellular membrane and consequently in its permeability;

b) being the dielectric it provides the conduction of impulses in the definite direction (without myelin coat may be "chaos" in the nervous system);

c) the corticosteroids, sex hormones, bile acids, vitamin D are formed from cholesterol.

There are following disturbances of lipide metabolism:

a) hyperlipemia (essential, genotypic, retention, transport) (Table 9);

b) atherosclerosis, arteriosclerosis;

c) obesity;

d) fatty infiltration and dystrophy (liver and oth. organs), fatty degeneration.

Arteriosclerosis is a chronic disease of the arterial system characterized by abnormal thickening and hardening of the vessels walls. Smooth muscle cells and collagen fibers migrate into the tunica intima causing it to stiffen and thicken; this decreases the artery's ability to change lumen size.

Atherosclerosis is a form of arteriosclerosis in which the thickening of the vessel walls is caused by hardening of soft deposits of intraarterial fat and fibrin that reduce lumen size. Atherosclerosis can take several forms depending on the anatomic vessels location, the individual's age, genetic and physiologic status, and the risk factors to which each individual may have been exposed. It is the leading contributor to coronary artery and cerebrovascular disease.

Lipid deposition is an early event in atherogenesis and occurs with excessive influx and deposition of macrophages containing oxidized low-density lipoproteins (LDL) into the arterial wall. This event occurs subsequent to endothelial injury. The lesions of atherosclerosis occur primarily within the tunica intima or the innermost layer. These lesions

include the fatty streak, fibrous plaque, and complicated lesion. The early ***fatty streak*** is a flat, yellow, lipid- filled smooth muscle cell that causes little or no obstruction of the affected vessel.

Table 9. Types of hyperlipoproteinemias according to HWO classification

Types	Hereditary origin	Acquared
Type I — OChM	Deficiency lipoprotein lipase	Systemic lupus erythematosus (SLE)
Type Iia — OLDL	Family hypercholesterinemia (deficiency receptors to LDL)	Hypothyroidism
Type Iib — OLDL + OVLDL	Combine familial hypercholesterinemia	Nephritic syndrome
Type III — Tremnant particles of ChM + TIDL	Family hyperlipoproteinemia of the III type	Obesity
Type IV — tVLDL	Combine family hyperlipidemia	Diabetes mellitus
Type V — OChM + OVLDL	Family hypertriglycerides	Alcohol intoxication

Legend: t — increase, Ch — chylomicrons, LDL — low density lipoprotei- des, VLDL — very low density lipoproteides, IDL — intermediate density lipoproteins.

Fibrous plaque is the characteristic lesion of advancing atherosclerosis and consists of lipid-laden smooth muscle cells surrounded by a fibrous matrix. The lesion is elevated and protrudes into the lumen of the artery. The core of the fibrous plaque consists of lipids and debris from cellular necrosis caused by insufficient blood supply. If the lesion progresses sufficiently, it occludes the arterial lumen at arterial bifurcation, curves, or regions where the arteries taper.

Complicated lesions occur as the fibrous plaques are altered by hemorrhage, calcification, cellular necrosis, and blood clots throughout the intimal layer. As the altered complex structure becomes rigid, it causes extensive vascular occlusion.

High blood pressure develops if arteriosclerosis elevates systemic vascular resistance. Cerebral or myocardial ischemia is a life-threatening manifestation of atherosclerosis that occurs in the vessels of the brain or heart.

ETIOLOGY

As it is well-known there are many various risk factors, which predispose to atherosclerosis. The main of them:

1. Age. Cholesterol is a product, which is difficult metabolized and subendothelium of the vessels is bradytrophic tissue. A lot of cholesterol is contained in β-lipoproteins (70-75%) and β-lipoproteids are increased in elderly persons.
2. Hereditary predisposition. There are the data about familial hypercholesterinemia with high level of LDL and VLDL ("atherogenous", "worse" cholesterol)
3. Hypodinamia and hypoxia predispose to atherosclerosis because they decrease oxidation of lipids and promote to accumulation with following consequences — infiltration, proliferation, degeneration with calcification, cellular necrosis and sclerotic processes progressing.
4. Stress. It is proved that neuro-emotional overtension may lead to disorders in trophycity of the wall of the vessels due to decrease of resistance to injurious factors.
5. Overeating especially with using of animal fats.
6. Intoxication by alcohol, smoking, microbes, chemical materials.
7. Hormonal disturbances as hypothyroidism, hypogonadism, Cushing's syndrome.
8. Pathology of the liver.
9. Diabetes mellitus.
10. Gout, obesity, xanthomatosis, hereditary forms of hyperlipoproteinemia and hypercholesterinemia.

PATHOGENESIS

Pathogenesis is based on the metabolism disturbances, which lead to hyperlipemia, hypercholesterinemia and hyperbetalipoproteinemia. HDL are β-lipoproteids containing a lot of protein and few lipids, and possess the antiatherogenous influence. They provoke a reverse transport of cholesterol from the cells, vessels, liver and promote its excretion from the organism in a form of biliary acids.

LDL — VLDL — are lipoproteins with low and very low density

containing a few proteins and a lot of lipids. LDL and VLDL are the atherogenic, they promote to accumulation of cholesterol in the wall of the vessel.

Hypertension, inflammatory processes in the vascular wall, formation of LP-IgG autoimmune complexes promote the sclerosis of the vascular wall. It leads to the disturbance of receptor-mediated (capture of LDL and transformation of macrophages into the foam cells, which are the base of lipid spots. Then the fibrous patches are formed, calcification and thrombogenesis are in progress.

Atherosclerosis is a reaction of the connective structures of the aorta and large arteries on falling out of cholesterol in to the subendothelium. Atherosclerosis doesn't happen without cholesterol.

I stage is deposition of lipids -» irritation of the histiocytes proliferation of the histiocytes.

II ***stage*** is xanthomatosis → histiocytes → capture of lipids → irritation of fibroblasts → thickening of the subendothelium, deformation of the elastic tissue consolidation of the connective fibers.

III ***stage*** — patches, nutrient material is received by histiocytes with difficulty, necrosis.

IV stage is atheromatosis, formation of ulcers, which can perforate thrombi occurs.

Why does the falling out of cholesterin provoke such morphology?

$C_{27}H_{46}0$ — is cholesterol, a substance which is difficult to metabolize. It provokes reaction as a heterologous substance in getting into the subendothelium (bradytrophic tissue). Triglycerides provoke the analogical reaction.

Pathological Substantiation of Therapy

The diet is relatively poor in easily assimilated carbohydrates, poor in animal fats. Corn, sunflower-seed oil, linseed oil promote "outburst" ions of Mg provide splitting of cholesterol. Many lipotropic food factors must be present — milk products as they form the lecithin. Vitamins B_6, B_2 with fatty acids cause "outburst" of cholesterol. Nicotinic acid remove the methylic groups and increase the quantity of p-lipoproteids.

Vitamins B_{12}, B_{15} — pantothenic acid — activates the oxidative processes. Rutin is recommended as the factor decreasing the permeability and owing to this closes the door for lipoproteids and cholesterol.

Introduction of small doses of mentioned above vitamins activates the mast cells and thereby lipolytic activity of the vascular wall,

stimulates the synthesis of thyroid hormones.

Heparinoids are almost avoided of anticoagulative properties, they retain the influence on lipoproteinic lipase.

The preparations, which block the synthesis of endogenous cholesterol on the level of acetic acid, were created. However they can block the synthesis of the adrenal hormones. Atromid (clofibrate — in England), phenoxal, cetamyfen.

Thyroidin, thyroxin increase the decomposition of cholesterol.

Sour clotted milk, mineral waters, laxatives intensify excretion from the intestine.

Physical training disturbs the synthesis of endogenous cholesterol.

Any disturbance which disintegrates the exchange and synthesis of lipids in the liver may be the cause of fatty degeneration of the liver:

— increased hepatic lipogenesis;
— decrease of oxidation of fatty acids;
— increased lipolysis of the adipose tissue;
— delay of secretion of lipoproteins of very low density (VLDL).

Combination of lipid and protein synthesis is necessary for production of VLDL in the liver and their disturbance lead to the accumulation of fat in the liver. Insufficient nourishment and deficiency of aminoacids disturb the synthesis of apolipoproteids and decrease the production of lipoproteids. The same result is observed in increased lipolysis in the adipose tissue in the starvation or diabetes mellitus, when the insertion of lipid and protein predecessors in exchange of lipoproteids occurs. Disturbance of formation of phospholipids is very important in pathogenesis of adipose infiltration. Sufficient contents of them in the liver secure the thin dispersion of fat and ability of its excretion from the liver. Phospholipids are present in composition of p-lipoproteins and make their going out from the hepatic cells easily. Some of fatty acids participate in formation of phospholipids and leave the liver with them. Besides, the fatty acids are oxidated better in a molecule of phospholipids. Choline and methionine, which give the methylic groups for the formation of choline, are the necessary components of basic hepatic phospholipid — lecithin. So the deficiency of choline, methionine and other lipotropic substances in food leads to the development of the adipose infiltration of the liver. Deficiency of endogenous lipotropic factor — lipocaine — leads to the same result. Lipocaine activates the formation of phospholipids in the liver, oxidation of fatty acids in it and preserves the liver from obesity.

Insufficiency of the factor is important in pathogenesis of hepatic obesity in diabetes mellitus.

Disturbance of the formation of choline is possible in deficiency of vitamin **B1**, folic and pantothenic acid.

OBESITY

Obesity is surplus of adipose deposits in the adipose tissue. Obesity is more often met in women at the age groups older than ;50. In the economically developed countries obesity among the adult population is met in 30-60% and the body mass exceeds the norm by 20%.

Etiology

Obesity is a result of disorder of homeostasis of energy exchange. Internal factors, which change the behavior of men as to the nourishment, take part in its appearance. These factors are determined by genetical, constitutional peculiarities of the person, and also by influence of the environment. The latter includes mother's nutrition in pregnancy, child's feeding in baby's age and early childhood, types of unconditioned reflexes connected with nutrition; family and national traditions, the level of well-off and availability of food; motor activity. Increased consumption of food is one of the basic causes of obesity. Primary disturbances of neurohormonal regulation, changes of adipocytic metabolism or genetic factors are rarely the cause of obesity. The primary (constitutional) — 55- 65%, secondary (symptomatic) and cerebral (16-20%) obesity are distinguished by etiology. The role of heredity in obesity is important. The structure and function of the systems, which regulate (he
alimentary behavior, peculiarities of adipocytic and myocytic metabolism can be inherited. It is observed, that obesity develops in some generations of one and the same family. However this information isn't the direct evidence of the role of heredity in obesity as we can't exclude the influence of the environment, habits concerning the kinds of food, and also the way of life. More convincing information is received in the experiment.

Pathogenesis

Three basic pathogenetic factors are important in the development of obesity: increased intake of food, which doesn't correspond to the energy expenditures; insufficient mobilization of fat from the depots; surplus formation of fat from carbohydrates (S. M. Leites).

The surplus consumption of food, which is provoked by increased

appetite, can be stipulated by increased excitability of the "nutritional center," which is situated in the anteriolateral nuclei of the posterior hypothalamic region. The changes, to which the nutritional center is reacting, can be the cause of prolonged nutritional excitation and as a result of alimentary obesity. So, all states, which decrease the level of glucose in blood, steady and quickly for example, some increase of the function of the pancreatic islands, are accompanied by feeling of hunger, which stipulates the possibility of overeating. The signals from the receptors of the alimentary tract are also important in activity of the nutritional center. A definite degree of extension of the stomach inhibits the activity of the nutritional center. In decrease of sensitivity of the nervous endings in the wall of the stomach the inhibition develops only in excessive extension of (the stomach, diet also creates the preconditions to overeating and obesity. Dysbalance of energy is possible in transition from the physical labour to the way of life without physical loading if the former degree of excitability of the nutritional center is preserved. Obesity can be connected with disturbance of fat mobilization from fat depots as a source of energy in normal function of the nutritional center.

The regulation of process of mobilization and deposition of fat is accomplished by the nervous and endocrine systems. So decrease of the tonus of the sympathetic nervous system can provoke the delay of mobilization and going out of fat from the adipose tissue. Disappearance of fat from the adipose tissue on the head and thorax with simultaneous deposition of it in lower half of the body is observed in.

Barraquer — Simons disease — progressive lipodystrophy connected with lesion of the centers of the diencephalon, spinal cord and nodes of the sympathetic trunk. Disturbance of mobilized fat influence of hormones is observed in pathology of the pituitary, thyroid gland, adrenal and sexual glands. Obesity, which is characterized by hyperinsulinism, resistance to insulin and hyperglycemia, can be observed. It is considered that basic damages are at the level of target cells. They are connected with decrease of quantity of receptors for insulin stipulating the resistance to insulin and compensatory hyperinsulinism. Now the peculiarities of the adipose tissue, quantity and size of fatty cells — adipocytes are taken into account in pathogenesis of obesity. The quantity of the adipose cells is a genetically stipulated factor and their size depends on the age, sex, influence of the regulatory and metabolic factors. Quantity of the

adipose cells is relatively constant and doesn't change with age. It is more in women than in men. The quantity of the adipose cells in young people is $3*10^{10}$, contents of fat in the adipocyte is 0.6 mcg, total quantity of fat in the organism is about 18 kg. There are cases of obesity with total quantity of fat more than 70 kg, with normal quantity of adipocytes, however the mass of one cell is 1.6 meg. In other cases the mass of adipocytes remains normal and their quantity reaches 910. Total quantity of fat can be equal to 100 kg and more.

Pathogenetical classification based on the criterion of size and quantity of adipocytes distinguishes two types of obesity: hypertrophic and hyperplastic.

Hypertrophic obesity depends on the quantity of fat in each adipocyte that is connected with increased concentration of insulin, hyperlipemia, decrease of the tolerance to glucose. Not infrequently this form of obesity is complicated by development of atherosclerosis and diabetes mellitus at young age.

Hyperplastic obesity is connected with increase of quantity of adipocytes, which depends on the genetic factors or the environment regulating the morphogenesis of the adipose tissue in the embryonal period and at early age. Obesity influence the organism unfavorably. The negative influence of obesity is manifested in less degree at young age, when adaptational possibilities are expressed better. And the quantity of complications connected with obesity increases with age. The mortality of people with obesity at 20-24 years old by 30% higher than in persons with normal body mass, and it is by 50% higher in persons of 40-55 years old. The pro-

longed obesity provokes a number or functional changes in the vitally important organs and also the disturbance of metabolism in connection with deposition of large quantity of fat and increase of the loading on most of vitally important organs. First of all the metabolism in the adipose tissue is disturbed, where the speed of synthesis of triglycerides and lipoproteins is increased, ability to mobilization of the adipose reserves is disturbed, hyperlipemia, increase of free fatty acid level, hypercholesterinemia are observed. Disturbances in carbohydrate metabolism are manifested in limitation of glucose metabolism, increase of glycogen content in the liver. Utilization of glucose is impaired in the muscular tissue in spite of hyperinsulinism. Respiratory coefficient equal to 0.7-0.74 is evidence that fatty acids are used as a source of energy.

Deposition of fat in the myocardium decreases significantly the contractile function of the heart. Obesity is often accompanied by atherosclerosis, increase of the arterial pressure, blood coagulation, development of thrombosis. The pulmonary ventilation is deteriorated, vital capacity is decreased, predisposition to the congestion and development of chronic inflammation in the respiratory tracts appear. Dyspnea arises even in small physical loading. The circulatory and respiratory hypoxias appear.

Combination of obesity with diabetes mellitus arises in the case of insulinoresistance connected with decrease of the number of receptors of insulin on the surface of the adipose cells.

Compensatory hypertrophy and hyperplasia of the pancreatic islands providing the increased secretion of insulin (hyperinsulinism) for overcoming resistance, is followed by exhaustion. In this case it is supposed that obesity is etiological factor of diabetes mellitus.

COMPREHENSION CHECK

Try to answer the following questions.

1. Name types of hyperlipoproteinemias due to WHO classification.
2. Characterize atherosclerosis: the main risk factors and pathogenesis.
3. Recall pathophysiological groundation of therapy.
4. Describe obesity. What is the role of genetical, constitutional and environmental factors in their development?
5. Make distinctions between hypertrophic and hyperplastic obesity.

UNIT 16

PATHOPHYSIOLOGY OF WATER-ELECTROLYTE METHABOLISM. ACID-BASE IMBALANCE

The water contents of the adult organism are on an average 60 % of the body mass. Most of water (35-40% of the body mass) is inside the cells (intracellular fluid). Extracellular fluid composes 15- 25 1 of the body mass and is subdivided into intravascular (5%), intercellular (12-15%) and transcellular (1-3%).

A person drinks about 1.2 1 of water, about 1 l comes into the organism with food and about 300 ml of water is produced in oxidation of the nutrients during a day. In normal water balance the same amount of water (about 2.5 1) is excreted from the organism by the kidneys (1-1.5 1), skin vaporization (0.5-1 1) and the lungs (about 400 ml) as well as feces (50-200 ml).

With aging the amount of total body water decreases. In old age the amount, of the extracellular fluid is increased but at the time the content of H_20 in the cells is reduced.

The intracellular fluid is presented in three conditions:

1. Water of the protoplasma bound with hydrophilic structures.
2. Water of attraction on the surface of the colloid structures.
3. Capillary water — in lacunas of the protoplasma — the most mobile, relatively free water of the cells.

In different pathologic conditions the volume of the intracellular fluid changes most frequently at the expense of the change of the mobile water volume.

The intracellular fluid is blood plasma. One of its important functions is formation of medium for normal vital activity of the cellular elements of blood. The volume of blood plasma composes 3.5- 6% of the body mass. 93% of it is pure water.

The intercellular or interstitial fluid is the fluid of the extracellular and extravascular space. It washes the cells directly and by ion and molecular contents it is close to blood plasma (except protein contents). This fluid is in constant exchange with blood plasma so that approximately 20 litres of fluid with the dissolved substances come into the tissues from the vessels per day and the same amount returns into the general blood flow and 3 litres of it return through the lymphatic vessels.

The transcellular fluid is a special fluid of the organism. It is related to

the digestive juices, the content of the tubules of the kidney, articulatory, cerebrospinal fluids, chamber humor of the eyes, etc. (Table 10).

Table 10. Average indices of water sectors, ion concentration, glucose in physiological state of water-electrolyte metabolism in adults

Age	Adult
Mass (average)	70 kg
Total mass of water	42 1 (60% of body mass)
Intracellular water	25 *i* (35-40% of body mass)
Extracellular water: 1. intercellular 2. intravascular 3. transcellular	15 1(15-25% of body mass) 101(12-15% of body mass) 4 1 (5% of body mass) 1 1(1-3% of body mass)
Posm	300 mosmol/1
P Na^+	135-145meg/I (extracellular plasma)
P K^+	4-5 mmol/1 (extracellular plasma)
Total blood protein	60-80 g/1
Glucose	5.5 mmol/1
pH	7.36-7.45
Diuresis	2.5 1
Blood urea	7-9 mmol/1
Plasma Creatinin	50-100 mmol/1

Changes ***of*** the volume of the organism water sections occur due to:

— primary changes of electrolyte composition of the fluid medium of the organism (shifts, water movement);

— primary dehydration of the organism;

— pathologic retention of water in the organism.

And the most mobile fluids of the organism — intravascular and interstitial — are the first to change their volume.

The fluid medium of the organism possesses a constant electrolyte composition and they are in the condition of osmotic equilibrium. However, the electrolyte composition of the extracellular fluids differs from that of the intracellular ones. The cellular fluids contain more ions of potassium (K), magnesium (Mg), phosphates ($HP0_4$) and the extracellular fluids contain more ions of sodium (Na), chlorine (CI), calcium (Ca), bicarbonates ($HC0_3$). The protein contents in the cells exceed considerably that of the intercellular fluid.

The constant volume and osmolarity of the extracellular fluid is maintained by the regulatory mechanism, mostly by the kidneys. In stimulation of the osmoreceptors of the hypothalamus area (in increased blood osmolarity) as well as volumoreceptors of the left atrium (in decreased blood volume), the release of vasopressin (ADH) by suprooptical and paraventricular hypothalamus nuclei increases. Vasopressin intensifies reabsorption of water in the tubules of the nephrons.

Stimulation of the receptors of the adducting renal arteriole (in the reduction of the renal blood flow and blood loss) and sodium receptors of the thick spot (macula densa) of the juxtaglomerular complex (in sodium deficiency) intensifies synthesis and release of rennin. Angiotensin II, which is formed under the influence of rennin, increases ejection of aldosterone by the adrenal glands. It increases reabsorption of sodium. Reduction of the extracellular fluid volume and angiotensin stimulate the center of thirst situated in the lateral portion of the hypothalamus.

Antidiuretic and antinatriuretic mechanisms are opposed by diuretic and natriuretic ones. The main factors of these mechanisms are: renomedullar, renal prostaglandins and atrial (from the heart) natriuretic factor (ANF, atriopeptide). ANF is produced in the cells of the atrium and it is peptide of 28 aminoacids.

It increases diuresis and natriuresis, relaxes the smooth muscles of the vessels and decreases the arterial pressure. The amout of ANF in the atrium and its secretion into the blood increases under the influence of intake of excessive amount of water and common salt, distension of the atria, increased blood pressure as well as stimulation of β-adrenoreceptors and receptors of vasopressin.

These mechanisms are in constant functioning and provide restoration of water-electrolyte homeostasis in blood loss and dehydration, excess amount of water in the organism as well as in changes of osmotic concentration of the extracellular fluid. However, in the sick organism these adjustive mechanisms can be "misled" and then they become involved in the pathologic process as its main pathogenetic factor (reduction of blood amount in the left atrium and arterial flow in cardiac insufficiency).

It is accepted to divide disturbance of water-electrolyte metabolism into dehydration and hyperhydration (retention of water in the organism) (Fig. 24). Depending on the change of osmotic concentration

(water and ratio), de- and hyperhydration are subdivided into three kinds: isoosmolaric, hypoosmolaric and hyperosmolaric. The normal osmotic concentration of the blood and intercellular fluid is about 0.3 osmol/l = 300 mosmol/l.

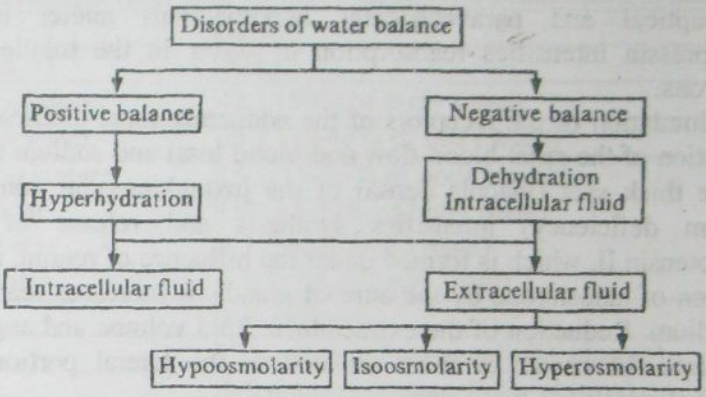

Fig. 24. Classification of the disorders of fluid homeostasis

DEHYDRATION

Dehydration (hypohydration, hypohydria, exicosis) develops in the cases when output of water exceeds its input into the organism (negative water balance). It may develop in disturbance of water input into the organisn (water starvation, dysphagia, atresia of the esophagus, comatous condition, etc.) or in its increased loss (diarrhea, vomiting, blood loss, loss of fluid with exudate — burn, etc.), as well as in combination of these conditions. In dehydration, first of all, the extracellular fluid and sodium ions are lost, in its more severe degree — potassium and the intracellular fluid.

Dehydration results in severe consequences connected with the decrease of the circulating blood volume (hypovolemia) and increase of its viscosity that may cause severe disturbance of blood circulation and microcirculation, collapse.

Disturbance of blood circulation results in development of tissue hypoxia and first of all, the central nervous system suffers from it. It may be manifested by loss of consciousness, hallucinations, comatous condition. The functions of the nervous centers, respiratory rhythm become disturbed and body temperature rises.

The marked decrease of the arteria pressure may be accompanied by

impairment of filtration in the tubules of the nephrons, oliguria, hyperasotemia and non-gas acidosis.

Compensatory reactions arise as a response to the developed disturbances. So, hypovolemia and reduction of renal blood flow promote hyperproduction of vasopressin and aldosterone. Reabsorbtion of water and sodium in tubules of the nephrons is intensified under the influence of these hormones.

Isoosmolaric hypohydration is a rare variant of disturbances, which are based on proportional volume decrease of fluids and electrolytes, as a rule, in the extracellular sector. Usually this condition arises immediately after acute blood loss but it is present for a short time and is eliminated due to work of the compensatory mechanisms.

Hypoosmolaric hypohydration develops due to loss of fluid enriched by electrolytes. Some states arising in definite forms of the kidney pathology (increased filtration and decreased reabsorption of the fluid), the intestines (diarrhea), the pituitary (deficiency of adrenocorticotropin [ACTH]), the adrenal glands (decreased production of aldosterone) are accompanied by polyuria and hypoosmolaric hypohydratation.

Polyuria can lead to the development of only extracellular hypoosmolaric hypohydration. In case of severely marked form of hypoosmolaric hypohydration there is observed secondary movement of the fluid in the organism: some part of it comes into the intracellular sector that is the osmotic pressure in the extracellular medium decreases. It may lead to the increase of the degree of the extracellular hypohydration in the simultaneous development of the intracellular edema.

Hyperosmolaric hypohydration develops due to loss of the fluid, which lacks electrolytes. It may arise due to hyperventilation, diarrhea, vomiting, polyuria, profuse sweating, long hyposalivation. Special attention should be drawn to diabetes mellitus as one of the causes of its development. Under the conditions of hypoinsulinism osmotic polyuria develops but the level of blood glucose remains high. The increase of osmotic pressure in the extracellular fluid involves the movement of water from the cells into the extracellular sector. And if the causative factor keeps on acting, the fluid is lost by the organism. It results in development of total hypohydration of the organism. The elevation of osmotic pressure of the extracellular fluid and dehydration of the cells causes thirst, intensification of protein lysis, fever, loss of consciousness, coma. It is expedient to introduce 5% solution of glucose or

hypotonic salt solutions. These disturbances are based on hypoxia connected with hypovolemia and arterial hypotension. Circulation hypoxia is sharply increased by the intra- and extracellular disturbances of microcirculation. These disturbances are conditioned by thickening of blood, increasing of its viscosity, stasis. Hypoxia combined with tissue dehydration leads to metabolism changes: protein lysis and development of hyperasotemia (at the expense of ammonium, because of dysfunction of the kidneys), production of urea (dysfunction of the kidneys). There may be acidosis (in loss of sodium and bicarbonates) or alcalosis (in loss of potassium and chlorine).

Hypoosmolaric hyperhydration develops in acute renal failure (in the 2nd degree — anuria), Parkhan syndrome (as a result of ejection of the large amount of vasopressin into the blood). It is characterized by the increased amount of water in the organism and decreased osmotic pressure in the extracellular sector, the water begins to enter the cells. Sodium-potassium balance is charged on either side of the membrane. Sodium passes into the cells and hence its amount in the blood plasma decreases. K^+ goes out of the cells into the extracellular sector. The person develops headache, nausea, vomiting, convulsions, coma and, at last', death.

Hyperosmolaric hyperhydration develops in drinking salt (sea) water in extreme situations. As a result, the osmotic pressure in the extracellular medium increases and the fluid passes from the cells into the intercellular space. Dehydration of the cells develops. But gradually adaptation to thй salt water may appear and there may be no serious disturbances of water-electrolyte metabolism.

Edema is a typical pathologic process, which is characterized by the increased amount of water in the extracellular space. It is based on water exchange disturbance between blood plasma and perivascular fluid.

Pathologic accumulation of fluid in the serous cavities of the organism is called hydrops (ascites — in the abdominal cavity, hydrothorax — in the pleural cavity, hydropericardium — in the pericardium).

Non-inflammatory fluid accumulated in differrent cavities and tissues is called transudate.

The mechanism of edemas is the following:

The fluid metabolism between the vessels and tissues takes place through the capillary wall. This wall is a complex biological structure through which water, electrolytes, some organic compounds (urea) are easily transported, but it is much more difficult to do it for proteins. It results in non-equal concentration of proteins in blood plasma (60-80

g/l) and tissue fluid (10-30 g/l).

The disturbance of water exchange between the capillaries and tissues is defined by the following factors:

1) hydrostatic blood presure in the capillarie;

2) colloid-osmotic pressure of blood plasma and tissue fluid;

3) permeability of the capillary wall.

The blood moves in the capillaries at a definite speed and under a definite pressure that results in production of hydrostatic force, which makes the water, go out of the capillaries into the intercellular (interstitial) space. The higher the blood pressure and the less the pressure amount of the tissue fluid, the more effect will be from the hydrostatic forces. The amount of the hydrostatic blood pressure in the arterial section of the human capillaries is 35-40 mm Hg and in the venous one 10-15 mm Hg.

Several principal pathogenic factors of edema are distinguished.

1. Positive water balance (dysfunction of the kidneys, intake of large amount of osmotically active substances, etc.).

2. Increased hydrostatic pressure mainly in the venous part of the vascular flow (local venous hyperemia or in cardiac insufficiency as well as inflammation).

3. Decrease of colloid-osmotic blood pressure (hyperproteinuria in fasting, nephrotic syndrome, hepatic insufficiency, etc.).

4. Increase of colloid-osmotic pressure in the tissue due to accumulation of osmotically active substances: electrolytes, proteins, metabolism products (in inflammation, allergy, hypoxia).

5. Increased permeability of the capillary vessels:

a) under the influence of the humoral factors (histamine, serotonine, kinines, prostaglandins, etc.);

b) in dystrophy of the walls of the capillary vessels (disturbance of neurotrophic supply, fasting, hypoxia, etc.).

6. Disturbance of lymph outflow (mechanic or dynamic lymphatic insufficiency).

7. Disturbance of the nervous and humoral regulation of water-electrolyte metabolism, ("wrong" switching on of the antidiuretic and antinatriuretic systems, disturbance of the sensitivity of volume and osmoreceptors, secondary aldosteronism, hypothyroidism) (Fig. 25).

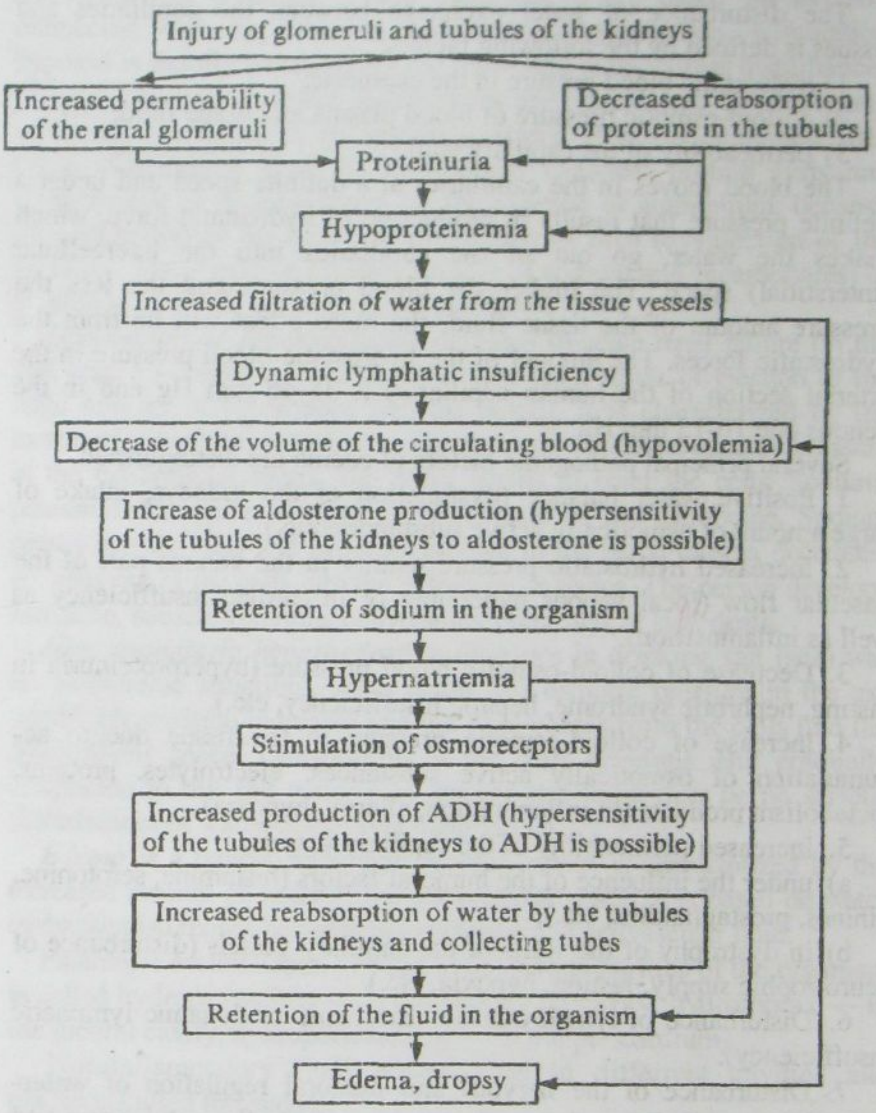

Fig. 25. Pathogenic participating in development of edemas in nephrotic syndrome

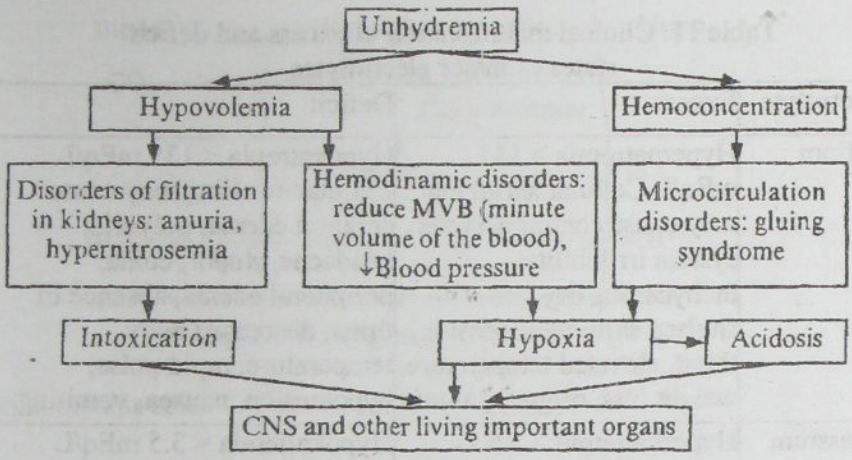

Fig. 26. Pathogenesis of unhydremic shock

Unhydremic syndrome — it is reducing fluid in blood, which can lead to unhydremic shock (Fig. 26).

Pathophysiology of electrolyte metabolism is presented in the table 11.

ACID-BASE METABOLISM

Acid-base metabolism is characterised by function of such organs as respiratory system, blood, renal system. Maintaining of acid-base homeostasis depends on 4 buffers system (Fig 27, 28, 29):

1. Hydrocarbonate buffer system H_2C0_3 / $NaHC0_3$ = 1/20 maintains constantly pH in plasma of blood and interstitial fluid.
2. Phosphate buffer system NaH_2P0_4 / Na_2HP0_4 = 1/4 participate in regulation of acid-base condition in the kidneys.
3. Hemoglobin buffer acts in erythrocytes.
4. Protein buffer regulates intracytes pH.

It is necessary to maintain acid-base balance because its disturbances can lead to different diseases. Characteristic of acid-base condition with mainly etiological factors and clinical manifestations see bellow (Table 12).

Table 11. Clinical manifestation of excess and deficit states of major electrolytes

Electrolyte	Excess	Deficit
Sodium	Hypernatremia > 147 mEq/L Cellular shrinking may cause central nervous system irritability, tachycardia, dry and flushed skin, hypertension, thirst, elevated temperature, weight loss, oliguria, anuria	Hyponatrenia < 135 mEq/L Cellular swelling may cause cerebral edema, polyuria, headache, stupor, coma, peripheral edema, absence of thirst, decreased body temperature, rapid pulse, hypotension, nausea, vomiting
Potassium	Hyperkaliemia > 5.5 mEq/L Depressed conductivity in heart, muscle cramping, parasthesias, nausea, diarrhea, associated with metabolic acidosis	Hypokaliemia < 3.5 mEq/L Cardiac irritability, dysrhythmias, vomiting, paralytic ileus, thirst, associated with metabolic alkalosis, inability to concentrate the urine
Calcium	Hypercalcemia > 12 mg/dl Decreased neuromuscular excitability, muscle weakness, central nervous system depression, stupor to coma, increased risk of bone fracture, vomiting, kidney stones	Hypocalcemia < 8.5 mg/dl Increased neuromuscular excitability, skeletal muscle cramps, tetany, laryngospasm, asphyxiation, death
Phosphate	Hyperphosphatemia >4.5 mg/dl See hypokalemia	Hypophosphatemia < 2 mg/dl Skeletal muscle depression, muscle weakness, hypotension, bradycardia, respiratory depression
Magnesium	Hypermagnesemia > 2.5 mEq/L Anorexia, muscle weakness, tremors, seizers, coma, anemia, bleeding, leukocytes alteration	Hypomagnesemia < 1.5mEq/L Hypocalcemia and hypokaliemia, neuromuscular irritability, tetany, convulsions, tachycardia, hypertension

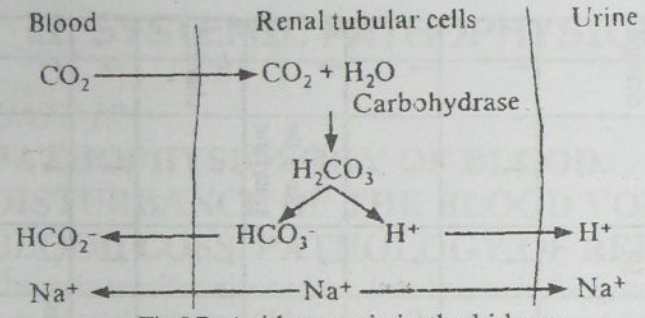

Fig 27. Acidogenesis in the kidneys

Renal tubular cells

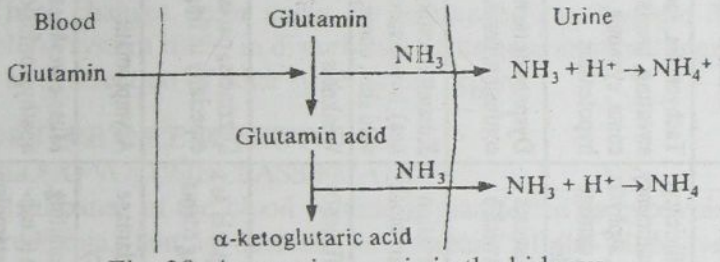

Fig. 28. Ammoniogenesis in the kidneys

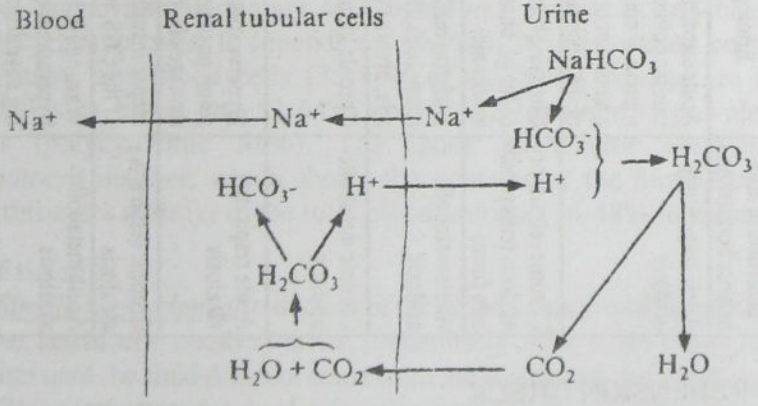

Fig. 29. Mechanisms of hydrocarbonates reabsorption in the kidneys

Table 12. **Characteristic of acid-base condition**

Disorders of acid-balance homeostasis	Etiological factors	Clinical manifestation	pH	CO_2	HCO_3^-
Acute respiratory acidosis	Acute respiratory insufficiency, cardiac pulmonary insufficiency, trauma of breast bone, asphyxia, trauma/tumor of CNS, damage of the respiratiry muscles	Tachycardia, tachypnoe, sweating, headache, letargy coma, cyanosis, arrhythmias, hypotension	decr. (↓)	incr. (↑)	un-changed
Chronic respiratory acidosis (compensa-tory form)	Chronic obstructive diseases of lungs, obesity (Pickwick's syndrome)	Dyspnea or tachypnea, confusion, coma	↓	↑	↑
Acute metabolic acidosis	Diabetes mellitus, starvation (complete), shock, heart block-ade, breathe colapse	Kussmaul respiration (hyperp-nea), hypotension, sweating cold skin, coma, arrhythmias	↓	↓	↓
Chronic metabolic acidosis	Chronic kidneys insufficiency	Weakness	↓	↓ less than in the acute form	↓
Acute respiratiry alcalosis	Hyperventilation, hypoxia as a result pneumonia, lung edema, damage of CNS	Dizziness, paresthesias especially in fingers	↑	↓	un-changed
Chronic respiratory alcalosis	Hepar insufficiency, damage of the CNS, pregnancy	Asymptomatic	↑	↓	↓
Acute metabolic alcalosis	Wasting HCl under vomiting, hyperadrenocorticism (Cush-ing's syndrome), aldosteronism	Muscle weakness, arrhythmias, apathy, confusion, stupor	↑	↓	↑
Chronic metabolic alcalosis	Prolonged vomiting	No clinical manifestations	↑	↑	↑

COMPREHENSION CHECK

Try to answer the following questions.

1. Characterize fluid and electrolyte homeostasis.
2. What are the consequences of fluid imbalance?
3. How is electrolyte imbalance characterized?
4. What is the mechanism of edema?

UNIT 17

PATHOPHYSIOLOGY OF BLOOD. DISTURBANCE OF THE BLOOD VOLUME. BLOOD LOSS. PATHOLOGY OF RED CELLS

The main manifestations of the disturbances in the system of blood are changes of total volume of blood; number, structure and function of blood cells (erythrocytes, leukocytes and blood platelets — thrombocytes) due to pathology of hemopoiesis and blood destruction; hemostasis; biochemical indices; physical and biochemical properties of blood.

These changes occur under the influence of pathogenic factors on the blood system itself, in disturbance of its neurohumoral regulation as well as in affection of other systems and organs.

DISTURBANCE OF THE TOTAL BLOOD VOLUME CLASSIFICATION

Disturbance of the blood volume is manifested as hypovolemia and hypervolemia, that is decrease or increase of the blood volume in comparison with the norm (normovolemia) constituting 6- 8% of the body mass or 65-80 ml of blood per 1 kg of the body mass. In their turn hypo- and hypervolemia are subdivided into simple, polycythemic and oligocythemic ones. It depends on whether there is normal correlation of plasma and blood cells (36-48% of the blood volume are formed elements of blood and 52-64% are plasma) or there is prevalence of cells (polycythemic form). The index of volume correlation is hematocrit number, which shows the contents of the formed elements (erythrocytes mainly) in the total blood volume (36-48% in the norm).

Etiology

Simple hypovolemia (reduction of the blood volume without any changes of the hematocrit number) arises immediately after acute blood loss and persists until the fluid does not come from the tissues into the blood.

Olygocythemic hypovolemia (decrease of the blood volume with prevalence of erythrocytes reduction) is observed after acute blood loss when the compensatory amount of blood coming from the depot and tissue fluid into the blood stream does not restore the volume and contents of blood.

Polycythemic hypovolemia (reduction of the blood volume due to decrease of the plasma volume in relative increase of erythrocytes) develops in the dehydratation of the organism (diarrhea, vomiting, increased perspiration and hyperventilation).

Simple hypervolemia (increase of the blood volume in normal correlation between red blood cells and plasma) occurs at once after transfusion of large amount of blood.

Oligocythemic hypervolemia (increase of the blood volume at the expense of plasma) develops at retention of water in the organism due to renal disorders in introduction of blood substituting fluids.

Polycythemic hypervolemia (increase of the blood volume at the expense of the growing number of red blood cells) is observed in the reduction of the atmospheric pressure as well as in different diseases connected with oxygen deprivation (heart failure and emphysema). It is considered to be a compensatory phenomenon.

Oligocythemic normovolemia occurs in anemia due to blood loss (the blood volume is normalized at the expense of the tissue fluid and the number of red blood cells hasn't been restored yet), hemolysis of erythrocytes and disturbance of hemopoiesis.

Polycythemic normovolemia is observed in transfusion of small amount of paced red cells.

BLOOD LOSS

Blood loss is a pathologic process occurring due to hemorrhage and characterized by complex of pathologic disturbances and compensatory reactions to reduction of the volume of the circulating blood and hypoxia caused by decrease of respiratory function of blood (Fig. 30, 31).

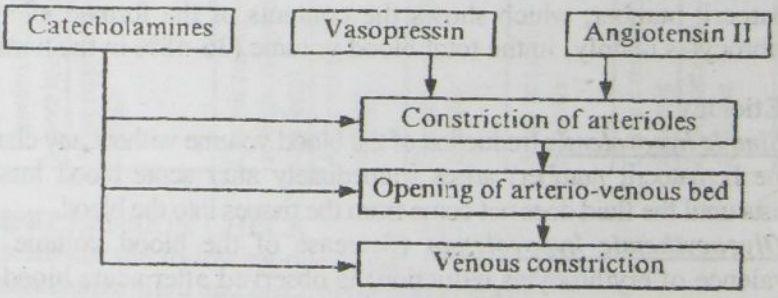

Fig. 30. Mechanisms of compensation of central blood circulation under acute blood loss

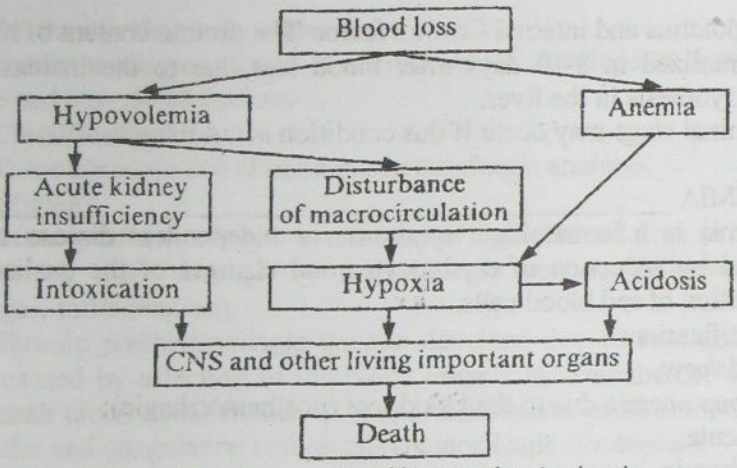

Fig. 31. Pathogenesis of hemorrhagic shock

Etiology

Etiological factors causing hemorrhage include damage of the vessel integrity of wounds, or affection by the pathological process (tumor, tuberculosis); increase of the permeability of the vascular wall (acute radiation disease), decrease of the blood coagulation (hemorrhagic syndrome).

Urgent Mechanisms of Compensation

1. Reflex spasm of the blood vessels leading to increased resistance of the vessels of the inner organs (except the brain and the heart) and the skin. Blood passes from the depot *into* the blood stream which results in elevation of the arterial pressure partly restoring blood supply of the vitally important organs.
2. Reflex acceleration and intensification of the cardiac contractions.
3. Penetration of the intratissue fluid into the vessels.
4. Reflex acceleration and deepening of respiration contributing to elimination of oxygen deficiency in the organism.
5. Increase of hemoglobin capacity to give back oxygen to the tissues (increase of dissociation of oxyhemoglobin in acidosis).
6. Increase of blood coagulation which stops hemorrhage.

Non-Urgent Mechanisms of Compensation

They are marked later as increased hemopoiesis and restoration of protein content of blood. On the 5th day the reticulocytes in blood increase, it's connected with the increase of hemopoietic activity of the bone marrow under the influence of increased production of

erythropoietins and internal Castle's factor. The protein content of blood are normalized in 8-10 days after blood loss due to the increase of protein synthesis in the liver.

Terminal stage may occur if this condition is not treated.

ANEMIA

Anemia is a hematologic syndrome or independent disease characterized by reduction of erythrocytes and changes of the qualitative composition of red blood cells.

Classification:

By etiology:

I group anemia due to the blood loss (posthemorrhagic):
— acute;
— chronic.

II group anemia due to increased blood destruction (hemolytic):
— acquired;
— inherited.

III group anemia due to disturbance of erythropoiesis.
— B_{12}-folic deficiency;
— Fe-deficiency;
— Protein-deficiency.

By type of hemopoiesis:
— anemia with erythroblast type of hematogenesis;
— anemia with megaloblast type of hematogenesis.

By abilities of the bone marrow to regenerate:
— regenerative;
— hyperregenerative;
— hyporegenerative;
— aregenerative.

By color index:
— normochromic (CI=0.85-1.15);
— hypochromic (CI < 1.15);
— hyperchromic (CI > 1.15)

By size of erythrocytes:
— normocytic (average size 7.2 mcm)
— microcytic (< 6.5 mcm)
— macrocytic (> 8 mcm)

By clinical course:
— acute;
— chronic.

Posthemorrhagic Anemia

Posthemorrhagic anemia is anemia which develops as a result of acute and chronic blood loss.

Classification

There are acute and chronic posthemorrhagic anemias.

Etiology

Acute posthemorrhagic anemia occurs after blood loss in vessels trauma or their damage by a pathologic process (atherosclerotic changes, inflammation).

Chronic posthemorrhagic anemia develops due to repeated blood loss caused by affection of the blood vessels in a number of diseases (stomach ulcer, hemorrhoids, etc.) and disturbance of thrombocytes — vascular and coagulation hemostasis (hemorrhagic syndrome).

Pathogenesis

During the first hours after acute blood *loss* acute posthemorrhagic anemia is manifested by relatively equal reduction of erythrocytes and hemoglobin and preservation of the normal color index (normochromic anemia).

On the 4th-5th day after blood loss there may be observed proliferation of the cells of the erythrocytic sprout of the bone marrow under the influence of erythropoietin. The number of polychromatophilic erythrocytes, reticulocytes, is increased in blood and single normoblasts (regenerative anemia) appear. The color index is reduced (hypochromic anemia) as the accelerated regeneration outstrips the maturation of the cells which can't manage to lose the signs of their immaturation (nucleus and granules) and can't be saturated with hemoglobin. Besides, massive acute blood loss may lead to deficiency of iron and decrease of hemoglobin synthesis.

Chronic posthemorrhagic anemia is accompanied by reduction of iron stock in the organism in repeated blood losses and thus iron deficient anemia with hypochromia and microcytosis of erythrocytes may occur. In inhibition of hemopoiesis such anemia may become hypo- and aregenerative with sharp reduction of regenerative forms of erythrocytes in the blood smear.

Hemolytic Anemia

Hemolytic anemia is anemia which develops as a result of increased erythrodiarrhesis when destruction of red blood cells prevails over their formation.

Classification

By etiology hemolytic anemia is subdivided into *acquired* and *hereditary*.

Etiology of Acquired Hemolytic Anemia

Toxic hemolytic anemia may develop under the influence of hemolytic poisons (compounds of arsenic, lead, nitrobensolum, phenylhydrasine, alcohol, bile acids, toxic products of nitrous exchange; mushroom poison, snake and bee venom, etc.). It may appear as an effect of the causative agents of infectious and parasitic diseases (hemolytic streptococcus, anaerobic infection, **Plasmo**dium malaria and leishmaniosis).

Immune (hetero-, iso-. autoimmune) hemolytic anemia develops in transfusion of type, group and rhesus incompatible blood, rhesus incompatibility of the mother and the fetus; formation of autoantibodies against one's own erythrocytes when their antigen properties are changed under the influence of medicamentous preparations, viruses, microorganisms or as a result of somatic mutation of immunocytes when "forbidden" clone of lymphocytes appear producing antibodies to normal antigens of erythrocytes (in leukosis, systemic lupus erythematosus, etc.). Mechanical damage of erythrocytes may occur in prosthesis of the blood vessels and cardiac valves, long marches of running of the hard ground (march hemoglobinuria), splenomegaly.

The causes of acquired membranopathy may be somatic mutation of erythroblasts under the influence of viruses, microorganisms, medicamentous preparations with formation of pathologic population of erythrocytes.

Pathogenesis

Mechanism of hemolysis in *acquired hemolytic* anemia consists in damage of the membranous structure of erythrocytes. Some hemolytic factors (for example, mechanical) have a direct harmful effect; others (hydrogen arsenide and nitrites) begin powerful oxidizers, cause metabolic, functional and structural changes in the membrane and stroma of erythrocytes leading to their hemolysis. Many hemolytic acids possess ferment activity destructing membranous lecithin.

Under the influence of hemolytic agents pores are formed in the membranes of red blood cells; ions of potassium, phosphates come out of the cell through them and ions of sodium come into the cell. Due to deviations of ion balance, water penetrates into erythrocyte it becomes swollen and has a spherical shape. Such spherocytes can't come through

interendotelial pores of the spleen sinuses and are phagocyted by the spleen macrophagocytes. When the volume of the erythrocyte is lager than the norm, hemolysis occurs and hemoglobin comes to plasma.

Hemolysis of blood cells in acquired hemolytic anemia occurs in the blood stream (Fig. 32, 33).

However, in rhesus conflict (hemolytic disease of newborns), antirhesus agglutinins formed in the organism of rhesus-negative mother cause hemolysis of rhesus-positive erythrocytes of the fetus or the newborn not only inside the vessels but also in the liver and spleen (intracellular hemolysis).

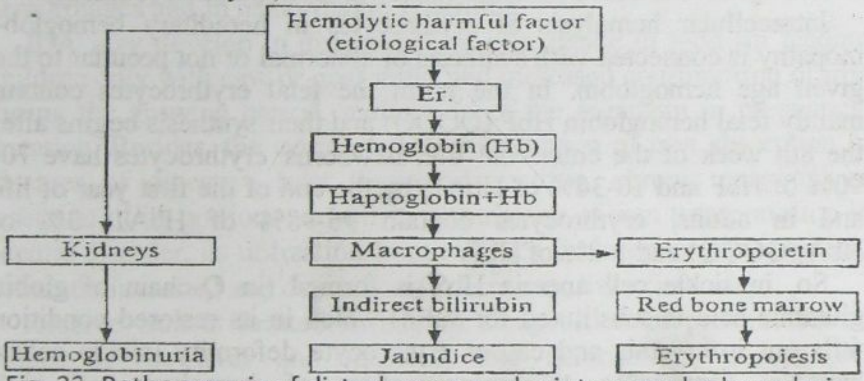

Fig. 32. Pathogenesis of disturbances under intravascular hemolysis

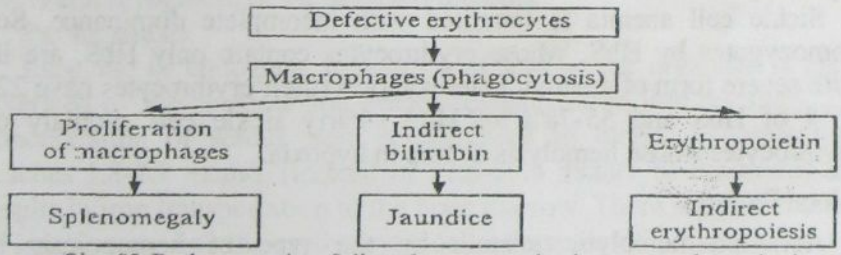

Fig. 33. Pathogenesis of disturbances under intercytes hemolysis

In *hereditary hemolytic anemia,* hemolysis is caused by reduction of osmotic and mechanical resistance of erythrocytes.

Hereditary hemolytic anemia is subdivided into hereditary membranopathy, fermentopathy and hemoglobinopathy caused by genetic defects of the membrane structure, activity of the erythrocyte ferments and hemoglobin synthesis. There are two kinds of hereditary hemoglobinopathy: anemias connected with disturbance of globin

chains synthesis and anemias brought about by hereditary defect of the primary structure of the globin chains.

In hereditary membranopathy (microspherocytic hemolytic anemia or Minkovsky — Shoffar disease) genetic deficiency in the membrane of erythrocytes of Ca^{2+}-dependent ATP-phase and phospholipids results in increased permeability of the membrane.

In hereditary fermentopathy, for example, glucose-6-phosphatedehydrogenasodeficient (G-6-PhDG) anemia, acute intravascular hemolysis of erythrocytes is caused by damage of the cellular membranes by peroxide as the erythrocytes with G-6-PGDG deficiency have reduced contents of the restored glutation (oxidant).

Intracellular hemolysis of erythrocytes in hereditary hemoglobinopathy is connected with synthesis of abnormal or not peculiar to the given age hemoglobin. In the norm the fetal erythrocytes contain mainly fetal hemoglobin HbF (QQQQ) and their synthesis begins after the 8th week of the embrional life; newborns' erythrocytes have 70-90% of HbF and 10-30% of HbA1; by the end of the first year of life and in adults, erythrocytes contain 96-98% of HbA1, 3% of HbA_2(QQQQ) and 1-2% of HbF.

So, in sickle cell anemia HbS is formed (in Q-chain of globin glutamic acid is substituted for valin) which in its restored condition falls out in crystals and causes erythrocyte deformity (sickle cells); hypoxia contributes to intensification of hemolysis of such erythrocytes.

Sickle cell anemia is inherited with incomplete dominance. So, homozygotes by HbS, whose erythrocytes contain only HbS, are ill with severe form of anemia; heterozygotes (their erythrocytes have 22-45% of HbS and 55-78% of HbA,) carry sickle cell anomaly of erythrocytes whose hemolysis occurs in hypoxia.

Blood Picture

Acquired hemolytic anemia by the type of hemopoiesis is erythroblast, by the degree of regeneration of the bone marrow it is a false hyperchromic (due to absorption of hemoglobin on one erythrocyte). In the blood smear there can be revealed cells of physiologic regeneration and degeneratively changed erythrocytes (poikilocytosis; torn fragmented erythrocytes and anisocytosis).

In hereditary hemolytic anemia one can note intensified regeneration of erythrocytic sprout, often with noneffective erythropoiesis when the nuclear forms of erythrocytes are destroyed in the bone marrow.

Iron-Deficient Anemia (IDA)

IDA is anemia caused by deficiency of iron in the organism as a result if disbalance between its intake, usage and loss. It is the most common type of anemia (80%).

Etiology

The most frequent cause of IDA development is repeated and prolonged, sometimes massive single, hemorrhages leading to the loss of iron together with erythrocytes. It is often observed in the uterus hemorrhages, more rare in gastrointestinal, renal, pulmonary hemorrhages and in hemorrhagic syndrome.

IDA may develop in disturbance of iron intake in food (in feeding children only with caw or goat milk) and increased consumption of iron during the growing period, maturation of the organism in pregnancy, lactation. Besides, the cause of IDA is reduction of iron absorption in diseases of digestive tract (hypoacid gastritis, chronic enteritis) or resection of its portions as well as disturbance of iron transportation in hepatic disorder, its utilization from reserves (in infection, intoxication, helmintic invasion) and deposition (in hepatitis, liver cirrhosis).

Reserve iron is located mainly in composition of protein ferritin (depot in the liver and muscles) and hemosiderin (it's in the macrophagocytes of the bone marrow, the spleen, Kupfer's cells of the liver) and myoglobin of the skeleton muscles.

Pathogenesis

Exogenic or endogenic deficiency of iron in the organism is characterized by the decrease and gradual exhaustion of iron reserve:.. The concentration of serous iron is decreased in blood, hyposideremia reaches 1.8-2.7 mcm/l (instead of 12.5-30.4 mcm/l in the norm) that results in iron transportation to the bone marrow. There ate disturbances of iron coming into the erythrocytic cells, decrease of heme synthesis in hemoglobin and some iron-contacting and iron-dependent ferments (catalase, glutathionperoxidase) in erythrocytes that increase their sensitivity to hemolyzing effect of oxidizes. The non-effective erythropoiesis is increased due to increased hemolysis of erythrocytes in the bone marrow and erythrocytes in blood. The life span of red blood cells is reduced.

The consequences of hemic and tissue hypoxia in iron deficient anemia are atrophic and dystrophic processes in tissues and organs especially manifested in the digestive tract (glossitis, gingivitis, dental

caries, injury of the esophageal mucous membrane, atrophic gastritis with achilitis) and the heart (myocardium dystrophy).

Blood Picture

IDA is anemia with erythroblast type of hemopoiesis, hypochromic, with low color index (0.6 and less). The number of hemoglobin is decreased more than the number of erythrocytes. The blood smear is characterized by hypochromic, "shadows" of erythrocytes, anisocytes, microcytes and poikilocytosis. The number of reticulocytes depends on the regenerative ability of erythrocytic stem (regenerative or more often hypogenerative anemia).

B_{12} and Folic-Deficient Anemia

B_{12} and Folic-deficient anemia is anemia which is connected with disturbance of nucleic acid synthesis and substitution of erythroblast type of hemopoiesis for megaloblast due to lack of cyanocobalamin (vitamin B_{12}) and folic acid (megaloblast anemia).

Etiology

By etiology these anemias may be acquired and hereditary. The causes common for B_{12} and folic-deficient anemias are the following:

1) lack of these vitamins in the food;
2) disturbance of absorption of vitamins in the small intestine;
3) increased consumption of vitamins in pregnancy;
4) disturbance of vitamin depot in diffuse affection of the liver (hepatitis, cirrhosis).

Besides, cyanocobalamin deficiency occurs as a result of disturbance formation if internal factor of Castle mucoproteid (transcorrin) in hereditary defects of its production by the cells of the gastric glands, in damage of the gastric membrane by tumor.

The cause of pernicious anemia (malignant anemia of Addison — Birmer) may be genetically determined deficiency of transcorrin (it's inherited by autosomic-recessive type) or autoimmune process.

Pathogenesis

In deficiency of cyanocobalamin (its coferment — methylcobalamin) there is no transportation of folic acid into its coferment form — tetrahydrofolic acid without which synthesis of timidinmonophosphate, one of the components of DNA is impossible. The cellular division is disturbed and actively reproducing cells of the hemopoietic tissue suffer first of all.

Reproduction and maturation of erythrocytes are retarded in the bone

marrow, erythroblast type of hemopoiesis is substituted for megaloblast, non-effective erythropoiesis is increased and the life span of erythrocytes is shortened. The number of leukocytes and thrombocytes is decreased. Inflammatory atrophic process in the mucosa of the digestive tract develops (glossitis, stomatitis and enteritis). As a result of cyanocobalamin lack, methylamonic acid toxic to the nervous cells accumulates in the organism.

Degeneration of the posterior and lateral columns of the spinal cord develops (funicular myelosis), the cranial and peripheral nerves are affected developing multiple neurologic symptoms.

Blood Picture

B_{12} and folic-deficient are anemias with megaloblast type of hemopoiesis, hyperchromic and macrocytic. The contents of erythrocytes and hemoglobin in blood in these anemias may be reduced sharply, however, the color index is higher than that one (1.4-1.3) due to presence in blood of a large volume of megaloblasts and megalocytes saturated with hemoglobin.

In blood there are a lot of degeneratively changed erythrocytes: poikilocytosis, anisocytosis, hyperchromic megalo- and macrocytes, megalocytes with inclusions of Zholli's cells and Cabot's rings, erythrocytes with basophilic granules.

The number of the cells of physiologic regeneration is decreased (reticulocytes, Polychromatophils). Leuko- and thrombopenia are observed.

COMPREHENSION CHECK

Try to answer the following questions.

1. What is disturbance of the total blood volume?
2. Characterize blood loss and urgent mechanisms of compensation.
3. Classify anemias.
4. Describe etiology, pathogenesis, blood picture under iron-deficiency, $B_{12}$and folic deficiency, and hemolytic anemias.

UNIT 18

PATHOPHYSIOLOGY OF THE WHITE BLOOD CELLS

LEUKOCYTOSIS. LEUKOPENIA. LEUKEMIA

Pathologic Changes of Leukocytes

Pathologic changes of leukocytes are manifested as the disturbance of their formation in the hemopoietic tissue, qualitative and quantitative deviations. These changes occur in consequence of primary damage of leukocytes in the hemopoietic tissue and circulating blood under the influence of different causes. The secondary changes of leukocytes are usually protective organism response to the pathologic processes in the whole organism.

The main point in pathogenesis of leukocyte pathology is the change of organism resistance, immunological and allergic disturbances, as leukocytes participate in phagocytosis, production of antibodies, and desactivation of biologically active substances (histamine, bradykinin and serotonin). Leukocyte pathology is accompanied by tissue dystrophies and local disturbances of blood microcirculation, as one of the functions of leukocyte is to provide regenerative tissues with the nutrients and stimulators of cell division. Granulocytes participate in development of vascular disturbances, as carriers of vasoactive substances (basophilic, eosinophilic) or influence on their synthesis and release from tissue basophiles, (neutrophiles).

The Disturbance of Leukopoiesis

There are the following disturbances of leukopoiesis:

1. The increase or decrease of leukocyte production in the hemopoietic tissue.
2. The disturbance of maturation of leukocytes in the hemopoietic organs.
3. The production of pathologically changed leukocytes.

Etiology

The causes of such disturbances are different: biological (bacteria, viruses and protozoa), physical (radiation, ultra-violet rays) and chemical factors. The endogenous factors are genetic defect!! of formation and differentiation of leukocytes.

Pathogenesis

I. The increase of leukopoiesis of reactive type can be caused by the increased production of humoral activators (colonystimu lating factor (CSF) and the decreased production of their inhibi tors (keilon, prostoglandins E, lactoferrin and isoferrin).

There is proliferation of leukopoietinsensitive cells of the bone marrow with their subsequent differentiation in mature leukocytes The leukocytes increase in blood results in leukocytosis.

The type of leukocytosis depends on etiological factor. Bacteri al endotoxins, strepto- and staphylococci and some products of the tissue disintegration (for example, in erythrocyte hemolysis and ischemia) provoke predominant increased production of CSF, stim ulating proliferation and differentiation of precursors of neutrophil granulocytes that results in increased level of neutrophiles in blood (neutrophile leukocytosis).

Acceleration of eosinophilopoiesis and release of eosinophilic granulocytes from the bone marrow into blood, observed in aller gic diseases is connected with the increased synthesis of CSF ir. lymphocytes after antigenic stimulation. It is also connected with the increased permeability of the bone marrow under the influence of histamine and other biologically active substances released in reaction of antigen-antibody.

Accelerated leukopoiesis of a tumor origin occurs under the in fluence of carcinogenic factors, causing gens mutation, which are responsible for multiplication and differentiation of blood — form ing cells of 11—IV class, which is characteristic for leukosis.

II. The decrease of leukopoiesis is caused by the disturbance of regulation of leukocyte production the deficit of plastic factors, necessary for leukocyte production (in protein starvation, deficiency of cyanocobalamine and folic acid). Leukopoiesis decreases in hereditary and acquired disturbance of cells-predecessors of granulo- and agranulocytes and stromal cell determining the differentiation of the trunkal cells towards myelo- and lymphocytopoiesis or in generalized affection of the whole leukopoietic tissue. It is also observed in hereditary neutropenia, ionizing radiation, tumor metastases, leukemic infiltrations, replacing normal leukocytes, drug allergy, caused increased damage of leukocytes in hemopoietic organs.

III. The disturbance of leukocyte maturation is caused by the blockade of differentiation at different levels of cell development. The

differentiation is provided by genetic regulation and certain metabolic reactions. Its changes are caused by: mutation, exo- and endogenic factors (causative agents of purulent and viral infections, medicinal allergens and intoxication). Often the disturbed maturation is accompanied by their increased production in response to tumor hyperplasia of blood cells. But, sometimes, it is connected with the decrease of leukocyte production. Besides, the appearance of immature leukocytes in blood is connected with the increase of the bone marrow permeability, which is also regulated by glucocorticoids. Usually immature cells are noticed in leukemoid reactions and nuclear deviation of neutrophile granulocytes to the left.

IV. Production of pathologic leukocytes may arise as a result of tumor transformation of leukopoietic tissue in leukosis, genetically conditioned structure disturbances (hereditary Pelger anomaly of granulocytes), and metabolism of leukocytes. For example, in dominant by inherited Pelger anomaly of leukocytes neutrophilic granulocytes are formed, which preserve round, rod-shaped or 2-segment nucleus having come into blood after maturation. Hereditary deficiency of myeloperoxidase, glucose-6-phosphatedehy-drogenase leads to reduction of the phagocytic activity of leukocytes. There may be non-effective leukopoiesis with shortened life of leukocytes.

Quantitative and Qualitative Changes of Leukocytes in Blood

The increase of leukocyte quantity is called *leukocytosis,* its decrease — *leucopenia.*

The norm is 4-9G/l or 4-9T0^9/l.

The quantitative changes are increased quantity of immature forms in blood and degeneration of leukocytes.

Leukocytosis

Leucocytosis — is the increase of total leukocyte quantity in blood — over 9G/l (9/109/1).

Classification

Absolute leukocytosis is the increase of leukocyte number in blood, caused by the increased production of leukocytes of reactive or tumor character in the organs or their increased coming from the bone marrow depot into the blood vessels.

Relative leukocytosis — is the increase of leukocyte number in blood caused by their redistribution from the parietal pool into circulating one or their accumulation in the focus of inflammation.

Leukocytosis is divided into neutrophilosis, eosinophilosis, basophilosis, lymphocytosis and monocytosis, depending on the type of leukocytes being increased.

Etiology

The causes of neutrophilosis are various. They are infectious factors (strepto- and staphylococci, fungi), the products of tissue malignant tumours, in myocardial infarction, hemolysis, disintegration of toxic metabolites in uremia, hepatic coma, physical factors (cold, heat), chronic myeloleukosis and psychical factors (fear, fury).

Eosinophilia is observed in allergic and parasitical diseases, chronic myeloleukosis.

Basophilia is caused by ulcerative colitis, chronic myeloleukosis after splenectomy and myxedema.

Some viruses (infectious mononucleosis, hepatitis, measles), microorganisms (causative agents of whooping cough, tuberculosis and syphilis), chronic lympholeukosis provoke lymphocytosis.

Monocytosis develops under the influence of viruses, microorganisms, protozoa, specific endocarditis.

Pathogenesis

There are the following mechanisms of leukocytosis:

1. The increase of leukocyte production in the bone marrow.
2. The acceleration of leukocyte entrance from the bone marrow into the blood, as a result of increased permeability of the bone marrow.
3. The redistribution of leukocytes to the circulating blood or to the focus of inflammation.

Usually, leukocytosis is accompanied by the disturbance of maturation in the bone marrow and the production of pathologic forms.

Reactive hyperplasia of the leukocytic tissue leads to the increase of the organism resistance. Neutrophilic leukocytosis and monocytosis have parallel increase of the phagocytic activity of leukocytes. Eosinophils play a compensatory role in allergic reactions due to antihistamine function of eosinophilic granulocytes. But, leukocytosis during leukemia may be accompanied by immunological hyporesistance. The organism gets auto- and secondary infection.

Blood Picture

The increase of total number of leukocytes is accompanied by the change of leukocyte formula (of separate forms of leukocytes in per cent, by counting 200 cells in the stained blood smear). Absolute or relative character of these changes is established with counting absolute

amount of different forms of granulo- and agranulocytes in one litre. The count is made on the basis of total amount of leukocytes in one litre of blood and leukocytic formula. So, absolute neutrophile leukocytosis in purulent inflammatory diseases is accompanied by decrease of the amount of leukocytes in percent in the leukocytic formula (relative lymphopenia). However the count of absolute quantity of lymphocytes on the back-ground of general leukocytosis allows establishing absence of inhibition of lymphocytic stem.

In leukocytosis, especially neutrophilic one, immature cells not infrequently appear in blood. A great number of generatively altered leukocytes in leukocytosis is noted in blood in sepsis, purulent processes, infectious diseases, disintegration of malignant tumor.

Leukopenia

Leukopenia — is the decrease of total leukocyte number in blood — below 4G/l *(4-109).*

Classification

There are absolute and relative leukopenias. Depending on the type of leukocytes, there are neutropenia, eosinopenia, lymphopenia and monocytopenia.

Etiology

Neutropenia is caused by infectious gripe viruses, measles, enteric fever toxin, rickettsia of typhus, physical factors (ionizing radiation), medicines (sulfanilamides, barbiturates, cytostatics), benzol, the deficiency of vitamin B_{12}, folic acid, anaphylactic shock, hypersplenism, genetic defects of neutrophile production and differentiation. Eosinophilia is observed in the increase production of stress, Itsenko — Cushing disease, corticosteroids, infectious diseases, introduction of corticotrophin and cortisone.

Lymphopenia develops under the influence of hereditary and acquired immunodeficiency, stress, radiation disease, miliary tuberculosis, myxedema.

Monocytopenia is found in all syndromes and diseases, connected with the depressed myeloid stem shot of the bone marrow hemopoiesis (for example, in radiation disease, severe septic conditions, and agranulocytosis).

Pathogenesis

The following mechanisms are in the basis of leukopenia:

1. The decrease of leukocyte production in the hemopoietic tissue.

2. The disturbance of leukocytes entrance into blood.
3. Their destruction in blood and hemopoietic tissue.
4. Redistribution of leukocytes in the vessels.
5. The increase discharge of leukocytes from the organism.

The defect of the tissue membrane leads to the decrease of leukocyte bile ability. It is called the syndrome of "lasy leukocytes'. As a result, the granulocytes come into blood from the bone marrow very slowly.

The increased destruction of leukocytes may be caused by the change of their physico-chemical features and permeability of leukocyte membranes due to ineffective leukopoiesis. It leads to increased lysis of leukocytes, including spleen macrophages, and by the action of the same pathogenic factors provoking cell destruction in the hemopoietic organs.

The redistribution of leukocytes is observed in hemotransfusional shock, inflammatory diseases, in altered ratio between the circulating and parietal pools of leukocytes.

Sometimes, leukopenia may be conditioned by the increased discharge of leukocytes from the organism (in purulent endometritis, cholecystoangiocholitis).

The main consequence of leukopenia is the decrease of the organism resistance caused by reduction of phagocytic activity of neutrophile granulocytes and lymphocyte function of antibody formation not only due to reduction of their total quantity but also due to possible combination of leukopenia with production of functionally inferior leukocytes. Such patients often suffer from different infectious and tumor diseases, especially in hereditary neutropenias deficiency of T- and B-lymphocytes. The examples of severe areactivity are AIDS of viral and radiation origin as well as agranulocytosis and alimentary-toxic aleukia. It is caused by different medicines, radiation and some infections.

Aleukia — is an aplastic damage of the bone marrow, accompanied by the sharp inhibition of total stopping of leukocyte production. The alimentary-toxic form develops in eating grains, infected by mould. Usually, we can observe pancytopenia in such cases — a sharp decrease of leukocytes (aleukia) and thrombocytes (thrombocytopenia).

However, we can observe some compensatory reactions, manifested as the reactions of some stems of leukocytes, when the other ones are inhibited. For example, neutropenia may be accompanied by compensatory increase of production of monocytes, macrophages,

eosinophiles, plasmatic cells.

The disturbance of correlation between mature and immature forms of leukocytes in blood.

The appearance of immature forms of leukocytes in blood is conditioned by the disturbance of their maturation in the hemopoietic tissue and the increase of the bone marrow permeability. These changes are usually on the background of increased leukopoiesis due to reactive and tumor hyperplasia of the leukopoietic tissue. If there is predominance of mature, segmentocellular cells, cells of the granulocyte kind (first of all neutrophile granulocytes) and there are no stab neutrophiles and metamyelocytes, such hematological picture is connected with inhibition of the bone marrow hemopoiesis. If there are a lot of mature leukocytes and no young forms, the bone marrow hemopoiesis is depressed.

Blood Picture

We must find out if there is a right or left nuclear deviation of the neutrophile granulocytes. Immature of Shillings forms of leukocytes (myelocytes, metamyelocytes, stab neutrophile granulocytes) are placed in the left part of the leukocyte formula, the malure ones (segmentonuclear neutrophile granulocytes) in the right' part. The increase of the young neutrophiles in blood is evidence of the left nuclear deviation. The prevalence of the mature forms (5-6 segments) on the background of absence of young cells is evidence of the right nuclear deviation.

There are the following types of the left nuclear deviation:

1. The regenerative type is indicative of reactive activation of leukopoiesis.

2. Hyperregenerative deviation reflects an excessive hyperplasia of the hemopoietic tissue. Then maturation is broken. There are many immature forms in blood. The number of stab neutrophile granulocytes and metamyelocytes increases sharply. Myelocytes and promyelocytes appear, the total number of leukocytes may be increased, unchanged and even decreased due to exhaustion of the myeloid stem after preceding activation.

3. In the degenerative type deep disturbances and inhibition of leukocyte production occur. On the background of general leukopenia there are many stab neutrophile granulocytes with degenerative range and no metamyelocytes and nucleus with decreased number of the segmentonuclear forms in blood.

4. Regenerative-degenerative deviation is observed in hyper-

production of the pathologically changed leukocytes in the bone marrow and their immaturation. In this case there is leukocytes and the number of stab neutrophile granulocytes, metamyelocytes and myelocytes with signs of degeneration increase in the blood smear.

A sharp increase of the immature forms is typical for the lenkaemoid reaction. Blood picture is close to leukemia but differs by etiology (the cause is often known — infection, malignant tumor:», acute hemolysis etc.) and pathogenesis (reactive hyperplasia of the leukopoietic tissue). This reaction is temporary, reversible and doesn't turn into leukemia. There are some types of leukaemoid reaction, they are: myeloid neutrophiles, eosinophiles, monocytes and lymphoid ones (in sepsis cancer metastases into the bone marrow, myeloid reactions in infectious lymphocytosis and mononucleosis - lymphoid type of leukaemoid reactions).

The right nuclear deviations is evident in the depression of leukocyte production in leukopenia (radiation disease, B_{12} and folic acid deficiency anemia). The right nuclear deviation is observed in 20% of healthy people.

Degeneration of White Blood Cells

They are: anisocytosis vacuoles in cytoplasm, toxigenic granules, the appearance of inclusions in cytoplasm, such as Cnyazcov — Dele's bodies basophilically stained small bundle of cytoplasm and others, the presence of large asurophilic granulation and absence of the normal one, the swelling of the nucleus, its hypo- and hyperseg- mentation, different degree of mutation of the nucleus and cytoplasm, cytolysis. Degenerative changes are most frequently observed in neutrophil granulocytes and monocytes. The causes are the disturbance in leukocyte metabolism, which leads to structural anomalies (in leukosis and hereditary enzymopathy), and the damage of leukocytes in the hemopoietic organs and blood under the influence of different pathologic factors (bacteria, viruses and antibodies).

Leukemia

Leukemia — is a disease of tumor nature, originating from blood cells with initial affection of the bone marrow.

Classification

Leukemia belongs to the group of hematopoietic tissue tumors, called hemoblastoses.

Leukemias are divided into *acute* and *chronic* forms depending on the substrate of the tumor growth and on the degree of keeping up the

ability to differentiate into mature cells. In *acute* leukemia the basic substrate of the tumor is blast cells of the 2nd, 3rd and 4th levels of hemopoiesis, that lost their ability to mature, in the *chronic* one maturing and mature cells, because the major part differentiates into mature cells.

According to the morphological and cytochemical peculiarities there are myelo-, lympho-, mono- and megakaryocytic acute leukemias, erythromyelosis and nondifferentiated forms (they come from the cells of the 2nd and 3rd levels of hemopoiesis, which are not identified morphologically). Chronic leukemia in its turn is divided into myelo-, lympho-, *mono-*, megakaryocytic types and chronic erythromyelosis.

Etiology

The role of a number of factors was proved in causing leukemia — oncogenic viruses, ionizing radiation, chemical carcinogenic substances and genetic anomalies.

Oncogenic viruses cause spontaneous leukemias in birds, mice, cats, cattle, monkeys and other animals. They belong to the C-type of RNA-containing viruses. The virus can be transmitted with feces, urine and discharge from the nose and pharynx and from the mother to descendants (for instance in visceral lymphomatosis in hens). Experimentally leukemia is caused by infusing cell-free filtrates of tumor cells of sick animals to healthy ones.

Virus origin of human leukemia was proved in respect to lymphoma of Berkitt (DNA-containing virus of Epstine-Barr) and of T-cell leukemia (of the C-HTLV type). Transmission of the T-cell leukemia virus via blood transfusion and sexual contact (like AIDS virus — HTLV-3) is considered possible. There is an indirect prove of the etiological role of the RNA-containing viruses — it is presence of the reverse transcriptase (RNA-depending DNA-polymerase).

Ionizing radiation is the cause of radiation leukemia in laboratory animals. There are data about increase of the number of cases of leukemia in children, exposed to radiation in the uterus and in patients, who underwent X-ray and radioactive isotope treatment.

Chemical carcinogens may cause acute leukemia in people subjected to contact with certain substances (benzene) or to be cured with medicines having a mutagenous effect (cytostatic immunodepressant, butadionum and chloramphenicol).

Genetic peculiarities of hematopoiesis also have an etiological role in causing leukemia. This is proved by high frequency of cases in

certain ethnic groups, family leukemia (there are cases of chronic lymphoid leukemias with dominant and recessive types of inheritance), concordance of form, clinic, and hematological signs of leukemia in 1/3 of monosigotic twins. Disturbance of somatic and sexual chromosome separation, their mutation also predispose hematopoietic tissue to the damage of tumor process. So cases of leukemia are more frequent in patients with chromosome anomalies (Down's syndrome, syndrome of Klinefelter, Shereshevsky — Terner's disease), genetic defects of the immune system.

Specific chromosome mutations were found in certain kinds of leukemia and are genetic markers for them. So an abnormal Ph' (Philadelphia) chromosome which was discovered by Nowel and Hangerford in Philadelphia city, is typical of chronic myelocytic leukemia. This chromosome appears as a result of deletion of the chromosome of the 22nd pair and translocation of the separated segment to the 9th pair (in 90% of the patients). Translocation of the 8th chromosome segment to the 14th has the same frequency in lymphoma of Berkitt, most likely because of the influence of Epsteine — Barr's virus.

Pathogenesis

Oncogenic viruses, ionizing radiation and chemical substances cause mutation of genes or epigenomic disturbance of regulation of multiplication and maturation of hematopoietic cells of the II and III levels.

Leukemia viruses can cause such chromosomal translocation that result in transmission of the oncogenes, localized in chromosomes, to the part of genome where they can be activated. Penetrating into cell genome, viruses can activate protooncogenes, coding various oncoproteins, some of them serve as growth factors (thrombocytic, epidermal, T-cellular or interleukin-2, insulin etc.), others are receptors of growth factor, others are proteinkinases, catalyzing phosphorylation of tyrosine. However, the ability to transform normal blood cells into tumor ones turned to be common for all the oncoproteins. So, a clone of tumor cells appears in the bone marrow, which is characterized by unlimited growth and low ability to differentiation. Fast growth of leukemic cells results in spreading (metastasing) of them in the whole blood system, including hemopoietic organs and blood.

Instability of leukemic cells genome leads to appearance of new mutations, both spontaneous and caused by continuous effect of carcinogenic factors, that results in appearance of new tumor clones.

Thus, leukemia has two stages of its development: monoclonic (more benign) and polyclonic (malignant, terminal). Transition of one stage into another is the indicator of the tumor progress — leukemic cells become very malignant. They become morphologically and cytochemically undifferentiated, the number of blasts with degenerative changes of the nucleus and cytoplasm increases in hemopoietic organs. Leukemic cells spread, forming leukemic infiltrates in various organs. As a result of selection those cells that were subject to the effect of the immune system, hormones of the organism and cytostatic substances (chemical, hormonal and radioactive) are destroyed and the clones of the tumor cells that are the most resistant to these effects dominate.

In leukemia first of all normal hematopoiesis is disturbed in the cells where the tumor transformation occurred. Tumor cells push out and substitute hematopoietic parenchyma of the bone marrow and its normal microenvironment. Besides, they can inhibit differentiation of cells-precursors of different stems of hematopoiesis. Inhibition of normal erythro- and thrombopoiesis leads to development of anemia and thrombocytopenia with hemorrhage signs.

Depression of normal granulo-, monocyto- and lymphocytopoiesis promotes disturbance of the immune reaction of the organism in leukemia, as humoral and cellular immunity reactions are inhibited (antibody formation). It leads to secondary infection and activation of autoinfection, weakenining of function of the immune supervision. In leukemia lymphocytes may lead to formation of forbidden clones which are able to synthesize antibodies to their own tissues. Autoimmune processes develop.

Blood Picture

Total amount of leukocytes in blood depends on the stage of leukemia (benign monoclonic or terminal polyclonic) and peculiarities of the course of the disease. In leukemia there can be normal amount of leukocytes, slightly increased (20-50-10^9/l and over) in blood or leukopenia. There is a nuclear shift to the left of leuko- gram due to increase of the number of immature forms of leukocytes. There can be various degenerative changes of leukocytes observed, morphological and cytochemical atypicity, making identification of the cells difficult, and also anemia and thrombocytopenia.

Appearance of a large number of blast cells in blood is typical for *acute leukemia.* There can be a "leukemic gap" observed when there are no transition forms between blast cells and mature granulocytes. This

indicates serious disturbance of leukopoiesis in hematopoietic organs — loss of the ability of tumor cells to differentiate.

Increase of the number of neutrophilic granulocytes — metamyelocytes, "bilobe" myelocytes — with a shift to the left to myelocytes and single myeloblasts — is typical for *chronic leukemia.* The number of eosinophilic and basophilic granulocytes can also be increased. Myeloid metaplasia of the lymphoid tissue is observed. The terminal stage is characterized by blast crisis when the number of blast cells — myeloblasts and the number of non-differentiated blasts increase in blood sharply.

Chronic lymphoid leukemia is characterized by lymphocytosis — 80-98%. Lymphocytes are mostly mature (B-lymphocytic kind of leukemia is more common), but there are single prolymphocytes and lymphoblasts in blood. The number of granulocytes, erythrocytes and platelets is decreased. This is caused by total substitution of all hemopoietic stem cells by lymphocytes (lymphoid metaplasia of myeloid tissue). Blast crisis occurs rarely in this form of leukemia (3-4%).

COMPREHENSION CHECK

Try to answer the following questions.

1. Name pathologic changes of leukocytes and explain the mechanism.
2. What is leukocytosis?
3. What is leukopenia? Explain etiology and pathogenesis.
4. Define leukemia, name etiological factors.
5. Characterize pathogenesis and blood data under acute and chronic leukemia.

UNIT 19

PATHOPHYSIOLOGY OF THE BLOOD COAGULATION

With the help of the system of hemostasis blood carries out one of its most significant functions — keeping itself in a liquid state and coagulation in case of a vessel's wall injury and, this way, stopping the bleeding and keeping the initial volume and composition of blood. The system of hemostasis has many components. These are platelets and other blood cells, vessel's wall, extravascular tissue, biological active substances, tissue factors (extrinsic pathway), plasma factors of blood clotting (intrinsic pathway), begin in a close interaction with anticoagulational, fibrinolytic and kallikrein-kinin systems. Disturbance of any of these components leads to hemostasis pathology.

Classification. Pathology of hemostasis is classified according to effecting of its components into disturbance of the extrinsic and intrinsic pathways. According to the etiology, these disturbances can be acquired and hereditary, as for the direction of pathological changes they can be leading to decreasing of blood clotting (hypocoagulation) and increasing of blood clotting (hypercoagulation), which can be local (thrombosis) and generalized (DIC) (Fig. 34).

DECREASING OF BLOOD COAGULATION ABILITY

Decrease of blood coagulation ability leads to increasing of bleeding (hemorrhage syndrome) — repeating bleedings, hematomas appearing both spontaneously and in case of not significant injuries.

Extrinsic pathway is disturbed in case of qualitative and quantitative changes in platelets (thrombocytopenia and thrombocytopa- thies), and also under effecting of vessels.

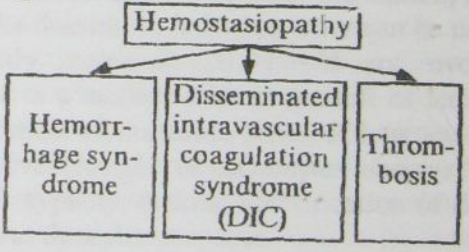

Fig. 34. Classification of hemostasis disturbances

Thrombocytopenia means decreasing of platelets count in blood (180-320 10^9/1). However, spontaneous bleedings occur only in case of decreasing of their number down to 30 10^9/1. Thrombocytopathy means quantitative defects and dysfunction of thrombocytes under normal or decreased content of them.

Etiology

Thrombocytopenia can also be caused by immune reactions in case of changing of antigen structure of thrombocytes under effecting by viruses, medicines, production of antithrombocytic antibodies (under chronic lymphoid leukemia and idiopathic thrombocytopenia), incompatibility of thrombocytic antigens of a mother and embryo. Besides, thrombocytopenia develops as a result of affecting the megakaryocytic branch of the bone marrow by ionizing radiation, chemical substances or replacing of it by tumor metastases, leukemia infiltrates. Decreasing of thrombocytopoiesis can be caused by deficiency of cyanocobalamin and folic acid, hereditary defect of formation of platelets (including the deficiency of thrombocytopoietin). Thrombocytopenia occurs as a result of mechanic injury of platelets under splenomegaly, artificial cardiac valves and also increased usage of platelets under local and generalized intravascular blood coagulation.

Thrombocytopathy can be caused by toxic substances and medications (alcohol, acetylsalicylic acid) ionizing radiation, endogenous metabolites (under uremia, cirrhosis of the liver); cyanocobalamin deficiency and hormonal disturbances (hypothyroidism). Genetic defects of the membrane structure and biochemical composition of platelets (deficiency of thrombostenin, factor 3, ATP, ADP, G-6- PDG, membrane receptors for V, VIII, XI factors, etc.).

Under hemorrhage vasopathies the injury of vessels' walls leading to disturbances of the extrinsic pathway and bleedings, occurs as a result of increasing of blood vessels' walls permeability and their destruction due to disturbance of collagen synthesis (under nutritious deficiency of vitamin C, genetic defects of collagen synthesis), under effect of biologically active substances (allergy), radiotoxins (radiation disease), immune hemorrhage vasculites, decreasing of antiathrophic function of platelets under thrombocytopenias, destruction of vascular walls by leukemia infiltrates. On 2 of the causes of bleeding can be lack of producing components of the VIII coagulation factor by endothelium of vessels (hereditary Willerbrand disease). This factor accumulates in platelets, and it's released during their degranulation.

It is necessary for normal adhesion of platelets to collagen of a vessels' wall, and thrombocytic clot can't be formed without it. Hemorrhage syndrome is also observed under increasing of peroxide oxidation of membrane phospholipids resulting in hyperproduction and hypersecretion by endothelium of strong inhibitors of platelets aggregation — prostacyclines. Besides , insufficiency of the extrinsic pathway can result from a disturbance of the nervous and hormonal regulation of vascular tonicity, decreasing of which leads to impossibility of plugging small vessels with a platelet clot.

Pathogenesis

There are 4 basic mechanisms of thrombocytopenia's development: decrease of production, increased destroying, increased consumption (clot formation), and redistribution of platelets. Disturbance of hemostasis and development of hemorrhage under thrombocytopenia is caused by the following mechanisms:

1. Increasing of permeability of the capillary bed for erythrocytes and other components of blood (diapedesis hemorrhage and fragility of vessels due to dystrophy of the wall in case of disappearing of angiotrophic function of platelets.
2. Decrease of adhesive-aggregational function of platelets.
3. Disturbance of the function of releasing the platelet factor:; of blood coagulation, ADP, serotonin, adrenaline, antiheparin factor that leads to insufficiency of platelet clot formation, absence of vascular spasm and delay of coagulation.
4. Decreasing of clot retraction as a result of a drop in activity of constrictive protein of platelets — thrombosthenin (platelet factor VIII).

There can be two mechanisms of thrombocytopathy development: formation of pathologic platelets in the bone marrow and destruction of platelets in all parts of the circulation system. Patho genesis of the disturbance of the extrinsic pathway under thrombocytopathies is the same as under thrombocytopenias, because i: is connected to disappearing of platelets function.

Disturoance of the intrinsic pathway, leading to development of hemorrhage, can be caused by the following factors:

a) acquired or hereditary insufficiency or pathology of the synthesis of plasma and platelet factors of blood coagulation and components of the kallikrein-kinin system;

b) inhibition or increased consumption of these factors;

c) increasing of endogenous anticoagulase;

d) activation of fibrinolytic system;

e) overdose of anticoagulants and fibrinolytics.

All of these cause disturbance of one of three stages of blood clotting and retraction of a clot or combined changes in it.

Etiology

The cause of the disturbance of the *1st stage of blood coagulation* — formation of thrombaplastin — is decreasing of the production of IX, X factors under pathology of the liver, production of antibodies to some factors (VIII, IX) under diseases with autoimmune pathogenesis (leukemia, collagenoses) or overdose of such universal anticoagulants as heparin. There are known genetic defects of synthesis of the VIII, IX and XI factors. Their deficiency causes development of hemophilia (hemophilia A, B, C).

Disturbance of the 2nd stage of hemostasis — formation of thrombin — develops not only under liver diseases but also under vitamin K hypo- and avitaminosis, which results in decreasing of II, V, VII factors' synthesis, which participate in this stage (under mechanic yellow enteritis, extensive resection of the small intestine, dysbacteriosis). Appearance of inhibitors of the V, VII factors is also possible (for instance under treatment with streptomycin sulfate), increased excretion of them with kidneys, genetic deficiency (of factor V under parahemophilia) or inactivation of them by the components of the anticoagulation system, antithrombins, heparin (under anaphilaxia, overdose of heparin).

Hemorrhage diathesis is linked to the disturbance of the third stage of hemostasis — the phase of fibrin production, which develops under decrease of fibrinogen synthesis in the liver, affected by a pathologic process, the lungs or a result of genetic hypo-, afibrinogenemia and defect of fibrinstabilizing factor (XIII). However disturbance of the third stage is more often a result of increase of fibrinolysis under injury (surgery) of the lungs, uterus, pancreatic gland, burns and shock. This is caused by increasing secretion in blood of activators of protofibrinolysin (plasminogen) of tissue or microorganism origin, phosphokinases, leuko- and erythrocyte activators, complex of kallikrein-kinin system and the system of complement, complex of heparin with fibrinogen, protofibrinolysin and adrenaline (these complexes provide nonenzyme fibrinolysis).

Pathogenesis

The main links in pathogenesis of the hemorrhage diathesis, de-

veloped under disturbances of any of the stages of blood clotting, are chronic loss of blood with its consequences as well as structural and functional changes at the place of hemorrhage (in the joints, internal organs, skin and other tissues) (Fig. 35).

INCREASING OF BLOOD COAGULATION ABILITY

Increase of blood coagulation shows in local (thrombosis) or generalized intravascular blood clotting, which results from disturbance of the extrinsic and intrinsic pathways.

Hypercoagulation may be caused by:

1. Increase of functional activity of the coagulational system due to increased production of procoagulants and: activators of blood clotting.
2. Increase of platelets count.
3. Decreasing of antithrombotic qualities of vascular wall.

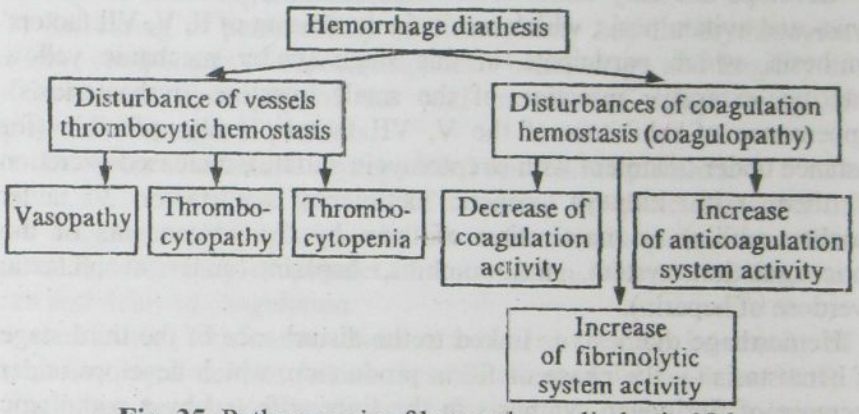

Fig. 35. Pathogenesis of hemorrhage diathesis 196

4. Decrease of functional activity of anticoagulational system.
5. Fibrinolysis failure.

Generalized (disseminated) intravascular blood coagulation (DIC-syndrome) — serious pathology of hemostasis that occurs under increased content of protocoagulants and activators of blood clotting, which leads to formation of numerous microdots in microcirculation vessels, and then to development of hypocoagulation, thrombocytopenia and hemorrhage due to cutting out of coagulation factors and increasing of functional activity of anticoagulational system and fibrinolysis of blood with further exhaustion of all three systems.

Etiology

Hypercoagulation can result from all kinds of shock, traumatic surgeries, obstetric pathology (premature placental detachment, manual detachment of placenta), acute intravascular hemolysis, uremia under renal insufficiency and all terminal states.

Pathogenesis

The main link of pathogenesis of the generalized hypercoagulation is balance disturbance of the kallikrein-kinin, coagulation, anticoagulation and fibrinolytic systems, under coming into the blood of big quantities of protocoagulants and their activators.

The phase of hypercoagulation is characterized by blood clotting in vessels and stop of the coagulation with development of serious dystrophic and functional disturbances in organs and tissues, often not compatible with life. In the next phase of hypocoagulation thinning of blood and loss of the ability to coagulate and aggregate platelets cause bleeding, which can rarely be stopped therapeutically. In case of favorable result there comes the first stage — rehabilitation phase, when the function of hemostasis normalizes.

COMPREHENSION CHECK

Try to answer the following questions.

1. Identify hemostasis disturbances.
2. What is DIC-syndrome?
3. What is the role of thrombocytes in blood coagulation activity?

UNIT 20

PATHOPYSIOLOGY OF THE RESPIRATORY SYSTEM

External respiration is a complex of processes occurring in the lung and providing normal contents of oxygen and carbon acid in blood. Three main processes take place in the lungs; alveolar ventilation, diffusion of the molecular oxygen and carbon acid through the alveolar-capillary membrane and perfusion (flowing of the corresponding amount of the blood via the pulmonary capillary vessels).

RESPIRATORY FAILURE

Respiratory failure is a pathologic process developing due to the disturbance of the external respiration. In respiratory failure the maintenance of gas contents adequate to the organism requirements isn't ensured. Even at rest respiratory failure may lead to hypoxia and gaseous acidosis or limits the organism abilities to fulfil physical work.

The main mechanisms of respiratory failure development consist in disturbances of ventilation, perfusion, diffusion as well as their quantitative ratio.

DYSFUNCTION OF THE RESPIRATORY CENTER

The alveolar ventilation is regulated by neurons of the respiratory center located in the medulla oblongata and pons, providing the certain depth, rate and rhythm of respiration. The function of the respiratory center may be disturbed due to direct effect of different pathogenic factors on the central nervous system or by reflex (effect on hemo-, baroreceptors, etc). Respiratory failure occurs in the decreased depth and rate of respiration, different kinds of periodic respiration.

ASPHYXIA

Respiratory failure is one of the causes of hypoxia, acidosis and hypercapnia development in the organism.

Asphyxia develops in case when the respiratory failure occurs acutely or subacutaly and reaches such a degree when oxygen stops to come into the blood and carbon dioxide is not discharged out of the blood.

The most frequently asphyxia occurs in compression of the respiratory tracts (strangulation), occlusion of their lumen (foreign body,

inflammatory edema), presence of fluid in the respiratory tracts and alveoli (drowning, lung edema, vomiting masses), in bilateral pneumothorax. In addition, asphyxia may develop in severe inhibition of the respiratory center, disturbance of the nerve impulse conduction to the respiratory muscles, sharp limitation of the thorax mobility.

There are three periods *in the* course of *asphyxia* that may be observed in the experimental animal, for example, in squeezing of the trachea.

The first period of asphyxia is characterized by rapid increase of the depth and rate of respiration, the inspiration phase prevails the expiration. We can observe general excitement, the increased tension of the sympathetic part of the vegetative nervous system (dilated pupils, tachycardia, elevation of blood pressure), convulsions are possible.

During ***the second period*** the respiration rate gradually diminishes in preserving maximal amplitude of the respiratory movements and the phase of expiration is intensified. We can observe that the tension of the parasympathetic part of the vegetative nervous system (the narrowed pupils, reduction of blood pressure, bradycardia) prevails.

During ***the third period*** of asphyxia the amplitude of respiration and its rate are decreased and at last respiratory standstill is observed. The arterial pressure is considerably decreased. After a short-term respiratory standstill there are usually several rare spasmodic respiratory movements (gasping respiration), which are followed by respiration paralysis.

The effects observed in asphyxia are connected at first with accumulation of carbon dioxide in the organism. Acting by reflex and via central hemoreceptors for H^+-ions, carbon dioxide excites the respiratory center making the depth and rate of respiration maximal. Besides, respiration is stimulated by reflex by reduction of the molecular oxygen tension in the blood. As the contents of $C0_2$ in the blood increase, the arterial pressure increases too. Experiments with inspiration of gas mixtures containing 10-20% of $C0_2$ showed that this elevation is connected with, first of all, reflex effect via hemoreceptors on the vascular motor center; second, with the intensified ejection of adrenalin into the blood; third, with the increased minute blood volume resulting from elevated vein tension and increased blood inflow in respiration intensification.

In further increase of $C0_2$ concentration in the blood, its narcotic effect begins to manifest, pH of the blood is reduced to 6.8-6,5. Hypoxemia increases and so does hypoxia of the brain. In its turn it

leads to inhibition of respiration and decrease of the arterial pressure. Finally, respiration paralysis and cardiac standstill occur.

DISTURBANCES OF THE EXTERNAL RESPIRATION REGULATION

At rest a man breathes without any visible efforts paying no attention to this process. This condition is called respiratory comfort and this respiration — eupnoea.

In pathology, under the influence of reflex, humoral or other effects on the respiratory center, the rhythm of respiration may change as well as its depth and rate, not infrequently accompanied by breathlessness. These changes may be a manifestation of compensatory reactions of the organism directed at supporting of gaseous content constancy of blood or a manifestation of impairment of normal regulation of respiration leading to reduction of the alveolar ventilation, to respiration insufficiency.

Bradypnoea is a rare breathing. Reflex diminishing of respiration rate may be observed in the increased arterial pressure (reflex from the baroreceptors of the aorta arch and the carotid sinus), in hyperoxia (due to switching off of the "hypoxic drive" — periodic excitation of hemoreceptors sensitive to the lowering of the molecular oxygen tension in the arterial blood).

Deep rare breathing may appear in the increased resistance to the air movement in the upper respiratory tracts — stenotic respiration. In this case, inspiration and expiration are accomplished slower than usually. Bradypnoe may develop as a result of direct effect of the pathogenic factors on the respiratory center, which decreases the excitability of the respiratory neurons.

Polypnoea (or tachypnoea) is a frequent superficial respiration. It develops as a result of reflex reorganization of work of the respiratory center. In a human polypnoea may be observed in fever, functional impairments of the central nervous system (hysteria), in lung troubles (atelectasis, pneumonia, congestion).

Probably, in some cases polypnoea occurs if there is more than usual stimulation of the respiratory center, on one hand, and excessive activation of the factors inhibiting it, on the other hand.

Besides, polypnoea may develop due to the pain locating in the body parts taking part in the act of respiration (the thorax, abdomen, pleura). The pain leads to limitation of the respiration depth and increase of its

frequency (sparing respiration).

Hyperpnoea or deep and frequent, respiration under the physiologic conditions occurs as a response of the respiratory system, directed at making the lung ventilation meet the requirements of the intensified metabolism, for example, during the muscular work. It improves the oxygenation of the blood and supports the acid- base balance in the organism by discharging out extra amount of CO_2.

Under the pathologic conditions hyperpnoea develops due to intensive reflex or humoral stimulation of the respiratory center, for example, in the reduction of the partial pressure of the molecular oxygen in the inspired air or in elevation of $C0_2$ concentration in it, in anemia, acidosis, etc.

The extreme degree of excitability of the respiratory center is manifested as *Kussmaul respiration,* which is mostly observed in the patients in diabetic coma. It is a deep noisy accelerated breathing when a deep inspiration is followed by intensive expiration with active involvement of the expiratoral muscles.

Apnoea is translated as absence of breathing but usually this word means temporary respiratory standstill. Apnoe may result in impairment of gas exchange in the organism, the severity of which depends on the rate of appearance and duration of apnoea.

Cough commonly develops in stimulation of the nerve endings of the glossopharyngeal and vagus nerves in the mucous membrane of the pharynx, larynx, trachea (the most sensitive area of its bifurcation) and bronchi. In addition, it may be caused by stimulation of the sensitive nerves or the pleura. Cough consists of short inspiration followed by immediate closing of the glottis, expiratory effort of the respiratory muscles develops simultaneously. It leads to the elevation of pressure in respiratory tracts, alveoli and pleural cavity. Then glottis opens and air leaves respiratory tracts at a high speed.

Sneezing occurs as a response to the stimulation of the nerve endings of the trigeminal nerve located in the mucous membrane of the nose (especially in the middle turbinate bone and septum). In contrast to cough, in sneezing the forced expiration occurring after the opening of the glottis goes through the nose not through the mouth.

Periodic breathing is a rhythm disorder of respiration when the respiration periods are alternated with the period of apnoea. There are two types of the periodic breathing — Cheyne — Stokes respiration and Biot respiration.

Cheyne-Stokes respiration is characterized by amplitude growing of respiration till the marked hyperpnoea and then it's diminishing to apnoea followed by a cycle of the respiratory movements also finishing with apnoea.

It is believed that in most cases Cheyne — Stokes respiration is a sign of brain hypoxia. It may occur in cardiac insufficiency, the diseases of the brain and its membranes, uremia. Some medicines (for example, morphine) may also cause Cheyne — Stokes respiration. It may be observed in healthy people at great height (especially during sleep), in premature babies, which is probably connected with imperfection of the nervous centers.

The cells of the brain cortex and subcortical formations are inhibited due to hypoxia — respiration stops, consciousness disappears, the activity of the vascular motor center becomes inhibited. However, hemoreceptors are still capable of reacting to the occurring changes of gas contents in the blood. Sharp intensification of impulsation from hemoreceptors along with direct effect on the centers of high concentration of carbon dioxide and stimuli from baroreceptors due to reduction of the arterial pressure are sufficient to excite the respiratory center and respiration is resumed.

Restoration of respiration leads to blood oxygenation, brain hypoxia diminishing and improving of the function of neurons of the vascular motor center. Breathing becomes deeper, consciousness becomes clear, the arterial pressure increases and the heart filling is improved. The increased ventilation results in elevation of the oxygen tension and reduction of carbon dioxide tension in the arterial blood. In its turn, it leads to slackening of the reflex and chemical stimulation of the respiratory center whose activity begins to extinct — apnoea comes.

Biot respiration differs from Cheyne — Stokes respiration by the respiratory movements, which are characterized by constant amplitude but both stop and begin suddenly. Biot respiration is mostly observed in meningitis, encephalitis and other diseases accompanied by impairment of the central nervous system, especially the medulla oblongata (Fig. 36).

Terminal Respiration

Apneustic respiration is characterized by convulsive unceasing effort to inspire, occasionally interrupted by expiration.

Apneustic respiration is observed in experiment on animal after cutting both vagus nerves and the trunkus cerebri between the pneumotaxic (in the rostral part of the pons) and apneustic centers (in

the middle and caudal parts, of the pons). It is believed that the apneustic center has an ability to excite the inspiratoral neurons, which are periodically inhibited by the impulses from the vagus nerve and the pneumotaxic center. The cutting of these structures leads to constant inspiratory activity of the apneustic center.

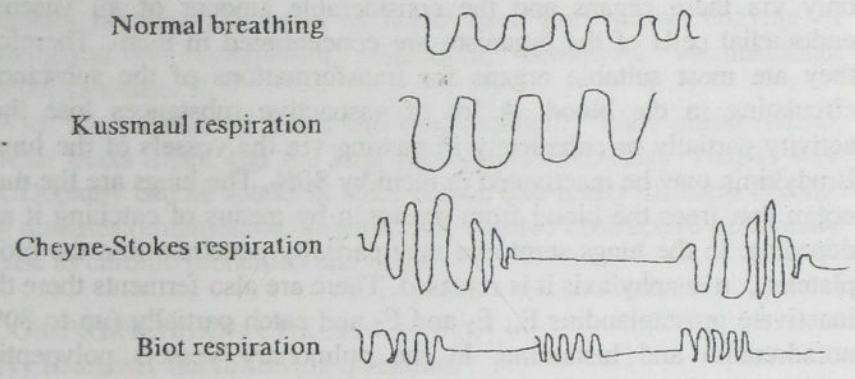

Fig. 36. Various kinds of periodical breathing

IMPAIRMENT OF NON-RESPIRATORY FUNCTION OF THE LUNGS

First of all the lungs have a protective function. Possessing a vast total area (50-100 square meters) they are the vastest surface of the organism that comes into contact with more and more aggressive environment. The lungs are capable of detaining harmful mechanical and toxic products in the inspired air. The deposited in the lungs particles are removed from the bronchus walls by the ascending flow of the mucus (mucociliary transport).

The lungs fulfil important metabolic functions taking part in protein, fat and carbohydrate metabolism. They are exclusively rich in lypolytic and proteolytic enzymes and may be compared with the liver in the intensity of lipid metabolism. The lungs regulate thie amount of fat coming into the arterial blood as they detain and metabolize a part of chylomicrons coming from the intestines via the lymphatic vessels. They may synthesize fat acids and phospholipids, in particular, dipalmitoilphosphatydilcholin composing surfactants. The protein synthesis also plays a significant role, as the structural base of the lungs is formed from collagen and elastin. The synthesis impairment,

intensified dissociation or hyperproduction of these proteins may be the cause of development of emphysema and pneumosclerosis. The carbohydrate metabolism also has a great significance, especially production of mucopolysaccharides composing the bronchial mucus.

Metabolism of many substances influencing the vessels takes place in the lungs. But you should bear in mind that the total blood comes only via these organs and the considerable amount of all vascular endothelial cells of the organism are concentrated in them. Therefore they are most suitable organs for transformations of the substances circulating in the blood. A lot of vasoactive substances lose their activity partially or completely in passing via the vessels of the lungs. Bradykinin may be inactivated in them by 80%. The lungs are the main organ that frees the blood from serotonin by means of catching it and deposing. In the lungs serotonin may partially penetrate into the blood platelets, in anaphylaxis it is released. There are also ferments there that inactivate prostaglandins E_1, E_2 and F_2 and catch partially (up to 80%) noradrenalin and histamine. In the pulmonary vessels polypeptide angiotensin I, possessing the pressing action, is transtormated into angiotensin II under the influence of the converting ferment, it is 50 times more active than its predecessor. The lungs play an important role in maintaining fibrinolytic and anticoagulant activity of the blood. There are a lot of fat cells containing heparin in the interstice of the lungs. The lungs take part in detoxication of a number of medicines (aminasinum, sulfanilamids, etc),

LUNG COLLAPSE AND PNEUMOTHORAX

The expansion of the lung is maintained by the pressure difference between the alveoli, which are normally in free communication with the atmosphere and the subatmospheric pressure of the pleural space. The causes of collapse (atelectasis) of the lung are pleural filling, bronchial obstruction with absorption of the intra- alveolar gas, and changes in surfactant function. The lung collapses when compressed by pleural effusions, tumors, other space-occupying intrathoracic lesions, or elevation of the diaphragm. In pneumothorax the lung collapses because air gains access to the pleural space permitting the negative pleural pressure to rise. This can occur as the result of thoracic trauma, perforation of the esophagus, extension of lung abscess or other infections through the pleura with formation of bronchopleural fistula or rupture of air-containing cysts or bullae associated with emphysema or

other forms of diffuse or localized lung disease.

Both the parietal and visceral pleura respond to pneumothorax by the exudation of fibrin associated with a proliferation of macrophages, giant cells, mesotelial cells and eosinophils known as reactive eosinophilic pleuritis.

APUDopathy in lungs may be caused by different pathological processes because the lungs as hepar have got various enzyme of detoxication — enkephalin, calcitonin, bombesin, vasointestinal peptide, substance P.

With the passage of years the lung gradually loses elastic recoil, alveolar ducts dilate and the lung parenchyma increases. That is why APUDopathy can be found in elder person and under different chronic lung diseases (emphysema, amyloidosis, chronic obstructive pulmonary disease as chronic bronchitis and oth.).

COMPREHENSION CHECK

Try to answer the following questions.

1. What disturbances of the external respiration do you know?
2. Explain the notion "asphyxia".
3. Characterize various kinds of periodical and terminal breathing.
4. What are impairment of non-respiratory function of the lungs?
5. What is the cause of APUDopathy in the lungs?

UNIT 21

PATHOPHYSIOLOGY OF THE SYSTEMIC BLOOD CIRCULATION

HEART DISEASE

Circulation insufficiency may occur due to the heart impairment (cardiac insufficiency) or change of the vessel functions (vascular insufficiency). We often observe combined cardio-vascular insufficiency.

Cardiac Insufficiency

Cardiac insufficiency develops in discrepancy between the required load on the heart and its capability of doing this work. There are three pathophysiological variants of cardiac insufficiency.

1. Cardiac insufficiency from overload develops in the diseases when the resistance to the heart ejection or inflow of the blood to a definite part of the heart is increased, for example, in heart failure, hypertension of the systemic or pulmonary circulation, arteriovenous fistulas or in doing excessive work.

2. Cardiac insufficiency in damage of the myocardium caused by infection, intoxication, hypoxia, avitaminosis, impairment of the coronary circulation, fatigue, some hereditary disturbances of metabolism.

3. Mixed form of cardiac insufficiency occurs in different combination of the myocardium damage and its overload, for example, in rheumatism, when we may observe combination of the inflammatory lesion of the myocardium and disorders of the valvular apparatus.

Cardiac Insufficiency Caused by Overload

Mechanism of Compensation

The cardiac overload may be due to the increased amount of the inflow blood or due to the increased resistance to the blood outflow. The first kind of the heart load (by volume) is observed during physical work, in heart failures accompanied by insufficiency of the valvular apparatus. During diastole in such failures the cardiac cavity is filled not only with the blood inflowing by normal routes, but also with the blood ejected from the cavity due to incomplete close of the valve during systole. The same is observed in congenital defects of the heart septums. The second kind of the increased loud on the heart (by

pressure) develops in stenosis of the outlet foramen from the cardiac cavity, for example, in stenosis of the foramen of the pulmonary trunk or aorta, atrioventricular foramen. The increased resistance to the outflow also arises in hypertension, generalized atherosclerosis, pneumosclerosis.

The heart is capable of quick adjusting to the increased load, compensating possible disturbances of the circulation while doing the increased work. Depending on the kind of load, this or that mechanism of compensation begins to act.

In the overload by blood, volume heterometric mechanism of compensation begins to work (Frank — Sterling's). The elevated blood filling of the cavities (or one cavity) of the heart is observed during diastole. It results in the increased distension of the muscular fibers. Stronger contraction of the heart is a consequence of such distension during systole. This mechanism is conditioned by the myocardium cell properties. However, when the degree of distension of the muscular fibers exceeds the permissible limit, the contraction force is decreased. The decrease of active tension occurs in distension of the myocardium segment by more than 25% of its initial length. In the permissible overloads the linear sizes of the heart are increased by 15-20%. The occurred dilatation of the heart cavities is accompanied by the increased best volume and is called tonogenie dilatation.

Homeometric mechanism of compensation begins to work in the increased resistance to the blood outflow. In this case, the length of the cardiac muscular fiber is not increased so sharply, but the pressure and tension are elevated having occurred in the heart contraction at the end of diastole. The increase of force of the heart contraction doesn't occur at once, but gradually with every subsequent heart contraction, until it reaches the level necessary for ensuring constancy of the minute heart volume.

Both mechanisms of the increased load compensation are not of equal value in energy respect. So, in equal increase of the outer heart work counted by multiplication of the minute heart volume by mean systolic pressure in the aorta, the cardial oxygen intake changes differently. In homeometric mechanism of compensation it is necessary to have a considerable elevation of the systole pressure to overcome the increased resistance to outflow. It may be achieved by the increase of the amount and speed of the muscular fiber tension. It is the phase of isometric tension that is the most energy consuming and it is the factor that determines consumption of ATP and oxygen by the myocardium.

Hence, the heterometric mechanism of compensation is more economic than the homeometric one and it may account for more favorable course of those pathologic process which are accompanied by Frank — Starling's mechanism, for example in valve insufficiency in contrast to foramen stenosis.

Acceleration of the heart contractions — tachycardia — may also serve as a compensatory mechanism, providing constant level of the minute blood volume. It may occur at the expense of direct effect of the elevated blood pressure in the right atrium on the rhythm driver — sinoatrial node as well as the nervous and humoral extracardial influences. From the point of view of energy it is the less beneficial mechanism of compensation because it is, first of all, accompanied by consumption of a great amount of oxygen. Second, diastole is considerably shortened and it is the period of restoration and rest of the myocardium. Third, hemodynamic characteristic of the heart gets worse, as the ventricles fail to be filled with blood during diastole and systole becomes less effective.

The moment of the commencing contraction of the atria approaches the end of the ventricular systole until at 170 beats per min it coincides with it (occlusion of the atria). On ECG the wave P overlaps the wave T.

The intracardial mechanisms of regulation are added by extracardial regulatory effects — the nervous and humoral ones. The main role between them belongs to the sympathetic part of the vegetative nervous system, discharging noradrenalin by the nerve ending and adrenaline by the cerebral substance of the adrenal glands. These sympathetic mediators (catecholamines) interact with the receptors on the myocardiocyte surface. In sympathetic excitation the force and speed of the heart contractions are considerably increased, the volume of the residual blood in the heart cavities is reduced at the expense of more complete removal of the blood during systole (in usual load about half of the blood remains in the ventricle at the end of systole). The rate of the heart contractions is increased. In the increased tension of the sympathetic nerves and discharge of a great amount of catecholamines the overload compensation is more effective at the expense of the intracardial regulatory mechanisms.

If the increased load on the heart is excessive, the compensatory mechanisms fail to manage the overload and acute cardiac insufficiency develops. The following changes develop in the cardiac muscle: accumulation of sodium and potassium ions in the cells, disturbances of synthesis of macroergic compounds, acidity decrease of the intracellular

media with subsequent impairment of process of contraction and relaxation of the cardiac muscular fiber. It results in reduction of the force and speed of the cardiac muscle contraction, elevation of the residual systolic volume and diastolic pressure, dilatation of the heart cavities. Acute cardiac insufficiency is accompanied by significant changes in the blood circulation — elevation of the venous pressure, reduction of the minute blood volume, tissue hypoxia. Along with metabolic there may be structural changes in the cardiac muscle, so that even in the further reduction of the load, the heart activity may not be normalized.

Acute cardiac insufficiency develops in the ventricular fibrillation, paroxysmal tachycardia, myocardial infarction, myocarditis, thrombosis of the valvular foramen, embolism of the pulmonary artery, the heart tamponade.

The following changes can be observed in acute cardiac insufficiency: insufficient filling up of the arterial system by the blood leading to ischemia of the brain with severe changes of its function resembling shock and not infrequently accompanied by loss of consciousness and convulsions.

In prolonged heart load, for example, in valve failures, hypertension, long-term mechanisms of compensation begin to act. The myocardium develops specific metabolic and structural changes leading to the increase of mass and work ability of the heart.

Myocardial Hypertrophy

According to dynamics of metabolic changes, the structure arid function of the myocardium in compensative hypertrophy of the heart, there are three main stages (F. Z. Meerson).

1. ***The emergency stage*** develops immediately after overloading and is characterized by combination of the pathologic changes in the myocardium and mobilization of the reserves of the myocardium and the organism on the whole. The pathologic changes include disappearance of glycogen, reduction of creatinphosphate level, decrease of the intracellular potassium and increase of sodium content, mobilization of glycolysis, accumulation of lactate. At this stage the load on the unit of the muscular mass and intensity of structure functioning (ISF) are increased, the heart becomes enlarged quickly, within weeks, due to the intensified protein synthesis and thickening of the muscular fibers.

2. ***The stage of completed hypertrophy and relatively stable hyperfunction.*** At this stage the process of hypertrophy is completed, the myocardium mass is increased by 100-120% and does not increase any

more, ISF is normal. There are no pathologic changes in metabolism and structure of the myocardium. The intake of oxygen, energy formation and the content of the macroergic compounds are within the norm. The hemodynamic indices are normal. The hypertrophy heart has adjusted to new load and compensates it for a long time.

3. ***The stage of gradual exhaustion and progressing of cardiosclerosis*** is characterized by profound metabolic and structural changes.

Chronic or congestive cardiac insufficiency develops, mainly due to metabolic disturbances in the myocardium in the prolonged hyperfunction of the heart or different kinds of the myocardium impairment. Because of insufficient ejection of the blood from the heart the blood filling of the organ along the inflow tracts is diminished. At the same time due to inability of the heart to pump the inflowing blood congestion develops along the outflow tracts, i. e. veins. As the volume of the venous vascular flow is approximately 10 times greater than the arterial volume, a considerable amount of the blood is accumulated in the veins.

In impairment of one of the ventricles the circulatory insufficiency acquires some specific features and therefore it is called insufficiency by the left-ventricle type or the right-ventricle type. In the first case the blood congestion is observed in the veins of the pulmonary circulation that may result in lung edema; in the second case it is observed in the veins of the systemic circulation, the liver is enlarged, there are edemas on the legs and ascites.

The hemodynamic indices in chronic insufficiency of the heart are changed as follows: the minute blood volume of the heart decreases from 5-5,5 to 3-4 l/min; the blood flow speed is 2-4 times slowed down, the arterial pressure changes a little. It may be explained by adequate increase of the peripheral resistance of the vessels. The venous pressure is elevated. The capillary vessels and postcapillary veins are dilated, the blood flow is slowed down in them and pressure is increased due to reduction of the pump function of the heart. The slowing dawn of the blood flow in the systemic circulation and circulatory disturbance in the lungs leads to the increase of the restored hemoglobin in the blood flowing through the vessels. It gives the skin and the mucous membrane a characteristic cyanotic color — cyanosis. The tissues lack oxygen, hypoxia is accompanied by accumulation of underoxidated products of metabolism and carbon dioxide. Acidosis develops aftewards. Acidosis and hypoxia lead to impairment of respiration regulation that brings about dyspnoea. To compensate

hypoxia, erythropoiesis is stimulated, the total volume of the circulatory blood is increased as well as relative content of the blood cells in it that promotes the increase of the blood viscosity and worsens its hemodynamic properties.

There is observed retention of sodium and water in the organism, it is one more example of compensation mechanism contradictoriness in the pathologic process. The mechanisms, which evolutionally arose to provide sufficient contents of salts and fluid in the organism, become harmful in cardiac insufficiency. In patients with the circulatory insufficiency the surplus of the intake salt is not excreted by the kidneys as in a healthy person but detained in the organism with water (secondary aldosteronism). Prolonged existence of circulation insufficiency leads to profound and irreversible disturbance of intracellular metabolism.

In combination with dysfunction of the digestive tract and progressive circulatory insufficiency the patient begins to suffer from severe cachexia called cardiac cachexia.

Non-Coronarogenic Impairments of the Heart

There are several experimental models of necrosis of the cardiac muscle. Its cause is not connected with pathology of the cardiac vessels. *Hypoxic necrosis* of the myocardium may be reproduced with the help of different kinds of hypoxia: hypoxic, hemic. The development of necrosis is promoted by fixation of the experimental animal in the uncomfortable position for example, stretching on the plane or additional load — running in the trainer.

Electrolyte-steroid cardiopathy with necrosis. According to Seleau's observations, when a significant amount of sodium salts in combination with some anions (sulfates, phosphates) are introduced to rates foci of impairment of degenerative-necrotic type appear in the heart.

Immune impairments of the heart are possible in introduction of the heterogenic serum into the organism of the experimental animal. It contains antibodies to the heart proteins of present species of animal (cardiocytotoxins).

Coronarogenic Impairments of the Heart

Ischemic Heart Disease. Myocardial Infarction

Diseases and pathologic conditions accompanied by disturbance of the myocardial circulation, the cause of which is impairment of the coronary arteries, mainly, of atherosclerotic character are united in

special nosologic unit called ischemic heart disease (IHD). IHD may be manifested mainly by functional disturbances and pain syndrome (angina pectoris) or lead to necrotic changes of the myocardium.

Myocardial infarction is a focal ischemia and necrosis of the cardiac muscle occurring due to cessation of the blood inflow by one of the branches of the coronary arteries or as a result of insufficient amount of blood to meet energy requirements. Atherosclerosis is the most frequent cause of impairment of the coronary artery's wall.

Risk factors leading to infarction include: hereditary ones; hypertension, diabetes mellitus, gout; environmental factors; sedentary, emotionally tensed life, excessive eating with a large amount of fats and lipoids, smoking. In most cases myocardial infarction develops due to calcification and ulceration of the atherosclerotic plaques with the following occlusion of the vessel by thrombus. Occlusion of one of the branches of the coronary artery is not always accompanied by mobilization of the collateral vessels, as other vessels of the heart are affected by atherosclerosis.

Stenosing sclerosis of the vessels creates sharp limitation of nutrients entering the cardiac muscle. Even insignificant increase of the vascular stenosis or the increased requirement of the muscle in oxygen may cause necrosis.

The following pathogenic variants of myocardial infarction development are possible:

a) occlusion of the vessel promoting absolute decrease of the coronary blood flow below the critical level (usually three fourths of initial lumen);

b) stenosis, which is not manifested at rest but on little exertion, physical or mental results in ischemia of the cardiac muscle,

c) considerable physical exertion or emotional stress which may cause discrepancy between the need in oxygen and possibility of the blood inflow with impairment of the cardiac muscle even without atherosclerosis impairments. In this case intensified secretion of catecholamines and hormones of the adrenal cortex plays an important role.

During the first minutes after the disturbance of circulation the 'e are changes on the electrocardiogram such as deviations of the segment S — T, changes of QRS complex and the wave T.

Morphologically, first of all, structural impairment of mitochondria are noted. Then swelling or picnosis of the nuclei occurs. The transverse striation of the muscular fibers disappears. The cardiomyocytes lose

glycogen and potassium and the number of lysosomas is increased in them.

Infarction develops in the area, which is supplied by the blood through the damaged vessel. The main consequence of infarction is local coagulative necrosis, myocyte lysis, the myocardium edema. There are several tones in the focus of infarction. The cells have got irreversible damages in the central area. There are necrotized muscular cells with signs of calcium load in the intermediate area. The accumulation of lipid drops prevails in the muscular cells in the external area of infarction. No necrotic impairments are seen in it. The dead cells are soon surrounded by neutrophylic granulocytes, which are further, substituted for macrophagocytes, lymphocytes and plasmocytes. Later on the resolving cardiomyocytes are substituted for fibroblasts and the connective tissue is formed.

Under the influence of ischemia the cardiomyocytes may have a capability to automatism, i. e. there appears the ectopic focus of excitation, promoting extrasystole.

Disturbance of conduction, numerous ectopic foci create conditions for repeated circulation of excitation and paroxysmal tachycardia development.

Myocardial infarction may be accompanied by acute or chronic cardial insufficiency that leads to hypoxia, acidosis, destruction of the brain and other organs and finally to death.

Myocardial infarction is characterized by pain and resorption of necrotic syndromes.

The pain in infarction is characterized by typical localization in the upper left part of the body and behind the breastbone. However, there are painless infarctions.

Acute myocardial infarction in a human is frequently accompanied by the increased function of the sympathoadrenal system and ejection of large doses of catecholamines into the blood. This causes the increase of the function of the heart, the level of free fatty acids in the blood. It results in reduction of glucose transport into the cardiomyocytes and intensification of glycolysis in them and the increased consumption of oxygen. In these cases the protection of the heart from catecholamines, for example, by using β-adrenoblocker to beneficial (Fig. 37, 38).

Resorption of the content of the damaged cells from the necrotized areas of the myocardium into the blood causes appearance of such intracellular ferments as creatinphosphokinase, aspartataminotransferase, cardiac isoferments lactatedehydrogenase as

well as myoglobin. It may be used for diagnostic purposes. Resorption of the cellular proteins is accompanied by leukocytosis fever, increased erythrocyte sedimentation rate (ESR).

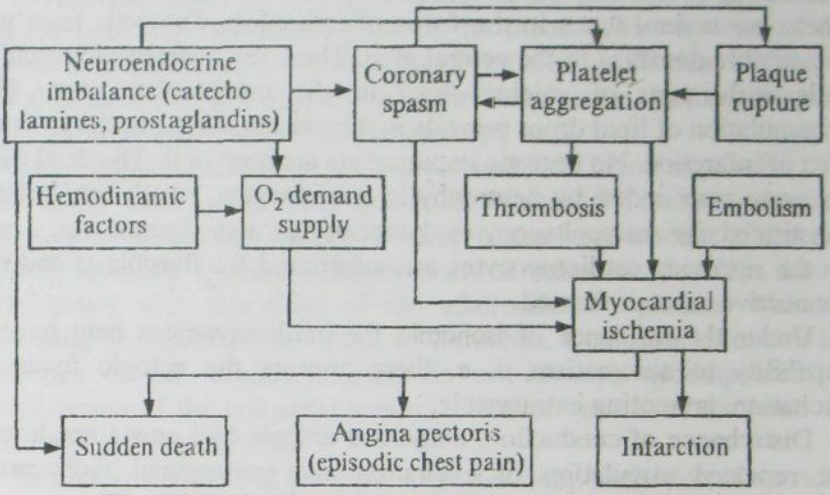

Fig. 37. Pathophysiologic causes and consequences of myocardial ischemia

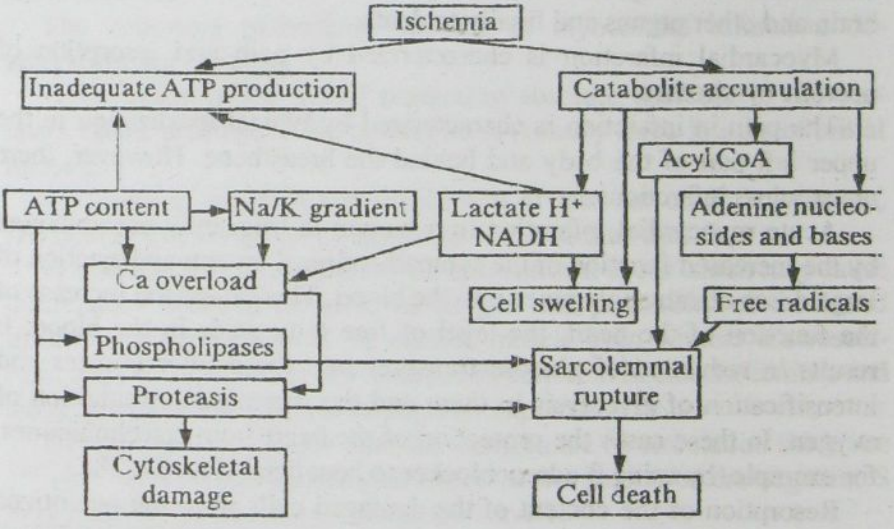

Fig. 38. Sarcolemmal damage is formed basis for irreversible ischemic cell injury

The appearance of the intracellular myocardial proteins in the blood flow may be accompanied by autoimmunization with production of anticardial antibodies and sensitized lymphocytes to the cardiac antigens as well as eosinophilia and hypergammaglobulinemia. Besides, the development of postinfarction syndrome (Dressier's syndrome) is associated with the appearance of autoantibodies. It is characterized by inflammation of the serous membrane of the heart, lungs, joints which does not react to antibiotics treatment but is controlled by cortisonum.

COMPREHENSION CHECK

Try to answer the following questions.

1. What is etiology and risk factors of heart disease?
2. Describe the main mechanisms of cardiac insufficiency compensation.
3. Characterize coronarogenic and non-coronarogenic impairments of the heart.
4. Explain the mechanism of myocardial infarction.

UNIT 22

DISORDERS OF CARDIAC RHYTHM

DISTURBANCE OF AUTOMATISM

It is known that ability to automatic formation of impulses depends on the cells located in the conductive system of the heart (p-cells). A spontaneous slow depolarization of the cellular membrane occurs in them during diastole.

1. Tachycardia is observed under the influence of the increased body temperature, distension of the area of the sinoatrial node, sympathetic mediators.

2. In stimulation of the vagus, the impulse generation is slowed down as well as the heart contractions — bradycardia.

3. Fluctuations of the vagus tension during respiration may cause respiratory arrhythmia (accelerate heartbeat on inspiration and its slowing down — on expiration). Normally respiratory arrhythmia is observed in children, rarely in adults.

DISTURBANCES OF EXCITATION

The other mechanism leading to appearance of ectopic foci of excitation may be difference of potentials between the neighbouring myocytes. All those cases of extraordinary contraction of the heart or only ventricles is called extrasystole.

The *sinus extrasystole* arises due to premature excitation of some part of the cells of the sinoatrial node. On electrocardiogram it doesn't differ from the normal contraction except the shortening of the diastolic interval T-P. Due to the shortening of diastole and reduction of the ventricular filling the pulse wave is decreased in extrasystole.

The *atrial extrasystole* is observed when there is a focus of ectopic excitation in different areas of the atria. It is characterized by distortion of the wave P shape (decreased, two-phased, negative) in preserved complex QRST and some lengthening of the diastolic interval after extrasystole. It is conditioned by the fact that the excitation going by retrograde way discharges a normal sinus impulse prematurely which coincides with the ventricular excitation. The next atrial impulse occurring after a normal interval turns to be somewhat behind the time from the moment of the end of the ventricular excitation. It is incomplete compensatory pause.

The *atrioventricular extrasystole* is observed in the additional impulse in the atrioventricular node. The wave of excitation from the upper and middle parts of the node is spreading in two directions: normal — in the ventricles and retrograde — in the atria. The negative wave P may precede complex QRS or overlap it. The diastolic interval after extrasystole is a little prolonged. Extrasystole may be accompanied by simultaneous contraction of the atria and ventricles. In atrioventricular systole of the lower part of the node, there is a compensatory pause, which is the same as in the ventricular extrasystole and the negative wave P follows QRS complex.

The *ventricular extrasystole* is characterized by complete compensatory pause after extraordinary contraction. It develops because the excitation of the ventricles is not transmitted through the atrioventricular node to the atrium. And the following normal impulse of excitation from the sinoatrial node is not transmitted to the ventricles, which are in the refractory phase. The next contraction of the ventricles occurs only after the transmission of the next normal impulse. Therefore the duration of the compensatory pause with the previous interval is equal to the duration of two normal diastolic pauses.

When there is a group of quickly repeated extrasystoles inhibiting the physiological rhythm completely, paroxysmal tachycardia develops. The normal rhythm of the heart is suddenly interrupted by an attack of contractions at the rate of 140-250 beats per minute. The duration of the attack may be different — from several seconds to a few minutes. Then it stops suddenly and the normal rhythm is restored.

The atrial form of paroxysmal tachycardia is most frequently observed.

THE DISTURBANCE OF CONDUCTION

The cardiac arrhythmia caused by disturbance of the impulse conduction is called blockade.

The cause of blockade may be impairment of the conductive tracts, which leads to prolongation of the refractory period and is accompanied by slowing down or complete cessation of the impulse conduction. The disturbances of conduction may occur between the sinoatrial node and the atria, inside the atria, between the atria and the ventricles and in one of the pedicle of the atrioventricular bundle. In intraatrial and intraventricular blockade the rate of the heart contractions does not change, and the disturbance is manifested in changes on the

electrocardiogram. The atrioventricular blockade may be accompanied by changes of the rhythm and the rate of the heart contractions.

The atrioventricular or transversal blockade may be complete and incomplete. The complete transversal blockade is also called blockade of the III degree. In the incomplete atrioventricular blockade the I and II degrees are distinguished.

The atrioventricular blockade of the I degree is characterized by prolongation of the impulse conduction from the atria to the ventricles with extension of P-Q interval by more than 0.2 sec. The contraction rate of the atria and ventricles is equal. The blockade of the II degree is accompanied by more marked impairments of the atrioventricular conduction, so that one or several impulses from the sinus node cannot be conducted to the ventricles, as the number of the atrium contractions is greater than that of the ventricles. There are several variants of the incomplete atrioventricular blockade of the III degree depending on the degree of the conduction impairment. They are: the atrioventricular blockade with the worsening conduction until one of the contractions is missed (periods of Wenkenbach — Samoilov) the blockade with every 3rd-5th ventricular contraction missing (Mobits' type blockade); every 2nd or one of 3-6 contractions is transmitted. In complete atrioventricular blockade the atria and ventricles are contracted each in their rhythm, independent of each other. The atria are contracted at the rate 70 per 1 min, the ventricles, depending on the location of the new rhythm driver contract 20- 40 times per min with the rhythm driver in atrioventricular node and 15-30 times per min with the driver in the ventricle (idioventricular rhythm).

The moment of transition of the incomplete blockade into complete one, when the atria do not transmit impulses to the ventricles is of special importance. A slow diastolic depolarization in the potential rhythm drivers occurs only some time after cessation of impulse transmission from the sinoatrial node. This period is called preautomatic pause, the ventricular asystolia is observed during this pause. As the blood doesn't come to the brain, there are loss of consciousness and convulsions (Morgagni — Adams — Stokes syndrome). Death is possible but usually when the ventricular contraction is resumed, these symptoms disappear. The syndrome may be repeated many times.

ARRHYTHMIA DUE TO SIMULTANEOUS DISTURBANCE OF AUTOMATISM AND CONDUCTION

In numerous ectopic foci of excitation flutter and fibrillation may occur.

In some cases the rate of the atrium contractions reaches 250-400 per minute. This condition is called flutter of the atria and may continue for several months and years, as the ventricles are not able to produce a high rhythm of the atria, a relative cardiac blockade may develop. The ventricles contract on every 2nd, 3rd or 4th contraction of the atria, as other waves of excitation get into refractory phase. The ventricle contraction may occur before their sufficient filling up with the blood, it results in severe disturbances of circulation.

When the number of the atrial contractions is 400-600 per a minute, we speak about fibrillation of the atria. Only some separate muscular fibers contract, and the whole atrium is under the condition of incomplete contraction. Its participation in pumping of the blood stops.

Not infrequently the ventricles contract before their filling up with the blood and contraction are not accompanied by pulse wave. Therefore, the pulse rate is less than the rate of the heart contractions. It is called pulse deficiency. This pathologic condition of the heart is called fibrillary arrhythmia. It occurs mostly in stenosis of the left atrioventricular foramen, thyrotoxicosis and obvious cardiosclerosis.

The ventricular fibrillation develops in some pathogenetic effects, for example, passing of the electric current through the heart, anesthesia with chloroform or cyclopropane, occlusion of the coronary artery or other cases of sharp hypoxia, the heart trauma, toxic doses of digitalis and calcium. Because of chaotic contraction of separate muscular fibers, the propulsive force of the contraction is practically absent, the patient loses his consciousness and die.

The ventricular fibrillation is effectively treated by passing a short powerful single electric discharge through the heart. It produces simultaneous depolarization of all myocardial fibers and asynchronic excitations of the muscular fibers cease. To prevent development of fibrillation, physicians use correction of the salt contents of the blood.

CIRCULATORY INSUFFICIENCY IN DISTURBANCE OF THE BLOOD INFLOW TO THE HEART

This kind of insufficiency develops in cases when the blood inflow to the heart by veins is little or the heart is not able to take all the

inflowing blood. The former is observed in hypovolemia (bloodless) or sharp accumulation of the fluid in the pericardium cavity that leads to difficulty in dilatation of the cavities during diastole.

The fluid accumulation in the pericardium cavity may be fast and slow. Fast accumulation occurs due to hemorrhage in wound or rupture of the heart or in quickly developing pericarditis. Because of poor stretching of the pericardium the pressure in its cavity increases preventing diastolic dilatation of the heart. It causes acute tamponade of the heart.

COMPREHENSION CHECK

Try to answer the following questions.

1. What's arrhythmia due to disturbance of automatism?
2. Explain mechanism of extrasystoles.
3. Characterize the atrioventricular or transversal blockade.
4. What is ventricular fibrillation?

UNIT 23

PATHOPYSIOLOGY OF THE CARDIOVASCULAR SYSTEM. HYPERTENSION. HYPOTENSION

PATHOLOGIC PROCESS IN THE RESISTIVE TYPE OF THE VESSELS

The task of the resistive vessels is maintaining the certain level of the arterial pressure. It means, that the first manifestation of the resistive vessel pathology is the significant deviation of the arterial pressure level from the normal arterial pressure. The corresponding pathologic states are called hyper- and hypotension. In the first case levels of the systolic and diastolic pressure are, accordingly, higher than 160 and 95 mm Hg. In the second case level of the arterial pressure is lower than 100/60 mm Hg. Level of pressure from 140/90 mm Hg is called "dangerous zone" (border hypertension).

Arterial hypertension is a persistent increase of the arterial pressure. There are primary and secondary arterial hypertension depending on its origin. Secondary increase of the arterial pressure is only a sign (symptomatic hypertension), consequence of some other disease (glomerulonephritis, stenosis of the aortic arch, adenoma of the hypophysis or of the cortical substance of the adrenal glands, others).

Primary hypertension is also called essential hypertension. It indicates, that its origin is unknown. Hypertensive disease is one of the variants of primary arterial hypertension. The main manifestation of the primary arterial hypertension is increase of the arterial pressure.

80% of all cases of arterial hypertension are primary hypertension. The remaining 20% are secondary arterial hypertension, 14% of them are connected with diseases of the renal parenchyma or renal vessels.

Etiology

There are many causes of primary hypertension, and some of them are still unknown. But it is indisputable, that overtension of the higher nervous activity under the influence of emotional effects has definite meaning. It's confirmed by frequent

Table 13. Salt-sensitivity in humans

White	Normal	Hyper-tensive
Salt sensitivity Salt resistant	30% 70%	55% 45%
Black Salt sensitivity Salt resistant	32% 68%	73% 27%

development of primary hypertension in people with "stress" professions. Negative emotions have special meaning, in particular emotions, which were not reacted by motion. Power of pathogenic effect of these emotions falls upon blood circulatory system. E. F. Lang called this hypertension "a disease of nonreacted emotions."

Hypertension disease — is "the disease of autumn of a man's life, it doesn't give him an opportunity to live till winter." (A. A. Bogomolets). So, age has a great importance in origin of the hypertensive disease. But primary hypertension is frequent even at young age. It is important, that men up to 40 have this disease more often, than women, but over 40 years it is on the contrary.

The *hereditary factor* has a definite role in development of primary hypertension. In some families this disease develops several times more often, than in remaining population. High concordance in hypertensive disease in monovular twins is also evidence of influence of genetic factors.

Lately epidemiological observations, made in some countries (Japan, China, some regions of Transcarpathians), had established close connection between the level of the arterial pressure and quantity of consumed table-salt. They suppose, that long consumption more than 5 g of table-salt a day causes development of primary hypertension in people, having hereditary predisposition to it (Table 13). Successful experimental simulation of "salt hypertension" confirms importance of excess consumption of table salt. There are clinical data about favorable therapeutic effect of low-salt diet in some forms of primary hypertension, which also confirm importance of quantity of consumed table salt.

The Nerve Factor

The role of the neurogenic factor in pathogenesis of hypertensive disease is presented in conception of Lang and Myasnikov. They thought, that "nerve overstrain", an etiological essence of hypertensive disease, is realized in disorder or trophicity of the cerebral centers of control of the arterial pressure. Experiments with animals confirmed that stimulation of structural formations of the cortex of the brain (the frontal pole, orbital gyri, motor zone of the cortex, temporal pole, gyrus of hippocampus, amygdaloidal nucleus) caused increase of the arterial pressure.

Change of the correlation between processes of stimulation and inhibition of structures of the cerebral cortex causes breakdown of their functions, development of neurotic disorders and disorders of the higher

nervous activity, development of lengthy pathologic increase of the arterial pressure. Increase of the arterial pressure is connected with stable excitement of the vegetative centers of the hypothalamus (vasomotoric center). Different additional influences intensify a focus of pathologic dominant in the vasomotoric center, inhibiting functions of other centers according to principle of negative induction.

Vasomotor impulses, arising in the hypothalamus (the highest integrator of the vegetative functions), reach nuclei of the medulla oblongata, then reach vessels by sympathetic nerves, causing increase of vasomotor component of the vascular tonus. It is accomplished with noradrenalin, a nervous mediator, that, activating o- adrenergic receptors of the arterioles, increases their resistance to blood flow, but doesn't influence on the myocardium.

Hypertensive effect is partly caused by excitement of the cortical substance of the adrenal glands under the pressure of sympathetic part of the vegetative nervous system. It causes coming of excess adrenaline and norepinephrine into blood. It is necessary for development of hypertension in such case, that a-adrenergic effect of adrenaline and norepinephrine in summary exceeds p-adrenergic effect of adrenaline, directed at decrease of the muscular tonus of the arterioles.

Function of the peripheral baroreceptors of the carotid sinus and aortic arch is closely connected with the action of the central mechanisms of the vascular tonus regulation. Their dysfunction is accompanied by marked and lengthy pressor reaction (Heimans' experiments). It is confirmed by Anochin's observation that sensivity of the carotid sinus baroreceptors is decreased in hypertension in the course of time.

Besides, it was established, that elimination of inhibiting influence of the baroreceptors on the vasomotor center and on the reticular formation of the truncus cerebri and hypothalamus causes fourfold increase of catecholamine secretion (medullar substances of the adrenal glands) and aldosterone secretion (the cortical substance).

The Renal Factor

The above-mentioned experiments of Holdblatt confirmed, that disorder of the renal blood circulation is accompanied by arterial hypertension. It was also proved, that progression of hypertension can be partly caused by changes in kidneys.

It is known now, that the kidneys can promote both increase and decrease of the arterial pressure.

Increase of the arterial pressure develops in stimulation of juxtaglomerular apparatus of the kidneys. Renin-proteolytic enzyme is formed in its cells. Substances for this enzyme is a-globulin of blood plasm — angiotensinogen. Secretion of renin depends on the degree of strain of the afferent vessels of the renal glomeruli.

So, disorder of the renal blood circulation (ischemia, decrease of the pulse and arterial pressure) stimulates this process. Increase of renin production is accompanied by increase of angiotensin-I concentration in blood (angiotensin-I is product of enzymatic reaction angiotensinogen → renin). This polypeptide (decapeptide) is transformed into angiotensin-II (octapeptide) under the action of converting enzyme of blood. Angiotensin II, unlike angiotensin I, has a direct influence on the wall of the precapillary vessels. Vasoconstrictive effect of angiotensin partly occurs by means of the sympathetic part of the vegetative nervous system (intensification of the function), the cortical substance of the adrenal glands (increase of aldosterone secretion) and kidneys (increase of sodium ions reabsorption).

This substance is the most effective of all known pressor agents.

Angiotensin II is quickly destroyed by enzyme angiotensinase in blood and tissues (mostly in the kidneys).

The healthy kidney (in disorder of blood circulation in the other kidney) produces increased quantity of angiotensinase, preventing development of stable hypertension.

Angiotensinase activity of the kidneys is sharply decreased in disorder of hemodynamic in both kidneys that causes stable increase of the arterial pressure. So, arterial hypertension (in disorder of blood circulation in the kidneys) is partly conditional by renin-angiotensin system and partly by decrease of production of specific and nonspecific angiotensinases.

But increased secretion of renin by the "ischemic" kidneys and increased quantity of angiotensin in blood are observed only within first days after narrowing of the renal arteries, and at the same time hypertension persists during a long time. This fact, and also development of stable hypertension after removal of both kidneys, caused appearance of supposition (Grollman), that chronic hypertension can be conditioned by absence (disorder) of some depressor function of the kidney (renoprival hypertension) or (and) by action of some extrarenal substances. That supposition was completely confirmed. Now it is known, that normal kidneys have ability to control action of renal and

extrarenal pressor substances (vasopressin, catech olamines, aldosterone), so they have antipressor (antihypertensive) function. It is considered, that this function is realized by substances of lipid origin: phospholipid inhibitor of renin, neutral lipids of the medullar substance of the kidneys, prostaglandins A and E. So, absence of this function of the kidneys also causes predomination of vasopressor mechanisms and, in this way, hypertension.

Prostaglandins — products of polyunsaturated fatty acids are of special interest. Probably, interstitial stellate cells of the medullar substance are the place of prostaglandin formation. Secretion of prostaglandins is controlled with the help of angiotensin II. Increased quantity of angiotensin II in blood stimulates prostaglandin formation.

The E-type prostaglandins cause hypotensive effect in the normal arterial pressure level. The A type prostaglandins don't cause decrease of pressure in healthy animals and people, but prevent development of Goldblatt's renal hypertension and renoprival hypertension in animals or decrease the increased arterial pressure in men. Besides dilating action on the arterioles, prostaglandins cause increased excretion of sodium with urine that also prevents development of hypertension. Renal kallikrein-kinin has the same action.

The Hormonal Factor

The endocrine glands take part in regulation of the arterial presure, so disorder of their function is an important link of hypertension pathogenesis. The adrenal glands are the *most* important. Ascit was said, experimental hypertension can he achieved by injection of aldosterone and desoxycorticosterone, especially with load of sodium chloride. Aldosterone mechanism takes part in maintaining the increased arterial pressure in human. It is considered that the main changes in the organism, caused by desoxycorticosterone and aldosterone, are connected with their influence on sodium metabolism. Action of their hormones causes retention of sodium ions in the organism as a result of its increased reabsorption from primary urine in the canals, especially in their distal part. Consequence of retention of sodium salts in the organism is their accumulation in the muscular elements of the arteries. Hypervolemia, endothelial edema and partial narrowing of the vessels develop because of accompanying retention of water. Besides, sensitivity of the vascular wall is increased to different pressor action — nervous and humoral (catecholamines, vasopressin, angiotensin II) as a result of increased concentration of sodium and

calcium ions in the vascular wall. Natriuretic atrial hormone is the antagonist of aldosterone and angiotensine in physiological conditions. This hormone is polypeptide (28 amino acids), synthesized mostly in the atria, and also in the ventricles of the heart. Its antihypertensive action is conditioned by the ability to intensify natriuresis and diuresis (suppression of reabsorption of sodium and water in the renal tubules, increase of glomerular filtration). Besides, this hormone suppresses production of aldosterone and encourages marked vasodilative effect due to inhibition of coming of calcium into the smooth muscular cells and emission of Ca^{2+} out of the intracellular depot. So, high level of myogenic and vasomotor component of the vascular tonus is achieved in conditions, when balance of the aldosterone and angiotensin II on the one hand, and natriuretic atrial hormone on the other hand, is shifted in favour of the former. Such disbalance arises in the early stages of arterial hypertension.

Stable hypertension cannot be accompanied by marked clinical picture during some time. But clinical experience shows, that the first complication of lengthy course of hypertension is local circulatory insufficiency, and then insufficiency of the corresponding organs and even systems. The most often clinical forms of complicated primary hypertension are cerebral circulatory insufficiency (including insult), hypertrophy of the myocardium with the following circulatory insufficiency, renal circulatory insufficiency and renal insufficiency (syndrome of the contracted kidney).

PULMONARY HYPERTENSION

Pulmonary hypertension is characterized by increase of pulmonary arterial pressure more than 26 mm of Hg, and is the cause of development of the so-called pulmonary heart (cor pulmonale) and right ventricular type of circulatory insufficiency.

By its origin pulmonary hypertension can he primary and secondary.

Development of secondary pulmonary hypertension is caused by diseases, primary affecting the pneumatic ways and alveoli (chronic bronchitis, bronchial asthma, chronic pneumonia, pulmonary emphysema, and pneumosclerosis), primary disorder of mobility of the chest (kyphoscoliosis, pleura fibrosis, chronic neuromyasthenia or polymyelitis) and also by diseases, that primary affect the pulmonary vessels (nodular periarteritis, thrombosis of the small blood vessels, embolism of the pulmonary artery and others) and the heart (mitral

stenosis, ventricular septal defect).

Primary pulmonary hypertension is rare, develops without diseases of the lungs and heart (pulmonary hypertension of the unknown etiology). Sometimes primary pulmonary hypertension is congenital.

The main mechanism of development of primary pulmonary hypertension is decrease of pO_2 in the alveolar air. In alpine conditions influence of this factor is more marked.

Low partial pressure of oxygen in the alveolar air has a direct influence on the smooth muscular elements of the lung vessels, causing stable increase of their tonus. One of the possible mechanisms of such direct influence is loss of calcium and absorption of sodium by the vascular wall, depolarization of the membranes and decrease of excitation, threshold.

Vasopressor effect of hypoxia is increased in development of acidosis and on physical exertion. On the other hand, hydrogen ions, vasoactive amines (histamine, serotonin), metabolic desorders has a role of the mediator of pressor effect of hypoxia on the lung vessels (A. I. Chomazuk, 1978).

Alkalosis decreases vasopressor effect of hypoxia. Adenosine, AMP, acetylcholine have vasodilatative action on the lung arteries. Action of bradykinin is variable.

ARTERIAL HYPOTENSION

Arterial hypotension is stable decrease of the arterial pressure, caused by decrease of tonus of the resistive vessels.

It is more often in people with asthenia constitution. It is characterized by decrease of physical development and feeding, general adynamia, undue fatigability, tachycardia, dyspnoea, vertigo, headache, syncopes.

There are physiologic arterial hypotonia (it isn't accompanied by painful symptoms) and pathologic (with typical symptom-complex). The latter can be acute and chronic.

Chronic arterial hypotension is divided into symptomatic (secondary) and hypotensive type of neurocirculatory dystonia (primary hypotension).

Level of the arterial pressure is determined by quantity of the heart emission, quantity of the circulatory blood and tonus of the resistive vessels. So, there are three hemodynamic forms of arterial hypotension: connected with insufficiency of contractile function of the heart caused

by decrease of circulating blood volume and caused by decrease of tonus of the resistive vessels.

Symptomatic chronic arterial hypotension (secondary) is the consequence of some general somatic acute and chronic diseases: of the heart (defects, myocarditis, myocardial infarction); of the brain (concussion); of the lungs (croupous pneumonia); of the liver (hepatitis, mechanical jaundice); of blood (anemia); of the endocrine glands; and also of exogenic and endogenic intoxications.

It is believed that the main etiologic and pathogenic factor of primary arterial hypotension is overtension of the main process of the cerebral cortex (stimulation and inhibition) — as in hypertensive disease. But unlike primary hypotension, this is predomination of inhibition and it's spreading on the subcortical vegetative formations (vasomotor center). Relaxation of effective vasoconstrictive influences, and at the same time predomination of cholinergic influences over adrenergic (typical for asthenic type of constitution) are the direct cause of decrease of resistive vessel tonus decrease of the peripheral resistance and arterial pressure.

COMPREHENSION CHECK

Try to answer the following questions.

1. What does primary and secondary arterial hypertension mean?
2. Characterize the role of the nerve, renal, hormonal and other factors in pathogenesis of hypertensive disease.
3. What factor does arterial hypertension depend on?

UNIT 24

PATHOPHYSIOLOGY OF DIGESTION IN THE ORAL CAVITY AND STOMACH

The function of the digestive system provides the intake of food and water which are transformed into simple chemical compounds to be absorbed and necessary for life maintenance and supply of energy and plastic material.

Different sections of the digestive system are interconnected due to continuity of the alimentary canal, common nervous and humoral mechanisms of regulation. This interconnection is especially evident in pathology as the dysfunction of the section of the digestive system brings about the impairment of others. The union of different organs of the digestive system is manifested in substitutional (compensatory) possibilities of this system.

DIGESTION IMPAIRMENT IN THE ORAL CAVITY AND STOMACH

Digestion impairment in the oral cavity may be connected with (1) impairment of mastication, which occurs in case of injury on absence of teeth due to dental caries or paradontosis, (2) dysfunction of the masticatory muscles due to paralysis (disease of the nervous system), (3) impairment of the tempora-mandibularis joints, (4) dysfunction of the salivary glands — besides alimentary function, the saliva plays a significant role of the media wetting the teeth and the mucous membrane of the oral cavity and giving pro tective and trophic effect.

In the normal conditions 0.5-2 1 of the saliva is excreted per day In pathology its amount arise up to 6-7 1. *Increased (hyper) salivation* is observed in stomatitis, gingivitis, pregnancy, pulpitis, parodontitis as well as preparation of the teeth with a drilling machine

As a result of hypersecretion the following processes occur:

1) reduction of K^+ concentration in the saliva and total molar concentration of nonorganic components of the saliva increases (Heidenhein);

2) neutralization of the gastric juice and impairment digestion in the stomach;

3) the loss of a large amount of the saliva leads to cachexia, dehydration.

The reduction of the saliva secretion (hyposalivation) is connected with

infections and feverish processes (calculus sialadenitis). The disturbances of salivation and microflora promote dental calculus formation. There is severe systemic lesion of the salivary and lacrimal glands (Shegren's syndrome), which is characterised by dryness of the mucous membrane of the oral cavity (xerostomia), eyes and upper respiratory tracts. Severe disorders carbohydrate metabolism may appear due to hyposalivation, because glucose and fat don't stimulate gastric acid secretion glands of the stomach and as consequences of this disorders the dysfuncion occurs.

The disturbances of the stomach may be caused by following factors:

1. Nervous-emotional stress.
2. Infectious factor.
3. Such toxic agents as alcohol, cigarettes, bile acid, corticosteroids and particularly aspirin.
4. The character of nutrition (regimen, rhythm, quality).

Depending on the extend of distruction, acute inflammation is divided into several types:

— acute gastritis;
— acute hemorrhagic gastritis;
— acute erosive or ulcer disease.

All these inflammatory processes in the stomach may be hyper-, hypo- and anacidity types. How does it influence on motility and digestive function of the stomach?

It is necessary to remember the main secretory processes in the stomach. There are four types of pathological gastric secretion (Fig. 39).

1. The excitable type is characterized by gastric juice secretion increasing in the mechanical and chemical stimuli.
2. The astenic type is characterized by increasing gastric secretion in the mechanical stimuli and reducing in the chemical one.

The inertion type is characterized by reducing in the mechanical stimuli and elevation under the chemical ones.

4. The inhibition type is characterized by depression of both mechanical and chemical stimuli.

The secretory process is best considered by dividing it into its three traditional phases — cephalic, gastric and intestinal. The cephalic phase is initiated by taste, smell, chewing and swallowing of palatable food. This phase is largerly mediated by direct vagal stimulation of parietal cells but may also involve vagal stimulation of gastrin release.

The gastric phase involves stimulation of mechanical and chemical receptors in the gastric wall. The chemical stimuli, the most important

of which are digested proteins and aminoacids, induce the release of gastrin, the most potent mediator of acid secretion. Fat and glucose in the stomach do not stimulate gastric acid secretion.

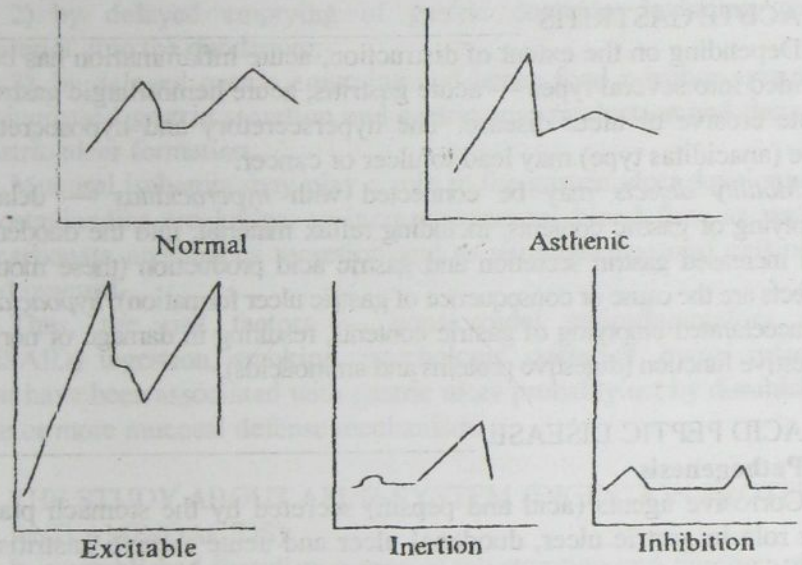

Fig. 39. Types of gastric secretion

The intestinal phase is initiated when food containing digested proteins enter the proximal small intestine.

Thus acetylcholine, gastrin and histamine stimulate the K^+, H^+, ATPase located on the luminal surface of the parietal cell and evoke secretion.

How does the normal stomach resist the corrosive affects of acid-peptic-gastric secretion? At maximal secretory rates the intraluminal concentration of hydrogen ion in the stomach is 3 million times (!) greater than that of the blood and tissues. Most important is so-called gastric mucosal barrier. A number of agents have been shown to damage the mucosal barrier, including alcohol, sigarettes, bile acids, corticosteroids and particularly aspirin, so to contribute possibly to the development of gastric mucosal erosions or ulcers.

The various secretory products, some of which are also present in the intramural autonomic nerve terminals, act as chemical messengers and modulate normal digestive functions by a combination of endocrine, paracrine and neurocrine mechanisms. Some of them act as the C cells of

the thyroid, the chromaffin cells of the adrenal medulla, the corticotrophs and melanotrophs of the pituitary and certain cells in the carotid body, the bronchi, the hypothalamus, and the sympathetic ganglia.

ACUTE GASTRITIS

Depending on the extent of distruction, acute inflammation has been divided into several types — acute gastritis, acute hemorrhagic gastritis, acute erosive or ulcer disease. The hypersecretory and hyposecretory type (anaciditas type) may lead to ulcer or cancer.

Motility defects may be connected with *hyperaciditas* — delayed emptying of gastric contents, including reflux material, into the duodenum and increased gastrin secretion and gastric acid production (these motility defects are the cause or consequence of gastric ulcer formation); *hypoaciditas* — accelarated emptying of gastric contents, resulting in damage of normal digestive function (digestive proteins and aminoacids).

ACID PEPTIC DISEASE

Pathogenesis

Corrosive agents (acid and pepsin) secreted by the stomach play a key role in gastric ulcer, duodenal ulcer and acute erosive gastritis. A specific infectious agent — the *Helicobacteria pylori*, has been implicated in predisposition to a number of forms of acid-peptic disease. The most likely mechanism is diminished mucosal defences through inflammation.

The *Helicobacteria pylori* is an extremely common pathogen, found in 50% of the world's population, expecially in the poorest countries, where sanitation facilities and standards of personal hygiene are unadequate. The most likely route of spread from person to person is fecal-oral.

As many as 90% of infected individuals show signs of inflammation (gastritis or duodenitis) on endoscopy, though typically many of these individuals are clinically asymptomatic. Despite this high rate of association of inflammation with *H. pylory* infection, the important role of other factors is indicated by the fact that only about 15% of infected persons have ever develop a clinically significant ulcer. These other factors (both genetic and environmental) must account for the individual variations and are pathophysiologically important.

Motility defects have been proposed to contribute to development of gastric ulcer in at least three ways:

1) by a tendency of duodenal contents to reflux backthrough an incompetent pyloric sphincter. Bile acids in the duodenal reflux material act as an irritant and may be an important contributor to a diminished mucosal barrier against acid and pepsin;

2) by delayed emptying of gastric contents, including reflux material, into the duodenum;

3) by delayed gastric emptying and hence food retention, resulting in increased gastrin secretion and gastric acid production and therefore gastric ulcer formation.

Mucosal ischemia may play a role in the gastric ulcer development. Prostaglandins are known to increase mucosal blood flow as well as bicarbonate and mucus secretion and to stimulate mucosal cell repair and renewal.

Thus, the risk factors — nonsteroidal antiinflammatory drug (NSAID) ingestion, smoking, psychologic stress, *H. pylori* infection that have been associated with gastric ulcer probably act by diminishing one or more mucosal defense mechanism.

THE STUDY ABOUT APUD-SYSTEM (DIGESTION PROTEINS AND AMINOACIDS)

It is established that disturbance of the structure and function of the stomach leads to disturbance of hormone production of the alimentary tract by Culchitsky's cells.

At present over 20 substances are known that are produced by neuroendocrine cells of APUD system (amine precursor uptake and decarboxilation). These hormones influence not only on digestion and absorption but also on circulation, metabolism, the nervous and endocrine systems. The hormones of the alimentary system are connected with hypothalamic pituitary system and other glands. For example, gastrin, cholecystokinine and glucogon stimulate the production of calcitonin and, therefore, play a definite role in disturbance of calcium exchange. Gastroinhibiting peptide (GIP) and secretin stimulate the production of insulin and glucogon that stimulate their role in pathogenesis of obesity and cachexia.

It is established that disturbance of hormone production of the alimentary tract results in deep disturbances of digestion, metabolism and activity of organs and systems. Hormone-producing cells of the alimentary organs may be liable to malignization and lead to development of cancerous tumours.

Pathophysiologic Groundation of Therapy and Search for New Preparations

The ratio of factors of agression and protection plays a significant role in pathology of digestion. Histamin, acetylcholin and gastrin are messengers of the I type. Via the central nervous system they transmit the stimulating impulse to the nuclei of the vagus. Then, the receptors of the cells, having received mechanical and chemical stimuli, eject the messengers of the II type — cyclic nucleotides stimulating parietal cells (HC1) and main cells (pepsin) of the stomach. There are the main agressive factors of the stomach. The process of protein digestion continues in the duodenum. The outlet of the acidic mass in the duodenum stimulates the production of secretin that stimulates the pancreas and production of bicarbonates.

Bicarbonates neutralize the acidic mass and as a result PH increases from 1.5-2.5 to 7.0 that activates proteolytic ferments (trypsin, chymotripsin, carboxypeptidases). Under their influence protein transforms into a mixture of free aminoacids and oligopeptides, which are observed through the epithelial cells of the small intestine. The protective factors of the stomach are as follows:

1. Mucus.
2. Bicarbonates of the pancreas, stomach and duodenum.
3. Regeneration of the epithelial cells.
4. Blood supply of the mucosa.

Therapy should be directed at:

a) intensification of the protective factors — film-forming preparation, cytoprotectors;

b) weakening of the agressive factors — prostaglandins;

c) antiacid preparations inhibiting acidopepsine secretion, Al, Mg (almagel);

d) cholinoblockades (atropin, gastrocelin, chlorosil) and histamine blockades (somatostatin, gapalgin (analogue of liencephaline) are effective because of a psychotropic effect.

COMPREHENSION CHECK

Try to answer the following questions.

1. Characterize digestion impairment in the oral cavity.
2. What is secretory and motility defects under acute and chronic gastritis?
3. What is the role of APUD-system of stomach on digestion, absorption and metabolism?

UNIT 25

PATHOPHYSIOLOGY OF DIGESTION IN THE INTESTINE

PEPTIC ULCER

Peptic ulcer is a recurrent disease characterized by areas of destruction of the mucous membrane under the influence of hydrochloric acid and pepsin. Peptic ulcers are most common in the antral section of the stomach and proximal section of the duodenum, sometimes in the distal part of the esophagus.

Etiology

The causes are factors of lesser intensity: external and internal.

External:

1. The character of nutrition (i. e. regimen, rhythm, quality).
2. Intake of flavouring substances (i. e. strong seasonings).
3. Alcohol and smoking.
4. Vitamin and microelement deficiency.
5. Change of place of residence.

Internal:

1. Genetic predisposition (8-10% of people are ill in the human population). Correlation between pepsinogens is genetically dominated. There are 2 types of pepsinogens: the 1st type includes five fractions of pepsinogens, the 2nd type — two fractions. There was established a correlation between the 1st type and ulcer. This factor is determined as "non-secreted". There are antigens A and B in the erythrocytes. Their content resembles the gastric mucosa, which plays the role of the protective mechanism.

The human organism has gens, which contribute to entrance of antigens A and B of the erythrocytes into the saliva. This phenomenon is called secretion production. The saliva is swallowed and these antigens enter the stomach interacting with the gastric mucosa.

Hence, if there are disturbances in coordination of this process, there are conditions for ulcer development.

Antigens A and B are absent in people having blood group I that is why they are predisposed to ulcer development.

2. Development of ulcer is observed in balance disturbance between *factors of aggression:* (1) hydrochloric acid and pepsin; (2) bile (as aggression factor can be brought into the stomach). It is called reflux. It

causes chronic gastritis, which also plays a factor role in ulcer and *factors of protection:*

— gastric mucosa;

— intestinal hormones (enterogastrin secretin);

— hormones of the mucosa of the stomach, intestines and pancreas (glucagon, somatostatin).

The leading factors of ulcer development are bacterial and neurogenic.

There was discovered an etiological role of *Helicobacteria pylori* in the development of recurrent ulcers of the stomach and duodenum. It is a gram-negative microorganism, which is isolated in 90% of patients with duodenal ulcer and in 60-70% with gastric ulcer. *Helicobacteria pylori* affects the gastric epithelium. The causative agent opsonized secretory IgA and serum immunoglobulin's, acts as "barrier destroyer" and thus promotes reverse diffusion of the acid and development of ulcerative defect of the gastric wall.

The neurogenic factor is connected with trophicity disturbance of the gastroduodenal area. Dystrophic process arises which is joined by peptic factor (pepsin + hydrochloric acid).

Dystrophy results from neuro-psychological overloading, accompanied by severe emotional stress.

Stress influence is spread to the sympathetic, the parasympathetic nervous system and the system of hypothalamus-pituitary- adrenal glands (the system of Hans Seleaux).

In the anterior portion of the hypothalamus there are trophotropic centres which influence metabolism. The main nerve of this system is the vagus whose branches go to the stomach. In the vagus excitation neurotransmitter of the parasympathetic nervous system — acetylcholine — is discharged. It influences the stomach as follows:

1. The vagus is the main secretory nerve of the stomach. It stimulates the production of hydrochloric acid and pepsin (this is peptically aggressive digestive factor).

2. The vagus effects on the circulation in the submucous layer of the stomach, i. e. acetylcholine dilates the vessels of the submucous layer. The arterial blood, without exchange in the submucous layer, flows into the veins. It results in development of hypoxia.

Regenerative abilities of the gastric mucosa are decreased. Healing of the mucosa is diminished and injurious effect of the peptic factor (HC1 + pepsin) is intensified.

In a healthy person the mucosa of the gastrointestinal tract is renamed every 1-5 days. At that moment the cells giving frequent mitoses are exposed to different negative effects.

In the posterior portion of the hyphothalamus there are centres of the symphathetic nervous system (it is ergotropic zone, i. e. a working one). It arranges its influence on the stomach through the sympathetic nervous system. Excitation of this system leads to ejection of noradrenalin, which influences all cells of the organism, the stomach in particular.

1. Noradrenalin constricts the vessels of the microcirculatory flow. It results in spasm and then hypoxia.

2. It promotes contraction of the smooth muscles of the submucosa of the stomach. Hypoxia increases, spasm may be very severe and long so that stasis (circulation arrest) occurs. It leads to haemorrhage in the gastric mucosa and erosion.

3. It exerts injurious influence on the cell membranes of the gastric mucosa, avoiding blood vessels.

Noradrenalin effects the cell through the membrane adrenoreceptor.

During stress the amount of noradrenalin in the blood and stomach is at its maximum. It activates the Haghemann's factor (XII factor of blood coagulation), which is the activator of the *callicrein-kinin* system.

The humoral agent of inflammation — bradykinin is formed. It effects the cell membrane where it activates the enzyme phospholipase A. This enzyme destroys the phospholipid layer of the membranes. The neurodystrophic process develops.

The intermediate portion of the hypothalamus realises the stress system of Hans Selye. Its main parts are the hypothalamus-pituitary-adrenal glands. The hormones of the adrenal glands — glucocorticoids (GC) are distinguished in this system. They are:

a) hydrocortisone;
b) cortizol;
c) corticosteron.

They influence the gastric mucosa and cause inhibition of the discharge of the gastric mucous by mucocytes (additional cells), intensify production of hydrochloric acid and pepsin.

Glucocorticoids have a special effect on noradrenalin, the so- called permissible effect.

Thus, in abundance of glucocorticoids, noradrenalin has more powerful injurious effect on the gastric cells.

During ulcer exacerbation there may be noted increased activity of

kallicrein-kinin system, which is 2-10 times increased in comparison with the norm. Bradykinin along with histamine is a humoral agent of pain.

These effects of the three pathogenetic parts are manifested in individuals on the definite target-cells. The aim point of these influences is formed by conditions promoting the development of ulcer.

DISTURBANCE OF INTESTINAL DIGESTION

The intestines fulfil secretory, motor, absorptive incretory and excretory function.

The intestines accomplish distant (cavitary) and membranous (parietal) digestion. Lately there has been distinguished an intermediate stage between cavitary and membranous digestion: hydrolysis of the nutrients in the mucous layers. Cavitary digestion takes place in the lumen of the intestines and consists in destruction of the overmolecular systems and large molecules. Membranous digestion takes place on the membrane of the columnar cells of the intestinal villi. The final stages of nutrient hydrolysis and trans to absorption occurs here.

Disturbance of distant digestion depends, first of all, on disorder of production of pancreatic juice and bile. Disturbance of enzyme production by the columnar cells plays the main role in pathology of membranous digestion.

Enzymes are produced by the columnar cells of the intestinal villi. Being produced on the cell surface enzymes participate in membranous digestion. The main way of penetration of enzymes into the intestinal juice is rejection and destruction of the columnal cells (under normal conditions the cycle of their renewal is 3 days).

The duodenum is the most important section of the small intestine containing secretion of the duodenal glands, bile and pancreatic juice.

The duodenum produced secretin, cholecysfokinin, and motilin, which regulate the alimentary system functioning as well as arenterin and disenterin effecting appetite, general metabolic processes and possesing neurotropic, in particular, hypothalamotropic effect.

INDIGESTION CONNECTED WITH DISTURBANCE OF BILE AND PANCREATIC JUICE SECRETION

Absence of bile (acholia) or its insufficient coming (hypocholia) into the duodenum arises due to disturbance of cholepoiesis and bile secretion. They are accompanied by indigestion and malabsorption of

fats, decreased peristalsis of the bowels and increased processes of decay and fermentation in them.

Serious indigestions cause changes of the pancreatic secretion, as the pancreas produces the main digestive enzymes. The main mass of proteins of the pancreatic juice (over 70%) is proteolytic ferments: tripsin, chimotripsin, elastase, carboxypeptidase (A and B) and callicrein. All these ferments as well as phospholipase A are produced in inactive condition (as symogens). The other ferments — lipase, a-amylase RNAase and DNAase are secreted in the active form.

Disturbance of secretion of the pancreatic juice is observed in occlusion or compression of the pancreas, cystic fibrosis, acute and chronic pancreatitis or duodenitis, in disturbance of neurohumoral mechanisms of the pancreatic secretion regulation. The secretory nerve of the pancreas is the vagus. Humoral regulation is accomplished by secretin, which activates excretion of water and hydrocarbonates, cholecystokinin (pancreosimin) stimulating enzyme production and pancreatic polypeptide inhibiting it.

In lack of the pancreatic juice, a considerable part of fat is not digested and excreted with feces (steatorrhea). Indigestion of proteins arises in insufficient production of peptidases by the pancreas as well as in their activation disorder. So, tripsinogen is activated by enterokinase of the intestinal juice and autocatalytically, the rest of proteolytic ferments and phospholipase A are activated by tripsin. In decreased pancreatic secretion there are hydrolysis disturbance of the food nucleic acids and to a lesser degree starch splitting.

Pancreatitis

Not infrequently inflammation of the pancreas has an acute course and may be accompanied by development of pancreatic shock dangerous for life.

Alcohol abuse and associated overeating is of great importance in etiology of pancreatitis. It also includes abundant fat food, bile stones and polyps of the pancreatic duct, sphincter of the hepatic- pancreatic ampule in traumas and surgical interventions, infectious factor (viral parotitis and hepatitis, cocci, bacterial infection), intoxication, including the effect of sonic medicines (immunodepressants, thiasides, corticosteroids, etc.).

The following disorders are important in pathogenesis of pancreatitis: increased secretion of the pancreatic juice, disturbance of

secretion discharge, increased pressure in the pancreas duct, bile and duodenal chyme (containing enterokinase) in the duct, microcirculation disorder, disturbance of trophicity and barrier properties of the exogenic pancreocytes. The main point in pancreatitis pathogenesis is premature activation of enzymes (tripsin, callicrein, elastase, phospholipase A directly in ducts and cells of the glands, which occurs under the effect of enterokinase, bile or autocalalytically in damage of pancreocytes (Fig. 40).

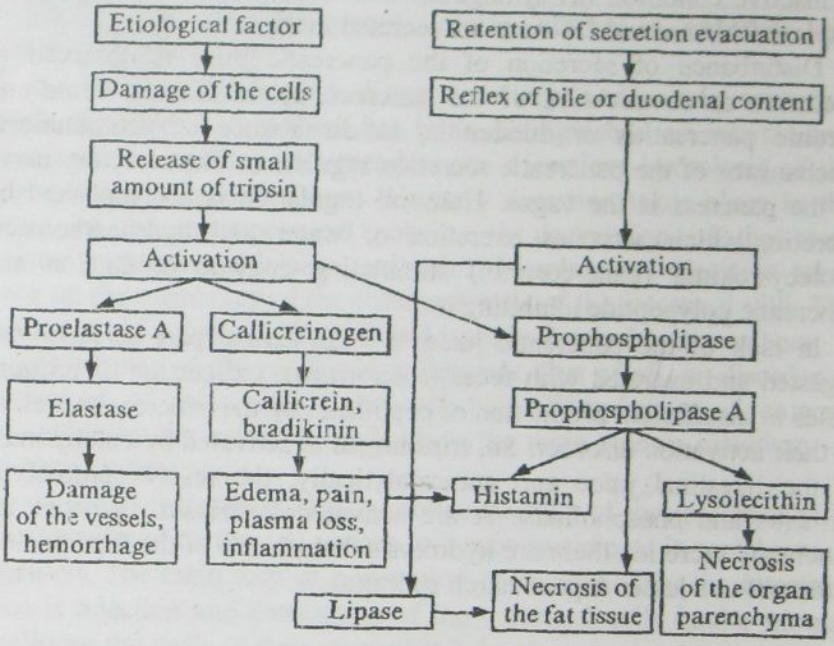

Fig. 40. Mechanisms of pancreatitis development

It results in autolysis of the gland tissue, necrosis of its separate areas and production of toxic (lysolecithin) and biologically active substances including kinins having powerful vascular and hypotensive effect. Coming of peptidases and other pancreatic enzymes into blood results in severe disturbances of hemodynamics, respiration and other vitally important functions (pancreatic shock). An important role is played by disturbance between proteolytic enzymes and their inhibitors. The latter are produced by the pancreas itself and other organs (the salivary glands, lungs) and they are used for treatment of pancreatitis.

A definite significance in pathogenesis of pancreatitis, especially of

a chronic form, belongs to disturbance of circulation in the pancreas (in atherosclerosis, hypertension) as well as immunologic factor (autoallergic). It is proved by detection of antipancreatic antibodies in the blood of some patients with cholecystopancreatitis.

Disturbance of Membranous Digestion, Absorptive and Excretory Functions of the Intestines

Membranous (parietal) digestion is accomplished by enzymes fixed on the surface of the striated edge, which is formed by mi crovilli of the columnar cells of the intestinal villi. It is characterised by conjugation of the processes of fermentation of the nutrients and their absorption, high rate of hydrolysis and sterility conditioned by small size of the pours between the microvilli (10-20 mm) where microorganisms can't penetrate. Enzymes of membranous digestion are synthetized inside the columnar cells and transported to the surface of their cellular membranes (oligosaccharides, oligopeptides, phosphatase, etc.) as well as absorbed partially *from* chyme (pancreatic amylase, lipase, etc.).

Disturbance of Membranous Digestion

It is caused by the following factors: damage of the villi and ultrastructiire of the surface of the columnar cells, change of the fermentative layer of the intestinal surface and absorptive properties of the membranes as well as peristalsis disorder when the transportation of substrate from the intestinal cavity to its surface is impaired. So, reduction of the digestive surface at the expense of atrophy and decrease of the number of the villi or microvilli is found in cholera, ileojejunitis, after intensive usage of some antibiotics (ne- omicin), gastrojejunostomy and stomach resection. The example of impairment of the fermentative layer of the intestinal surface is milk intolerance in lactase deficiency (P-galactosidases) or saccharose intolerance in saccharose deficiency (a-glucosidases).

Disturbance of Absorptive and Excretory Functions of the Intestines

Absorption of the nutrients, hydrolyzed to the stage of monomers is accomplished mainly in the small intestine. During the process of membranous digestion hydrolysis of the nutrients and their transportation through the cell membrane are closely conjugated. Therefore, all factors causing disturbance of membranous digestion lead to malabsorption.

The syndrome of malabsorption may be primary (hereditary) or secondary (acquired). The hereditary syndrome of malabsorplion is more often characterized by selective deficiency of enzymes or transport carriers. As a result absorption of one or several nutrients related by their structure is disturbed. This group of malabsorption includes monosaccharidase intolerance (intolerance of lactose, saccharose, isomaltose): insufficiency of peptidases (celiaca or glutenic disease); malabsorption of aminoacids (cystinuria, triptofanmalabsorption, methyonin malabsorption) and vitamins (cyancobalamin, folic acid). The acquired syndrome of malabsorption is observed after gastrectomy, in intestinal diseases (enterocolitis, Crohn's disease, etc.), diseases of the pancreas (pancreatitis, cystic fibrosis), liver and after long radiation and medicameritous therapy.

Absorption of the nutrients in the small intestine may be disturbed in weakening of the cavitary digestion in the stomach and intestines as well as in disorders of blood and lymph circulation. Disorders of blood circulation disturb release of the absorbing substances, their concentration ingredients and energy supply of the active transport. Weakening of the active transport also arises under the influence of poisons blocking enzyme activity and in water — electrolyte disbalance. Ions of sodium and ATP-energy are of special importance in the active transport of glucose, aminoacids and other compounds.

Increased permeability of the intestinal wall vessels in inflammation and hyperemia may be accompanied by absorption of sub stances of antigenic nature and the organism sensitization.

Excretory function of the intestines is closely connected with the absorptive one. The intestines excrete the terminal products of hemoglobin and cholesterol metabolism, metal salts, lactic acid, purins, some hormones, phenols, salicylates, sulfanilamides, dye- stuff, etc. In renal insufficiency there is compensatory increased excretion of nitrous "wastes" (urea, uric acid, etc.).

Disturbance of the Motor Function of the Intestines

Disturbance of the motor function of the intestines may be manifested by increase or decrease of peristalsis and local (segment forming and pendulum-like) movements.

Increased motor functions of the intestines arise in inflammatory processes (enteritis, colitis), under the influence of mechanical or chemical stimuli by undercooked food, due to the effect of bacterial toxins, in disturbance of the neural and humoral regulations. The

contraction of the intestinal muscular membrane increases. It is inhibited in the vagus stimulation. Serotonin, P substance, gastrin, motilin activate the intestinal peristalsis and vasoactive intestinal peptide and glucagon inhibit it.

The example of the disturbed neural and humoral regulation of the intestines mobility is "syndrome of the irritated intestines". The negative emotions change the motor and absorptive functions of the intestines and become the cause of pain and diarrhea frequently followed by constipation.

Increase of peristalsis usually leads to accelerated movement of nutricious masses in the bowels, aggravation of their digestion and absorption, diarrhea. Promoting excretion of the toxic substances from the organism (in food intoxication) or excess of the indigested food, diarrhea may play a protective role. However a prolonged diarrhea, especially at children's age leads to dehydratation of the organism and loss of electrolytes (Na^+, K^+). Hypovolemia develops and in severe cases there may be cardiovascular collapse.

Ileus

Acute intestinal obstruction (ileus) (from Greek *ileotum* — lock) may be mechanical (in compression, volvulus of the mesentary, occlusion by feces) and dynamic (due to spasm or paralysis of the muscular membrane of the bowels). Obstruction arises due to congenital abnormality, helminthiasis, postoperative complication, in undernourishment and taking food of poor quality.

So, paralytic obstruction (postoperative and in peritonitis) is frequently conditioned by powerful discharge of the sympathoadrenal system and activation of α- and β-adrenergic receptors, which inhibit contraction of the muscular membrane of the bowels. Spastic obstruction in carcinoid (serotonin-producing tumour from argiroffinocytes of the small intestine) may be connected with increased activity of the muscular membrane of the bowels under the influence of serotonin excess.

Disturbances of water-electrolyte metabolism are of primary significance conditioned by secretion disorder (usually it is increased) and reverse absorption of the alimentary juices. There are vomiting, dehydratation (up to 5-7 l of the alimentary secretion are lost per day), loss of ions of Na, K, H, hydrocarbonates and chlorides. There are hypovolemia, hypotension and hemoconcentration that result in disturbance of blood circulation and the condition resembling shock. K

ions loss promotes intestinal atony development.

In ileus there is also acid-base disbalance. Frequently excretion of hydrocarbonates (the pancreatic and intestinal juice) exceeds leakage of the H ions (the gastric juice) resulting in development of nongas acidosis. Acidosis is also promoted by aggravation of blood supply of the kidneys. When excretion of the acidic gastric content prevails, there is nongas alkalosis. The following processes play an important role in pathogenesis of ileus, they are indigestion, the processes of fermentation and decay, formation of toxic substances and their absorption in blood (autointoxication). Formation of increased quantity of biologically active substances, especially kinines, are also of great importance, they arise due to premature activation of the pancreatic enzymes (the intestinal content gets from the distended and overfilled intestine into the pancreatic duct).

The disturbances of the neurohumoral regulation are very important in development of all above-mentioned changes, they occur under the influence of reflex stimuli (distention of the bowels, pain, etc.). They are especially significant in strangulation ileus (twisted mesentery, hernia) accompanied by compression of the mesentery and disturbance of blood supply of the affected area of the intestine.

Intestinal Autointoxication

The human intestines, especially in the large and lower section of the ileum have abundant microflora consisting mainly of obligatory anaerobic sporeless bacilli Bacteroides and Bifidobacterium. Optionally anaerobic colon bacillus, lactic acid bacteria, streptococci and others constitute about 10% of microflora. Normal microflora of the intestines plays a protective role inhibiting development of pathogenic microorganisms and promoting natural immunity. Microflora of the bowels synthetizes vitamins.

I. I. Mechnikov was the first to suggest using microbial antagonism for fight with intestinal autointoxication.

Diarrhea

It's altered bowel (or constipation) movements. There are the following forms of diarrhea:

1. The acute form lasts 2-3 weeks. The causes: viral, bacterial, parasitic and fungal infection, heavy metal, food poisining, pelvic inflammation.

2. The Traveler's disease — bacterial infection (E. coli, Salmonella,

viral, parasitic infections).

3. The disease of homosexual men without acquared immune deficiency syndrome (AIDS) (amebiasis, Campylobacter, rectal syphilis, spirochetosis, chlamydia trachomatis infection, rectal gonorrhea, herpes simplex).

4. Disease in patients with AIDS.

5. Chronic and recurrent diarrhea. Irritable bowel syndrome, inflammatory bowel disease, malabsorption syndrome, colon cancer.

Mechanism of diarrhea is connected with osmotic disturbances — generalized malabsorption of some salts, glucose, galactose or fructose; secretory damage due to enterotoxins, tumor products (VIP, serotonin).

COMPREHENSION CHECK

Try to answer the following questions.

1. What is external and internal etiological factor causing pep- tic ulcer?

2. Characterize pathogenesis of ulcer disease.

3. Describe disturbances of membranous digestion, absorptive and excretory functions of the intestines.

4. Identify different kinds of ileus and their mechanisms.

5. What is diarrhea?

UNIT 26

PATHOPHYSIOLOGY OF THE LIVER. HEPATIC FAILURE. JAUNDICES

PATHOPHYSIOLOGY OF THE LIVER

The liver is the most important glandular organ providing the constancy of the medium of the organism ("a big chemical laboratory" by Ludwing).

The following processes take place in the liver:

1. The creation of bile pigments synthesis of cholesterol, synthesis and secretion of bile.
2. The detoxication of toxic products coming from gastrointestinal tract.
3. The synthesis of proteins (proteins of plasma of blood among them), their deposition, transamination and desamination of aminoacids, the formation of urea, the synthesis of creatinin.
4. The synthesis of glycogene from monosaccharides.
5. The oxidation of fatty acids, the formation of acetone and ketone bodies.
6. The deposition and exchange of vitamins (A, B, K), the deposition of iron, copper, zinc ions.
7. The regulation of the balance between coagulant and anticoagulant blood system, the formation of heparin.
8. The destruction of some microorganisms, bacterial and other toxins.
9. The deposition of plasma of blood, the regulation of a total amount of blood.
10. Hemopoiesis in the fetus.

All these functions of the liver aimed at maintaining homeostasis are disturbed in the liver pathology which can be manifested both as independent liver diseases (e. g. viral hepatitis), and hepatic syndromes (jaundice, cholemia, portal hypertension and others).

There can be distinguished primary and secondary affection of the liver.

Various liver diseases are mainly caused by such pathologic processes as inflammation, the disturbance of peripheral blood circulation, metabolism and tumors. Inflammatory affections of the liver are called *hepatitis,* primary changes in metabolism of hepa- tocytes

followed by dystrophy are called *hepatosis* and metabolic liver diseases and diffuse growth of the connective tissue on the background of dystrophy or parenchyme necrosis is called *cirrhosis* of the liver.

The Causes of Hepatic Failure

By etiology all sorts of the liver affections are subdivided into inherited and acquired. Etiological factors causing the liver diseases and syndromes are:

1. Infectious — viruses and bacteria (viruses of viral hepatitis, pathogene of tuberculosis and others).

2. Toxic substances — exogenous (alcohol, medicines — sulphanilamides, Chlortetracycline, tetracycline, cytostatics; industrial poisons — carbon tetrachloride, arsenic, insecticides; vegetable poisons — aphlatoxin, muscarin) and endogenous (the products of the tissue decomposition in burn, necrosis, toxicosis of pregnancy).

3. Physical factors — ionizing radiation (X-ray hepatitis); mechanical trauma.

4. Alimentary factors — protein, vitamin deficiency in the organism, fat food.

5. Allergic reactions — during the injection of vaccines, serums, food and medicine allergens.

6. The disturbance of blood circulation in the liver of the local (ischemia, passive hyperemia, thrombosis, embolism) and general character (in cardio-vascular insufficiency)

7. Endocrine and metabolic disturbances in the organism (diabetes mellitus, hypothyroidism, adiposal syndrome).

8. Tumors — primary (hepatocarcinoma) and metastatic (in cancer of the stomach, lungs, mammary gland, leukemic infiltrates).

9. Hereditary defects of metabolism (hereditary enzymopathy), inborn defects of the liver structure as a result of the intrauteral development.

Pathogenesis

While considering the pathogenesis of the liver affections of various etiology one should distinguish two kinds of pathologic reactions:

1. Direct damage of the liver by the etiological factors (viruses, chemical substances, the disturbance of blood circulation) which manifest themselves by dystrophic changes of the liver including necrosis.

2. Autoimmune damage of the liver as a result of the formation of the autoantigens (pathologically changed components of hepatocytes

emerging in direct affection of the liver) and the development of autoallergic reactions of humoral and cellular types. These reactions intensify the liver damage due to microcircular disturbances (in the influence of BAS, which are activated during the reaction antigen-antibody) and immune cytolysis with the participation of T-killers.

As a rule inflammatory (hepatitis) and metabolic (dystrophical hepatitis) affections of the liver result in the development of cirrhosis. A high frequency of combined disturbances of the liver and organs of the digestive system, spleen (hepatolienal syndrome), kidneys (hepatorenal syndrome) as a result of anatomical and functional connections between these organs is typical of the liver pathology. However not only pathologic structure and functional disturbances but also compensatory reactions are intended to stop pathological process in the organ and are characteristic of the liver pathology. These are the following reactions: the intensification of the metabolic processes in the liver (energy, desintoxication), phagocytosis, the increase of the excretion of toxic substances; the redistribution of blood; the development of anastamosis. The liver is capable of regeneration which can be evident both during resection and in diffuse affection of the liver tissue (regenerational hypertrophy of the liver). In liver insufficiency one (several) or all liver functions get lower than the level which is necessary to provide a normal life activity of the organism. The hepatic failure is subdivided into various kinds according to the following signs:

1) by the number of dysfunctions there can be distinguished partial and total insufficiency;

2) by the cause of the disease — acute and chronic;

3) by the the disease outcome — lethal and nonlethal.

Depending on principal pathogenic mechanisms hepatic failure can be:

1) hepatocellular (dystrophic and necrotic disturbances of the liepatocytes);

2) excretory or cholestatic (as a result of the disturbance of chole forming and chole excretory function of the liver);

3) vascular (disturbance of blood circulation in the liver).

As a rule the combination of several mechanisms in the development of functional inferiority of the liver can be observed. Cholestasis — the disturbance of the chole outflow followed by the accumulation of its components in the liver and blood as a result of the weakening of the excretory function of hepatocytes (a primary cholestasis) or some obstacle to chole outflow in chole ducts (a secondary cholestasis).

A *general pathogenesis* of hepatic insufficiency can be presented as the following chain of changes:

1. A change of molecular architectonics of hepatocyte membranes.
2. Intensification of free radical peroxic fraction of lipids.
3. Partial or complete destruction of membranes increase of their permeability.
4. Release of hydrolases from their lysosomes and following intensification of damage of the cell membranes.
5. A release of necrosogenic factor and interleukin of damaged macrophages and promoting development of inflammatory and immune reactions in the liver.
6. Formation of autoantibodies and auto sensibilized T-killers, that evoke functional autoallergic damage of hepatocytes.

Every enumerated pathogenic link is a certain stage of development of hepatic insufficiency can become a predominant one and this circumstance must be taken into consideration while choosing a type of treatment.

Signs of Hepatic Insufficiency and Mechanisms of its Development

A disturbance of participation of the liver carbohydrate metabolism consists in decrease of abilities of hepatocytes to convert glucose into glycogen and split glycogen to glucose. This causes is a characteristic sign of hepatic insufficiency. After meal hyperglycemia develops and on an empty stomach — hypoglycemia.

A reduction of glycogen in the pathoiogically-alterated liver results in weakening of its disintoxication function, where glycogen takes part converting into glycuronic acid.

A disturbance of participation of the liver in lipid metabolism *is characterized by decrease of abilities of hepatocytes:*

a) to convert more aterogenic form of cholesterol (free cholesterol) into less aterogenic cholesterol — ester;

b) to form phospholipids with antiaterogenic effect.

Both these changes lead to increase of the level of free cholesterol and to decrease of antiaterogenic phospholipids of blood, thus promoting cholesterol deposition on the vessels walls and atherosclerosis development.

A disturbance of participation of the liver in protein metabolism *consists of three types of changes:*

reduction of synthesis of albumins of hepatocytes, that leads to

hypoalbuminemia and hypoonkia, and at the stage of development of portal hypertension promotes development of ascites;

decrease of biosynthesis of ferments and proteins — proto-coagulants (prothrombin, proconvertin), that causes development of coagulopathies with an inclination to bleeding. A decrease of intestinal absorption of fat-dissolved vitamin K prornotes that too, being the cause of hepatic failure combined with a disturbance of bile-forming and bile-excreting functions of the liver;

reduction of intensity of desamination of aminoacids and synthesis of urea from aminogroups and ammonia, that leads to decrease of urea in blood.

A disturbance of biosynthesis of ferments by hepatocytes consists in reduction of hepatocytes ferments secretion, which they produce (cholinesterase, ANDP, NAD, etc.). Besides, damage of hepatocytes is accompanied by the increase of their going out of intracellular ferments into blood: alkaline-transaminase and glutamate-transaminase.

A disorder of vitamin metabolism *consists in:*

a) reduction of internal absorption of fat-dissolved vitamins A, D, E, K;

b) decrease of ability of hepatocytes to convert provitamins into active vitamins (e. g. carotene into vitamin A);

c) disturbance of process of formation of cofactors from vitamins (e. g. acetyl-cofactor A from lactopin acid, piruvate of cocarboxilase from vitamin B).

All enumerated changes lead to development of endogenous (hepatic) hypovitaminosis.

A disturbance of antitoxic ("barrier") function of the liver is characterized by decrease of disintoxication by the liver: internal poisons — phenol, indol, skatol; poisoning metabolites: low-molecular fat acids (valeric, capronic), sulphur-containing acids (cystine, methionin); exogenic poisons (fungic, microbic, parasitic, chemical, etc.). Inactivation of colloid particles and microorganisms with cupfer cells is also decreased.

A disturbance of formation and secretion of bile by the liver leads to development of jaundice. The outcome of progressive hepatic insufficiency is hepatic coma.

Hepatic Coma

Hepatic coma is a syndrome, caused by a toxical lesion of the central nervous system with profound disorders of its functions (loss o f consciousness, absence of reflexes, cramps, a disturbance of blood

circulation, and respiration). There are distinguished two variants of hepatic coma development: shunt and hepatic-cellular.

Shunt Hepatic Coma

This variety of coma arises as a consequence of severe affection of the liver of a sclerotic (cirrhotic) character.

Cirrhosis of the liver can be an outcome of acute and chronic hepatitis, chronic venous-stagnative hypoxia of the liver, and may be accompanied by the development of portal hypertension. Long- lasting steady portal hypertension leads to the development of porto-caval anastamosis (through hemorrhoidal, esophageal, umbilical viens), by which some part of blood, sometimes a considerable one, is "thrown" out into general blood stream passing the liver. It causes intoxication of the organism with products of metabolism, which normally are inactivated in the liver. This variant of hepatic coma has its own peculiarities: firstly, coma can arise in relatively small disorders of gall-forming (biligenesis) and gall-excretion (bilification) functions of the liver (jaundice is absent at all or is poorly manifested). Secondly, its arising is closely connected with functional condition of intestinal digestion and with a character of consumed food. Food rich in protein increase the ability of coma development being the cause of absorption of toxical products of protein disintegration, coming into a general blood stream, for example, ammonia, carbaminoxydated ammonium, cadaverin, methionin.

Hepatocellular Coma

Hepatocellular coma appears in massive necrosis of the hepatic parenchyma, when its homeostatic and barrier functions are decreased essentially.

Several interconnected pathogenic mechanisms are the base of coma development.

Hypoglycemia is one of them. It was demonstrated in the experiment, that an extirpation of the liver in animals leads to their death in 5-8 hours because of acute hypoglycemia. The term of their life is prolonged till 20-40 hours by artificial supporting of the normal level of glucose.

The severe acidosis is another essential mechanism of coma development. It was demonstrated, that the acid-base correction allows prolonging the life of animals till 2-3 days.

The intoxication of the organism is an important pathogenic part of coma. It is conditioned by appearance and increase of the level of substances in blood, which exert the general toxic and, especially, cerebrotoxic influence.

The disturbance of aminoacidic and albuminous metabolisms is important in a mechanism of coma development.

The impaired liver isn't able to support the proper quantity and correlation of separate aminoacids and fractions of protein in blood. Excess of one and deficiency of another aminoacid make the normal metabolism of proteins impossible in the tissues of the organism. Increase of aminoacids in blood and their appearance in urine is a manifestation of this. The level of free ammonia is increased in blood. It is conditioned by disturbance of its transformation into urea in the ornithine cycle of hepatocytes. Besides, the part of urea, which is excreted by mucous membrane of the intestine, is split in it by ureasis with the formation of ammonia, which is sucked in blood. Excess of ammonia damages the cells of the organs and tissues, suppresses the fermentative reactions in them.

Many damaged hepatocytes are exposed to the destruction. The substances, containing in them, get into blood and exert the pathogenic influence on the cells of the organs and tissues, including the cells of the nervous system. Bile pigments take part in intoxication of the organism too: the level of free (unconjugated) bilirubin is increased in blood.

It influences toxically on the cellular membranes.

The quantity of highly toxic products of decay of aromatic aminoacids (indole, skatole, phenol) and also of albuminous putrefaction (putrescine, cadaverin) in blood is increased.

Systemic hemodynamics is disturbed due to general intoxication: the cardiac ejection is decreased, arterial hypotension develops, the volume of the circulating blood is reduced. Disturbances in the system of blood coagulation (deficiency of prothrombin, fibrinogen and others) are the cause of development of bleedings, hemorrhages in the microvessels of the organs and tissues. The progressing general hypoxia appears.

JAUNDICES

Jaundice is a syndrome, which appears due to increase of bilirubin content in blood and is characterized by yellow coloring of the skin, mucous membranes, sclerae as a result of deposit of the bile pigments in them in disturbance of biligenesis.

The unconjugated (free) bilirubin is the basic bile pigment, which is present in blood in the norm. Level of unconjugated bilirubin depends on intensity of hemolysis of erythrocytes. Unconjugated bilirubin is toxic and isn't filtered in the glomeruli of the kidneys and is absent in

urine, even if its level exceeds the norm.

Hepatocytes catch actively the unconjugated bilirubin and turn it into the conjugated (constrained) one. Conjugated bilirubin is turned into urobilinogen in the bile ducts and in superior part of the small intestine excreting in a composition of bile, and turned irito stercobilinogen.

Urobilinogen is absorbed in the small intestine together with fatty acids and get into the blood of portal vein system, caught by hepatic cells and destroyed in them. The part of stercobilinogen is absorbed together with water in the lower section of the large intestine into the inferior cava vein system through porto-caval anastomoses. It is slightly filtered in the kidneys and excreted with urine giving it a straw-yellow color, because stercobilinogen is dissolved in water and not bound with protein.

The jaundices are divided into three kinds depending on their origin: hemolytic ("suprahepatic"), mechanical ("subhepatic"), hepatogenous proper.

Hemolytic Jaundices

The cause of appearance of hemolytic jaundice is excessive destruction of erythrocytes, the increase of unconjugated bilirubin in the blood is observed at the background of anemia and hemoglobinemia. It is a result of excessive formation of unconjugated bilirubin from hemoglobin, and inability of normal hepatic cells to catch and transform the unconjugated bilirubin, which is present in blood in excess.

Hypoxia also promotes this process. Hypoxia develops due to hemolysis of erythrocytes and limits the activity of ferments of hepatocytes, including participation in deglucuronizaton of unconjugated bilirubin. Excess of unconjugated bilirubin in blood conditions the coloring of the skin and mucous membranes, the increase excretion of stercobilin and urobilin with the foces and urine. However, the cholemic syndrome (bile acids don't come into blood) and digestive disturbance in the intestines (acholic syndrome is absent in other jaundices) are absent. Hepatocellular jaundice can be combined with hemolytic one, if hepatocytes are damaged simultaneously with hemolysis; as well as with mechanical jaundice as a result of occlusion of the biliferous canals by bile thrombi and stones from bilirubin, cholesterin and calcium.

Mechanical Jaundice

The cause of its development is a steady disturbance of bilification from the bile capillaries, gallbladder or its duct into a lumen of the duodenum. It is stipulated by narrowing or total closing of their lumen (the stones in the biliferous tracts, inflammatory process in them,

presence of parasites in the gallbladder, dyskinesia of the biliferous tracts, tumors). The disturbance of bile outflow is accompanied by increase of its pressure in the bile capillaries, their walls and reverse diffusion of many components of bile in the blood capillaries. The rupture of the bile capillaries is possible in the cases of acute total obturation of the biliferous tracts. Bile, coming into contact with the hepatic tissue, provokes its damage and development of inflammatory process, that is called *biliary hepatitis*. The development of two syndromes is typical for obstructive jaundice: cholemia and acholia.

Cholemia is a complex of disturbances, which are conditioned by appearance of bile components in blood and mainly of bile acids, glycocholic and taurocholic in particular. Yellow coloring of the skin, sxleras is provoked by increase of the level of conjugated bilirubin in the blood. Conjugated bilirubin appears in urine in combination with bile acids (cholaluria) that gives a specific color to urine. The level of Cholesterin is increased in blood (hypercholesterinemia), that leads to appearance of xanthomas (frequently in the epidermis of the skin of eyelids).

The skin pruritus, which is provoked by irritation of nervous endings by bile acids, is observed in cholemia. Cholemia is characterized by decrease of activity of inhibitory neurons of the cerebral cortex that is accompanied by heightened irritability and excitability. Later the other centers of the brain and spinal cord are inhibited. Depression, disturbance of daily rhythm of sleep and awaking, slight fatiguability, decrease of tendon reflex are observed.

Acholia syndrome is characterized by disturbances at first of cavitary digestion. It arises as a result of absence of bile in the intestines. Disturbance of lypolysis and fat-soluble vitamins splitting; presence of fat in feces (steatorrhea); discoloration of feces because of absence of stercobilinogen in it; dysbacteriosis, which is combined with aggravation of putrefaction processes and fermentation in the intestines and, as a result, meteorism; decrease of the tone and depression of intestinal peristalsis, which leads to constipation, alternated with diarrheas; hypovitaminosis of the vitamin K, disturbance of synthesis of proteins, including procoagulants; increase of permeability of the microvascular walls that stipulates the development of hemorrhagical syndrome in combination with hypo-coagulation are registered by it.

Hepatogenous Jaundice

Hepatocellular (parenchymatous) and enzymopathic varieties of jaundices are related to hepatogenous jaundice.

Parenchymatous jaundice appears as a result of a direct lesion of the hepatic tissue by agents of infections — parasitogenic (viruses, bacteria and their toxins, malaria Plasmodiums and others) a id noninfectious origin (organic and inorganic poisons, for example, tetrachloride hydrocarbon, high doses of alcohol; hepatotrophic antibodies and sensitized lymphocytes; tumors and others). The type and manifestation of disturbances of hepatic functions depend on the degree of damage and mass of impaired hepatocytes. Damage, beginning from the change of the structure of the cellular membranes and (or) suppression of aciivities of ferments, is increased and may be completed by destruction of the hepatic cells in many cases. The bile-synthetic and bile-secretory functions of the hepatocytes are disturbed in the zone of lesion almost by any variant of damage of the liver. However, definite peculiarities of disturbance of pigmental metabolism are typical of various stages of development of pathologic process. Early specific signs of lesion of the hepatocytes in a first stage (preicteric) are the appearance of urobilinogen in blood and urine (the cause of this is damage of fermental mechanisms and catching and oxidation of this pigment); high level of hepatic transaminases in blood (alanine, aminotranspherase, aspartataminotranspherase and others), which easily penetrate through the damaged cellular membrane.

The process of conjugation of unconjugated bilirubin with glucuronic acid is disturbed in the second stage (icteric) in connection with decrease of activity of glucoronyl transferase. Quantity of forming bilirubin diglucuronide (conjugated bilirubin) is decreased as the result of this. The damaged hepatocytes start to secrete the bile synthesis not only in bile capillaries, but also in blood capillaries parallel to this. It stipulates the appearance of free bile acids in blood, increase of the level of total bilirubin in it owing to conjugated, and also its appearance in urine. Besides, crashing of bile capillaries by damaged edematic hepatocytes hamper the evacuation of bile from them and make the conditions for increasing of its resorption in blood capillaries of the liver. The coming of bile into the intestines is disturbed due to manifestation of cholemia.

The total lack of ability of hepatocytes to catch and transform unconjugated bilirubin in conjugated one occurs in the first stage in the case of serious lesion of the liver (stage of precoma). The level of unconjugated bilirubin begins to increase in the blood, in connection with this the contents of conjugated bilirubin in the blood begin to

decrease and, as a rule, urobilinogen disappears. Disturbance of the barrier and other functions of the liver, appearance of toxic forms of bilirubin and other metabolites in blood lead to the essential disturbance of homeostasis of the organism and threat of hepatic coma development.

Enzymopathic jaundices are conditioned by disturbances of intrahepatocytic metabolism of bilirubin. In these cases we speak about a partial form of hepatic insufficiency, which is connected with decrease of impossibility of synthesis of number of ferments which take part in pigmental metabolism. By origin this jaundice is mainly hereditary. At the same time some forms are registered after heaving earlier diseases of the liver. The forms of jaundice are distinguished depending on the mechanisms of development.

Gilbert's syndrome. It's jaundice which is based on development of the disturbance of active catching and transport of unconjugated bilirubin from blood into the hepatic cells. The cause of it is a genetic defect of synthesis of proper ferments. The increase of the level of total bilirubin is stipulated by increase of contents of free (unconjugated) bilirubin in it.

Crigler — Nagar syndrome. This variant of enzymopathic jaundice develops as a result of deficiency of glucoronyltransferase — the key ferment of transformation of free bilirubin into conjugated one.

Dubin — Johnson syndrome. This variant of jaundice appears as a result of defect of ferments, which participate in excretion of bilirubinglucuronide through the membrane of the hepatic cells in bile capillaries. As a result of this direct bilirubin comes not only into bile capillaries, but also in blood.

COMPREHENSION CHECK

Try to answer the following questions.

1. Describe the main causes of the hepatic failure.
2. Name signs of hepatic failure and mechanisms of its development.
3. Why does hepatic coma occur?
4. Distinguish the types of jaundice and characterize their mecha- r ism.

UNIT 27

PATHOPHYSIOLOGY OF THE KIDNEYS. RENAL INSUFFICIENCY

GLOMERULONEPHRITIS.
NEPHROTIC SYNDROME

The kidneys are very important organs for supporting homeostasis (constancy of the internal medium of the organism), providing constancy of fluid volume (isovolemia) and osmotic concentration (isotonia), ion composition (isoionia), concentration of hydrogen ions (isohydria).

The kidneys are also important for excretion of the products of nitrous metabolism and different foreign substances from the organism. Disturbance of excretion is one of the significant manifestations of renal insufficiency.

The kidneys are characterized by intensive blood supply, high level of energy metabolism which defines their increased sensitivity to disturbances of blood circulation.

The kidneys are also incretory organs participating in regulation of the vascular tension (renin-angiotensin system, prostaglandins) and erythropoiesis (erythropoietin, erythropoiesis inhibitor).

The protein composition of the renal tissue is characterized by antigenic similarity to proteins of the connective tissue and some microorganism, in particular streptococci. That's why some diseases of the kidneys (acute and chronic diffuse glomerulonephritis) depend on diffuse impairments of the connective tissue and diseases of streptococcus origin.

The Main Dysfunctions of the Kidneys

The amount of urine produced by the kidneys for a time unit is equal to difference between the amounts of fluid having been filtered in the glomeruli and reabsorbed in the tubules. The decrease of the daily amount of urine (diuresis) less than 500 ml/day is called oliguria, absence of urine excretion or the decrease of the daily diuresis less than 100 ml/day is called anuria. They may result from dysfunction of the glomeruli or tubules.

In clinic there is used determination of clearance index. It shows the amount of plasma or blood serum (in milliliters) which is completely cleared from the exogenic and endogenic substances while passing through the kidneys per 1 minute. Clearance is counted by formula:

$$C=UV/P, \text{ where}$$

C — clearance of the investigated substance (ml/min);

U — concentration of the investigated substance in urine (mg/ ml);
V — diuresis (ml/min);
P — concentration of the investigated substance in plasma (mg/ ml).

To determine the amount of glomerulus filtration there are used exogenic (polysaccharide inulin), as well as endogenic (creatinine substances), which are filtrated in the glomeruli and are not reabsorbed and secreted in the tubules. In the norm creatinine varies within 180-90 ml/min. It means that 130-90 ml of plasma is cleared from creatinine by the healthy kidneys per minute and the same amount of initial urine is formed.

The amount of filtration clearance is 400 ml/min for phenol red.

Dysfunction of the Glomeruli of Nephrons

Disturbance of filtration. Disturbances of diuresis may be first of all promoted by changes of the amount of the glomerulus' filtration (in the norm 100-140 ml/min). There are renal and extrarenal mechanisms of filtration disturbance. The decrease of filtration may be in the following cases:

1. In decrease of the hydrostatic pressure on the capillary walls. It is connected with the decrease of the arterial pressure 80 mm Hg due to shock and collapse of different genesis, blood circulation insufficiency and decrease of the volume of the circulating blood.

2. In elevation of the blood oncotic pressure above 25-30 mm Hg due to hemoconcentration because of dehydratation of the organism.

3. In the increased pressure in the capsule of the glomeruli above 25 mm Hg which is observed in the delayed reabsorption of fluid in the proximal part of the tubules of the nephrons, in occlusion of the tubules lumen by cylinders, necrotic masses and in obstruction of the ureter (necrosis, clots, calculi and tumors).

4. In the change of the condition of the glomerular filter — reduction of the number of the functioning glomeruli (2 min in the norm), total filtration surface (about sm^2 in the norm), the number, square and diameter of the pores (up to 5 mm in the norm), thickening of the glomerular membrane (80-120 mm in the norm) and its physical and chemical properties. Such disturbances are observed, first of all, in inflammatory process affecting the glomerular membrane (glomerulonephritis, etc.).

Damage of the renal filter and decrease of the glomerular filtration and diuresis resulting from it may be observed in dystrophy of the glomerular membrane due to disturbances of blood supply of the kidneys hypoxia or different toxic influences.

The following factors influence the increase of filtration:

1. Increase of the hydrostatic pressure on the wall of the glomerular capillaries which is observed in the increased volume of the

intravascular fluid.

2. Decrease of the oncotic blood pressure (hypoalbuminemia).

The increase of the permeability of the glomerular membrane.

The sign of the increased permeability of the glomerular membrane is proteinuria — excretion of plasma proteins with urine above the amount prevent in the physiological conditions (30-100 mg/day) as well as presence of proteins with large relative molecular mass (above 70,000) in urine.

The mechanism of proteinuria caused by increased permeability of the glomeruli is due physical and chemical changes in the basal membrane. Such changes in the glomerular membrane may occur in hard work, loss of fluid in babies and in overcooling. Protein in urine may appear after having meal with large amount of proteins, especially in children (alimentary proteinuria).

Organic proteinuria (in acute and chronic glomerulonephritis, nephritic syndrome and other organic impairments of the kidneys) is characteristic of presence of plasma proteins with high relative molecular mass of 70,000-820,000 in urine.

Intermediate position is taking by proteinuria in circulatory insufficiency, in infectious diseases and some toxic conditions, in thyrotoxicosis, mechanic and parenchymatous jaundice, enterocolitis, intestinal obstruction and burns.

When proteinuria is not connected with renal impairment but brought about by the inflammatory process in the ureter it is called extrarenal or false proteinuria (usually protein is no more than lg/l).

The injury of the glomerular membrane may be accompanied by coming out of erythrocytes into the glomerular lumen and their appearance in urine (renal glomerular hematuria) as "shadows" (lixiviated erythrocytes).

Renal hematuria should be differentiated from extrarenal one, brought about by trauma or inflammation of the ureter. There is a large amount of fresh erythrocytes in it.

Disturbance of substance excretion. Dysfunction of the glomeruli is manifested by delay of excretion of nitrous metabolism products and their increased concentration (residual nitrogen) in blood — azotemia. It is caused by accumulation of urea, uric acid, creatine, creatinine, ergothylanine and ammonia in blood as well as to less extent aminoacids, toxic products resulted from decay in the intestines — indican, fenol, indole and skatole.

The level of azotemia may be different — from the slightly exceeding the upper limit of the normal quantity of residual nitrogen (35.7 mmol/l) to 142.8-357 mmol/l. The main factor is decrease of the amount of the glomerular filtration.

As a result of excretory dysfunction of the glomeruli there is delay of excretion of phosphates, sulfates and organic acids and their increased concentration in blood — hyperphosphatemia, hypersulfatemia, hyperacidemia. Anions of these substances push out hydrocarbonates in the extracellular fluid, decrease the alkaline reserve of blood to 18-13.5 mmol/l (25-31 mmol/l in the norm) that results in acidosis (renal azotemic acidosis).

There is accumulation of ions of magnesium and potassium in the extracellular space and blood (hyperkaliemia, hypermagniemia) with decreased concentration of sodium (hyponatremia) and chlorine (hypochloremia) in blood plasma.

Renal Insufficiency

There are acute and chronic renal insufficiency.

Acute renal insufficiency is characterized by acute disturbance o f the stability of the internal medium of the organism due to considerable and quick decrease of the rate of the tubular filtration (in the norm 120 ml/min, in oligo- and anuria — 1-10 ml/min).

Etiology

Acute renal insufficiency (ARI) is connected with 3 groups of factors: prerenal, renal and postrenal. About the renal group of insufficiency we have told before.

Prerenal factors *of ARI are:*

1. Blood loss burns, incontrollable vomiting, profuse diarrhea, the use of diuretics resulting in sharp decrease of the volume of the intravascular and extracellular fluids.

2. Vascular forms of shock (septic, anaphylactic), accompanied by reduction of the arterial pressure.

3. Acute (myocardial infarction, embolism of the pulmonary artery) and chronic cardiac insufficiency.

Postrenal factors *are:*

1. Obstruction of the ureter (calculi, tumors).

2. Retention of the urine at the level of the bladder outlet (adenoma of the prostate).

Pathogenesis

The main mechanism of ARI development is temporary ischemia of

the kidneys conditioned by hypovolemia, spasm of the afferent arterioles, disseminated intravascular blood coagulation with microthrombosis or direct damage of the renal vessels. In consequence there are marked decrease of the filtration pressure and tubular filtration, switching off of a definite number of the nephrons.

Under the influence of the nephrotoxic factors (toxic, infectious) along with disturbance of the cortical blood flow, direct damage of the glomerular and tubular structures becomes important. The rate of the glomerular filtration may be decreased for the second time due to obstruction of the tubular lumen by necrotic masses or due to leakage of the filtrate through the wall of the damaged tubules into the interstice.

Increased pressure in the capsule of Shumlyansky-Bowmen or in the interstice results in decrease of effective filtration pressure.

In damage of the cells of the proximal tubule reabsorption of Na^+ is disturbed. Its increased concentration in the distal tubules is taken by mascula dense that results in activation of renin-angiotensin system.

There are four stages in the clinical course of ARI:

— initial;
— oligo-, anuria;
— polyuria;
— recovery.

The most characteristic and marked disturbances are observed in the stage of oligo-, anuria. Along with sharp decrease of diuresis up to its complete stop, there are hyperazotemia, disturbance of water-electrolyte homeostasis and acid-base balance. The main clinical manifestations of this stage are the brain edema, interstitial lung edema, the clinical picture of water intoxication of the organism, severe disturbances of circulation — decrease of contractile function of the heart, arrhythmia as extrasystole, bradycardia, blockade, hypotension with transformation into hypertension, dyspnoea by Kussmaul's type (a sign of acidosis), severe dysfunctions of the nervous system — headache, vomiting, loss of consciousness, convulsions, coma, anemia.

Most of patients suffering from acute renal insufficiency die. In providing effective therapeutical measures there is transition into the stage of diuresis restoration and polyuria in 5-10 days.

Chronic Renal In sufficiency. Uremia

Etiology

The etiological factors of chronic renal insufficiency (CRI) are

chronic progressing diseases of the kidneys of inflammatory (chronic glomerulonephritis, chronic pyelonephritis, etc.), vascular (hypertension, stenosis of the renal artery) and metabolic (diabetic glomerulosclerosis, amyloidosis, gout) origin.

Pathogenesis

CRI develops as a result of simultaneous or subsequent decrease of the mass of the acting nephrons and reduction of the renal functions.

The initial signs of CRI appear in reduction of the mass of acting nephrons (MAN) to 50-70% of the original amount of the nephrons, clinically marked picture develops in reduction of MAN to 30-10%. Further reduction of MAN and glomerular filtration (below 10% of the norm) leads to terminal stage of renal insufficiency — uremia. The main manifestations of CRI are conditioned first of all, by azotemia. Over 200 toxic substances were revealed. The whole accumulation in blood in CRI determine the organism intoxication and associated symptoms. They are anorexia (loss of appetite), dyspeptic signs (vomiting, diarrhea), reduction of the body mass, general weakness, headache, apathy, disorders of taste, hearing, tormenting itching, dyspnoe, progressing anemia, uremic pericarditis, myocarditis, pleurisy, arthritis, convulsions and coma.

Glomerulonephritis

Glomerulonephritis is a bilateral disease of the kidneys of the inflammatory origin. There are acute and chronic (diffuse) glomerulonephritis.

Acute (Diffuse) Glomerulonephritis

Experimental models. In 1901 V. K. Linderman observed the main manifestations of nephritis in the rabbit in the intravenous introduction of nephrotoxic serum of the guineapig immunized with suspension of the rabbit kidney.

In 1933 by using the same scheme of experiment, a Japanese scientist Masugi reproduced the clinical picture of nephritis in rabbit by introducing serum of the duck blood immunized with the tissue of the rabbit's kidneys. Masugi received another variant of nephritis model in the scheme rabbit — duck — rabbit.

At present there are two phases of pathogenesis of the experimental glomerulonephritis: *heterologic,* conditioned by fixation of the nephrotoxic antibodies (IgG, IgM) on the basal membrane of the glomeruli of the nephrons and *autologic,* connected with production of complement-fixing antibodies for nephrotoxic globulin.

Etiology

Acute glomerulonephritis arises in (or after) some infection, mostly of streptococcus nature. It is considered, that A group hemolytic streptococcus is a specific "nephritogenic" strain. Other infections play a definite role, including viruses, parasites. Glomerulonephritis may arise in cooling, diffuse lesions of the connective tissue (lupus erythematosis, rheumatoid arthritis, nodular periarteritis). Heterologic serum is used in therapy.

Pathogenesis

There are two main mechanisms of glomeruli damage:

1. Affection of the basal membrane of the glomeruli of the nephrons by antibodies, so-called nephrotoxic glomerulonephritis (it has a quick progressive course). Glycoprotein is a carrier of antigenic proteins of the basal membrane.

2. Development of the inflammatory process in the glomeruli due to fixation of the immune complexes on the basal membrane — immunocomplex glomerulonephritis.

The mechanism is characterized by either exogenic (of infectious or noninfectious origin) or endogenic (tissue protein, DNA) antigen. The formed antibodies (IgG, IgM) begin to interact with the mentioned antigens in blood serum and then as immune complexes (antigen-antibody-complement) enter the glomeruli accumulating on their basal membrane. The impairment of the immune complexes and nephrotoxic antibodies is realized by induction of the immune inflammation.

Glomerulonephritis developing after the streptococcal infection, in systemic lupus erythematosus, serum disease and others is related to the immune complexes.

Clinical and pathophysiological manifestations of acute glomerulonephritis reflect changes of the renal, mainly glomerular and extrarenal functions. The classical course of the disease is characterized by violent onset, oliguria, proteinuria, hematuria, azotemia, arterial hypertension, edemas which develop due to retention of sodium, hypoproteinemia, hypervolemia, and increased permeability of capillaries and disturbance of the nervous system.

Chronic (Diffuse) Glomerulonephritis

Etiology

Chronic glomerulonephritis may result from acute one, but more often it develops primary. There are the following forms of the acute glomerulonephritis:

a) infectious (poststreptococcal, in malaria, syphilis, tuberculosis);

b) non-infectious (serum, vaccine, medicamentous, in intoxication by different poisons, traumatic, in thrombosis of the renal veins);

c) in diffuse diseases of the connective tissue (rheumatoid arthritis, lupus erythromatosus, hemorrhagic vasculites, etc.);

d) special (radiation, hereditary, etc.)

Pathogenesis

Hypersensitivity of the delayed type plays a certain role. The following forms are distinguished clinically in the functional compensatory phase:

1. The latent form (65% of all cases with chronic glomerulonephritis) is manifested by isolated urine syndrome — moderate proteinuria, hematuria. Some patients (20-25%) are observed to have edemas and transitory hypertension.

2. The hypertensive form (32% of patients) is characterized by stable increase of the arterial pressure. 1/3 of patients have edemas, 2/3 — hematuria, all patients have proteinuria and half of them have cylinduria and leukocyturia.

3. The nephrotic form (2-4% of patients) which is distinguished by edematous syndrome (2/3 of patients) marked proteinuria and cylinduria (in all patients) and characteristic changes in blood (hyperproteinemia and hyperlipidemia).

4. The mixed or nephrotic hypertensive form (2.4% of patients) from which is characterized by edemas and hypertension (in all patients).

Nephrotic Syndrome

Nephrotic syndrome includes various affections of the kidneys and other organs which are characterized by marked proteinuria, hypovolemia, dysproteinemia, hyperlipidemia and edematous syndrome (Table 14).

Etiology

By origin nephrotic syndrome is divided into primary and secondary.

Primary nephrotic syndrome is not connected with the kidneys disease. Frequently its development is based on genetically conditioned defects of metabolism (lipoid nephrosis) or transplacental transfer of specific antirenal antibodies from the mother to the fetus (congenital family nephrosis).

Secondary nephrotic syndrome may be caused by some diseases of the kidneys (glomerulonephritis) or other organs (nephropathy of the pregnant women, diabetes mellitus, amyloidosis, lupus erythematosus, serum

disease, staphylococcal sepsis, etc.). It may be observed in intoxication with salts of heavy metals, burns, raciactive affection, rejection of the renal transplant, using of some riedicines (sulfa drugs, penicillin, corticosteroids) and in disturbance of blood supply of the kidneys.

Table 14. Consequences of albuminuria under nephritic syndrome

Proteinuria	Consequences of diminished amount of proteins in blood
Albumin	Hypooncia, edema
Antithrombin III	Predispose to thrombosis and thromboembolism
Factors of blood coagulation	Hemorrhagic syndrome
Components of compliment	Decreased resistance to infections
IgG	Decreased resistance to infections
HDL	**Predispose to atherosclerosis**
Proteins with microelements	Deficiency of Fe, Zn, Cu
Proteins transporting hormones	Endocrine disturbances

Pathogenesis

Most of nephrotic conditions are caused by immunological mechanisms, mostly by sensitivity of the delayed type. Exogenic factors may be the sources of antigens: bacterial, viral, parasitic, riedicamentous, food, compounds of heavy metals, etc. DNA, denaturated nucleoproteins, proteins of tumor origin and thyroglobulin may serve as exogenic antigens. Antibodies produced in response to these antigens are mostly of IgM class.

The damage of the glomeruli of the renal is connected with deposit of amyloid, glyco- and lipoproteins, fibrinogen with activation of humoral and cellular links of the inflammatory reaction on the surface or in the basal membrane of the capillaries. As a result the structural integrity of the basal membrane is lost, its composition and physical and chemical properties are changed and its permeability for plasma proteins is sharply increased.

For those forms of nephrotic syndrome where immunological mechanisms are not proved, the most suitable are metabolic and physico-chemical mechanisms. So, nephrotic proteinuria is explained

by decrease of the constant electric charge of the wall of the capillary net, and disappearance of sialoprotein from it. At the places of maximal loss of ions and sialoproteins, polymorphno-nu- clear leukocytes are accumulated whose lysosomal ferments exert direct damage effect on the basal membrane of the capillary vessels. General changes in the organism (hypoproteinemia, dysproteinemia, hypoalbuminemia, hyper-α_2-globulinemia) can lead to edematous syndrome. Simultaneously, secondary aldosteronism develops due to hypovolemia (the cause of which is "leakage" of fluid into the tissues, decrease of the renal blood flow and increased production of renin).

Hyperlipidemia, which is characterized by nephrotic syndrome, is brought about, mainly, by thriglycerides, cholesterol and patho-genetically it is connected with protein metabolism and suppression of the lipolytic activity of blood plasma.

Pyelonephritis

Pyelonephritis is infectious inflammatory disease of the mucous membrane of the urinary tract and renal parenchyma (simultaneous or subsequent) with predominant affection of the intestinal tissue.

Etiology and Pathogenesis

The disease arises due to penetration of the causative agent of infection into the kidneys by hematogenic way or by spreading it upwards by the urinary tract. The causative agents are mostly colon bacillus, cocci.

Development of the disease and transition of acute pyelonephritis into chronic one is promoted by different conditions causing urine congestion (constriction, occlusion of the ureter, adenoma of the prostate), dystrophy of the urinary tracts, general diseases, which reduce the reactivity of the organism (diabetes mellitus, atherosclerosis, obesity, chronic intoxication, etc.)

COMPREHENSION CHECK

Try to answer the following questions.

1. Describe acute and chronic renal insufficiency.
2. What is uremia?
3. Explain etiology and pathogenesis of glomerulonephritis.
4. Characterize nephrotic syndrome.

UNIT 28

PATHOPHYSIOLOGY OF THE HYPOTHALAMIC-HYPOPHYSIAL SYSTEM. STRESS AND GENERAL ADAPTATION SYNDROME (GAS). DYSFUNCTION OF THE PITUITARY AND ADRENAL GLANDS

GENERAL STRUCTURE OF THE NEUROENDOCRINE SYSTEM. TYPES OF THE ENDOCRINE GLANDS

There are two main types of the neuroendocrine system: the first (sometimes called cerebropituitary) includes 5 parts. The higher regulation center is the cortex of large hemispheres, which may exert great influence on the function of a number of the endocrine glands via the lower sections. The second quite important part having regulatory function is the hypothalamus definite nuclei of which form substances of hormonal activity, having abilities to neurosecretion (neurocrinia). Some neurosecretory cells of the hypothalamus produce peptide neuropituitary hormones (vasopressin and oxytocin), accumulating in the posterior lobe of the pituitary and coming into blood from there. They are addressed to the peripheral target cells. Others produce oligopeptides, which come into anterior lobe of the pituitary and stimulate or inhibit production of the pituitary hormones. The stimulating oligopeptides are called releasing factor or liberins and the inhibiting ones are called statins.

The next, third part is the anterior lobe of the pituitary (ALP), it mainly plays a role of intermediate regulation, producing several tropic hormones stimulating hormonal activity of the three "peripheral" pituitary-depending endocrine glands: sexual, thyroid and adrenal cortex.

The fourth part is represented by the indicated endocrine glands, which synthesize and eject the corresponding hormones into blood.

The last fifth part of the neuroendocrine system includes target cells where hormonal effects of peripheral pituitary-dependent endocrine glands are realized.

As a rule secretory activity of the endocrine tissues is regulated according to the principle of negative reverse connection. It means that

increased concentration of the hormone or signals about the results of reaction of "target tissue" on it inhibit or weaken stimulating effect on synthesis or secretion of this hormone. Decreased concentration or weakening of signals of realization of its effect cause an adverse effect.

Stress and General Adaptational Syndrome

One of the achievements of modern medicine is the important role of the endocrine glands, in particular, the system of the hypothalamic-adrenal system in the organism adaptation to the influence of pathogenic factors. The theory of a Canadian scientist Hans Selye about stress is widely spread.

The term "stress" *indicates nonspecific reaction of the organism arising under the influence of any strong effects (stressors) and accompanying by reconstruction of the organism protective systems.* Selye noticed that despite the variety of stressors (trauma, infection, overcooling, intoxication, narcosis,' muscular loading, strong emotions, etc.), they all lead to the same types of changes in the thymus, adrenal glands, lymphatic nodes, blood composition and metabolism (Fig. 41). While experimenting on rats, he observed the typical triad, which included hypertrophy of the cortical substance of the adrenal glands, involution of the thymic-lymphatic apparatus and hemorrhagic ulcers on the mucous membrane of the stomach and duodenum.

Stress is manifested as a general adaptation syndrome that consists of three subsequent stages: anxiety reaction, resistance stage and exhaustion stage. Anxiety reaction means immediate mobilization, it consist of shock and antishock stages. In the shock phase there are muscular and arterial hypotension, hypothermia, hypoglycemia, pachyemia, eosinopenia, increased permeability of the capillaries. Involution of the lymphoid tissue, negative nitrous balance, ulcerous injuries of the stomach give evidence of catabolic processes prevalence. The phase of antishock is characterized by reverse changes (increase of blood pressure, muscular tonus, glucose in blood) resulting in development of the next stage — the stage of resistance. The main pathogenic part of the antishock phase is steady increase of corticotropin and corticosteroid secretion. In the stage of resistance the cortical substance of the adrenal glands is hypertrophic and it secretes a large amount of glucocortecoids, which intensify glyconeogenesis.

Selye called protective reactions of the organism promoting life due to realising a large amount of adaptive hormones (catecholamines, gluco- and mineralocorticoids). In prolonged effect of the injurious

agent adaptation is disturbed. The transition of resistance stage into the stage of exhaustion is characterized by exhaustion of the functional reserves: atrophy of the cortical substance of the adrenal glands, reduction of the arterial pressure, proteolysis.

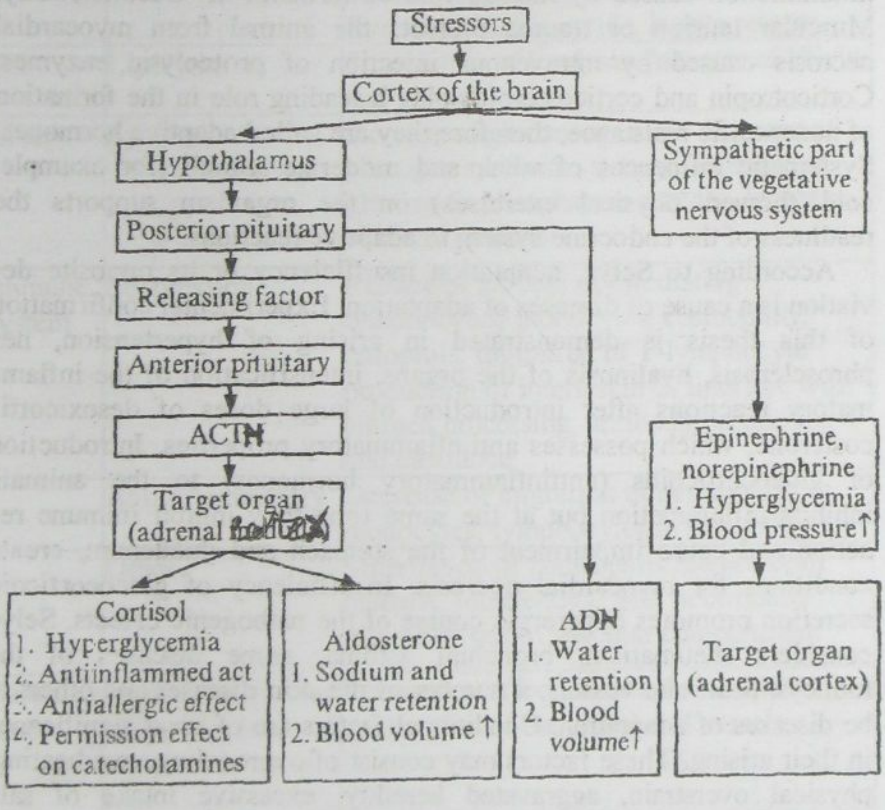

Fig. 41. The "fight and flight" scheme in stress syndrome

The stress outcome depends on the ratio of the force and duration of the stressor effect and potential abilities of the organism protective forces.

The biological significance of the adaptation syndrome consists not only of the increased resistance during the second, the most prolonged stage in relation to the factor causing stress, but also in creation or increase of nonspecific organism resistance to other different factors in not strong and prolonged stress. It is manifested in increased

survival after the influence of lethal agents or in diminishing inflammation, prevention of hyperergic reactions, impairment of the heart, kidneys and other organs arising under the influence of pathogenic factors. For example, bloodletting (stressor) may reduce inflammation caused by introduction of formalin in- tracutaneously. Muscular tension or trauma protects the animal from myocardial necrosis caused by intravenous injection of proteolytic enzymes. Corticotropin and corticosteroids play a leading role in the formation of nonspecific resistance, therefore they are called adaptive hormones. Systematic influences of weak and moderate stimuli (for example, cold shower, physical exercises) on the organism supports the readiness of the endocrine system to adaptive reactions.

According to Selye, adaptation insufficiency or its opposite deviation is a cause of diseases of adaptation. Experimental confirmation of this thesis is demonstrated in arising of hypertension, nephrosclerosis, hyalinosis of the organs, intensification of the inflammatory reactions after introduction of large doses of desoxicorticosterone, which possesses antiinflammatory properties. Introduction of glucocorticoids (antiinflammatory hormones) to the animals inhibits inflammation but at the same time they inhibit immune reaction and cause impairment of the stomach and duodenum, create conditions for myocardial necrosis. Insufficiency of glucocorticoid secretion promotes hyperergic course of the pathogenic effects, Selye considers rheumatism, bronchial asthma, some diseases of the kidneys, heart and vessels, a number of the skin diseases and others to be diseases of adaptation. Conditional factors are of great significance in their arising. These factors may consist of overcooling, overheating, physical overstrain, aggravated heredity, excessive intake of salt. Combined introduction of corticosteroids and sodium chloride creates the background for development of necrotic changes of the myocardium by different stimuli.

The theory of Selye was developed on the basis of the study of the endocrine mechanisms of adaptation reactions of the organism. Before W. Cannon, L. Orbelly and their disciples created a study of adaptational-trophic role of the sympathetic part of the vegetative nervous system in the protective compensatory reactions. Some manifestations of stress (ulcers) are observed in pituitary ectomized animals. Therefore, it is impossible to consider all the variety of these manifestations to be only hormonal reconstruction. Stress is a complex

neurohumoral reaction with participation of the nervous system and endocrine glands. It is necessary to note some underestimation of specificity of response to pathogenic stimuli by Selye. But it should be underlined that the Selye's theory exerted and goes on exerting *great* influence on medicine development. It gave theoretical groundation to corticosteroid therapy. A new approach to the problem of aging is.based on this theory. Nonspecific therapy (bloodletting, autohemotherapy, and acupuncture) was explained on its basis. Nowadays the main theses of this theory are being successfully developed.

Disorders of the Hypothalamic-Hypophysial Systems

Panhypopituitarism

In the human the total insufficiency of the pituitary function may be congenital or acquired. The most often causes of this disease are tumor, postnatal necrosis of the pituitary, injury of the basis of the skull, inflammation, thrombosis and viral infection. The affection of the glands in the embryonic period leads to a dwarfism (hypophysial nanism), hypogenitalism, and decrease of the function of the thyroid gland, endocrine-methabolic disorders and decrease of the reactivity.

When more than 95% of the mass of the gland are destroyed the adult people develop hypophysial cachexia or Simmond's disease. Ii: is characterized by severe cachexia and atrophy of the thyroid adrenal and sexual glands, the muscle tissue, visceral organs, destruction of the bone tissue, hair and teeth falling, functional disorders of the vegetative nervous system, hypoglycemia, increase of the sensitivity of the body to insulin. Most of disorders are connected to the termination of the production of somatotropin and thyrotropin.

Hypofunction of the Adenopituitary

The decreased production of any *hormone* of the pituitary is characteristic of the partial insufficiency of the adenopituitary. For example, early falling out or depressing of the somatotropic function of the pituitary leads to the development of dwarfism or pituitary nanism. The general diminution of the speed of synthesis of proteins leads to atrophy of the muscular and connective tissue, which is externally manifested by the flabbiness and aging of the skin. The sexual organs stay in the infantile condition. Partial gonadotropic insufficiency leads to infantilism: in the girls it leads to the absence of the menstruation, infertility; in boys it leads to the hypoplasia of the testis, incomplete physical development and hypogenitalism.

Hyperfunction of the Adenopituitary

Hyperfunction of somatotropin in the human body is exhibited as pituitary gigantism or acromegaly, depending on the age the pathology begins. Hypophysial gigantism develops in excessive secretion of somatotropin at the young age, before the epiphysial cartilages get closed. Hormonal shifts at the later age period, after closing the epiphysial sutures and completion of the growth, are the cause of acromegaly.

The source of the hypersecretion of somatotropin is the eosinophilic adenoma of the pituitary. In this disease separate parts of the body are disproportionately enlarged, the features of the face are sharply enlarged. Simultaneously splanchnomegaly (enlargement of the liver, the spleen and the heart, etc.) develops. These changes are stipulated by the growth of the soft tissues." In acromegaly the concentration of the somatotropin in the blood can exceed normal parameters 100 times and more. The pathologic influence of excessive quantity of somatotripin on the organism is determined by the ability of the hormone to increase the permeability of the cell membrane to amine acids. Also it has an ability to accelerate their inclusion in synthesized proteins, to stop disintegration proteolysis. Increased lypolysis and inhibition of the fat formation from the carbohydrates increase the mobilization of fat from depot, contents of non-estherised fatty acids in blood, their oxidation on the liver and formation of ketone bodies. It is due to the effect of somatotropin on different links of the carbohydrate metabolism that during acromegaly, hyperglycemia and diminution of sensitivity to insulin are always observed. Pathologic effect of somatotropin on the connective, bone and cartilage tissue is stipulated by ability of this hormone to stimulate pathologic formation of oxyproline (the most important component of collagen) and chondroitine sulphate. These and other effects of somatotropin are explained by the formation of a special albuminous factor — somatomedin, which is formed in the liver under the influence of somatotropin. The other form of hyperfunction of adenopituitary is the Itsenko — Cushing's disease that is characterized by magnification of the corticotropin output and as a consequence — excessive secretion of cortizol and other glycocorti- coids by the adrenal glands (Table 15, 16).

Table 15. Effects of glucocorticoids

Target tissue	Effect	Mechanism
Muscle	Catabolic	Inhibition of glucose uptake and metabolism. Decrease of protein synthesis. Increase of amino acids, lactate release
Fat	Lipolytic	Stimulating of lipolysis. Increase of FF As and glycerol release
Liver	Synthetic	Increase of gluconeogenesis. Increase of glucogen synthesis, storage. Increase of glucose-6- phosphatase activity. Increase of blood glucose
Immune system	Suppression	Reduce of number of circulating lymphocytes, monocytes, eosinophils, basophils. Inhibition of T-lymphocyte production of interleikin-2. Interfere with antigen processing, antibody production and clearance
	Antiinflammatory	Decrease of migration of neutrophils, monocytes, lymphocytes to sites of injury
	Other	Stimulation of neutrophils release from marrow. Interferance with neutrophils migration out of vascular compartment
Cardiovascular	Increase of cardiac output. Increase of peripheral vascular tone	Permission effect on catecholamines, contraction of the peripheral vessels
Renal	Increase of glomerular filtration rate. Aid in regulating water, electrolyte balance	Na^+ and water retention
Other	Permissive action. Resist ance to stress. Insulin antagonism	Increase of blood glucose

Table 16. Principal diseases of the adrenal gland

Glands part	Hyperfunction	Hypofunction
Cortex of the adrenal glands	Bilateral hyperplasia ACTH excess (affects mainly zona fasciculata and reticularis) Enzyme deficiencies Adenoma Primary hyperaldosteronism (Conn's syndrome) (zona glomerulosa) Hypercorticalism (Cushing's syndrome) (zona fasciculata) Virilization (zona reticularis) Carcinoma Cushing's syndrome Virilization Feminization (rare)	Bilateral adrenal gland destruction (Addison's disease) Autoimmune Infection Tuberculosis Histoplasmosis AIDS-related (CMV, disseminated Mycobacterium avium complex) Ischemia, shock Bacteremia (meningococcus, Pseudomonas) Hemorrhage, anticoagulation Metastatic tumor (lung carcinoma, other carcinomas, Kaposi's sarcoma)
Medulla of the adrenal glands	Pheochromocytoma Hyperplasia (rare) Other: ganglioneuroma, neuroblastoma	—

Dysfunction of Neurohypophysis

The increased secretion of vasopressin promotes the accumulation of the liquids in the organism. It plays an important role in the pathogenesis of reflex anuria (for example in pain shock) and edema, especially cirrhosis of the liver, when it disturbs the inactivation of the hormones.

The insufficiency of vasopressin arises when the pituitary is removed, when the supraoptic, paraventricular nucleus or hypothalamo-neurohypophyseal neurons gets affected. As a rule diabetes insipidus develops.

Both absolute and relative insufficiency of vasopressin disturbs the reabsorption of water in the tubules of the nephron that results in polyuria and hypotension. The patients excrete 38 liters of urine

with low relative density per day. Sometimes diuresis consists of 10-12 liters, and in cases — 40-43 liters.

Hypofunction of the Cortical Substance of the Adrenal Glands

After adrenal ectomy the depot of glycogen in the liver and muscles is exhausted. It is due to a reduction of glucose-6-phosphatase activity, the speed of glycogenolysis in the ceils of the liver is reduced. The formation of glucose from amine acids is delayed simultaneously. All this leads to hypoglicemia, reduces sensitivity to insulin, increases the tolerance to glucose.

On the later stage of adrenal insufficiency blood pressure is decreased. Hypotension is conditioned by reduction of the volume of the circulating blood, bradicardia and the weakening of the vasoconstrictor action of catecholamins, for which corticosteroids are psrmisive factor.

In the genesis of the acute adrenal gland insuffisiency the major role is played by the disorders of the water-electrolyte metabolism. In physiological conditions aldosteron supports work of sodium "pump", ensures the reabsorption of sodium ions in the distal parts of the tubules of the nephron, but glucocorticoids increase the glomerular filtration.

After removal of the adrenal glands the sodium ions go out of the body with the urine and that's why the contents of sodium in plasma of blood are reduced. At the beginning there is marked polyuria and than oliguria and anuria. Simultaneously "water poisoning", i. e. high cells hydration develops. It is explained by the fact that due to disorders of sodium pump the intracellular concentration of sodium ions and the osmotic pressure are increased. The sharp increase of concentration of potasium ions in plasma is the cause of disturbance of bioelectric processes, force and rhythm of cardiac contractions (up to ciliary arrhythmia), weakening of the contractive ability of the striated muscle tissue.

In a terminal stage of acute adrenal gland insufficiency, the urination completely stops. The pulse and the breathening are slowered down. The animal goes in coma and dies. The life term of dogs and cats with ectomized adrenal gland ranges from 2-3 days up to 9-11 days.

Acute adrenocortical insufficiency in a human can happen due to hemorrhage in the adrenal glands.

Chronic insufficiency of cortical substance of the adrenal gland in a human is known under the name of Addisson's disease, (bronzed disease). It arises more often because of tuberculosis of the adrenal glands, atrophy of the cortical substance after heavy infectious diseases or prolonged treatment by corticosteroid preparations.

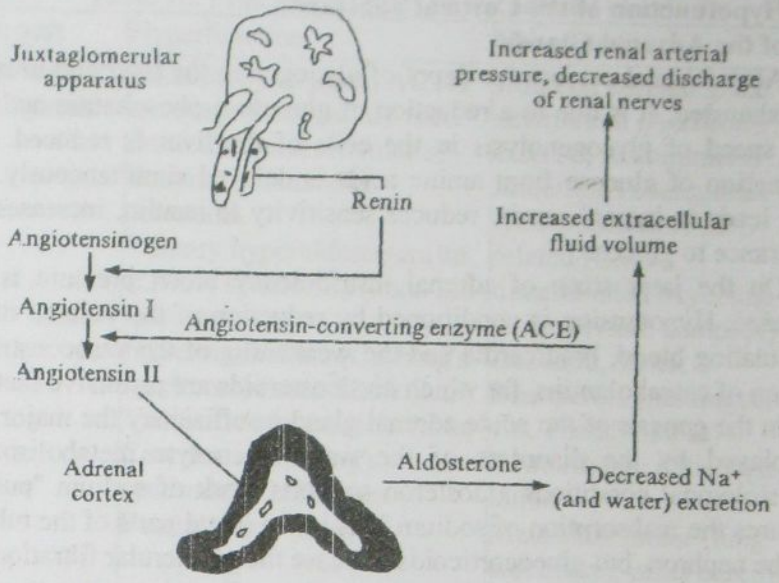

Fig. 42. Feedback mechanism regulating aldosterone secretion

Chronic hypoadrenocorticism is characterized by emaciation, fast psychical tiredness, bad appetite, dysfunction of the alimentary canal, arterial hypotension, progressing of hyperpegmentation of the skin. The mechanism of hyperpegmentation is connected with intensification of melanostimulating activity of the hypophysis, which is concomitant to the increase of corticotropin secretion during hypoadrenocorticism. In the patient with Addison's disease, different pathogenic effects such as trauma, infection, hemorrhages and even tooth extraction can cause acute insuffisiency of the cortical substance of the adrenal glands.

Hyperfunction and Dysfunction of the Cortical Substance of the Adrenal Glands

The excessive secretion of cortisole (Itsenko — Cushing's syndrom) aldosteron (hyperaldosteronism), androgens (adrenogenital syndrome) or estrogens (corticoestroma) are the leading pathogenic points, determining the clinical picture of hyperfunction and dysfunction of the cortical substance.

Etiology of Itsenko — Cushing's syndrome and Itsenko — Cushing's disease is various, but the clinical symptoms and the pathogenesis of disturbances are very similar. The disease arises as a result of the excessive secretion of corticotropin in adenohypophysis tumors or diencephalic

regulation disorder; the syndrome is the result of the primary affection of the cortical substance of the adrenal glands by tumor.

Under the influence of excessive aldosterone, sodium and water ions are retained in the organism (Fig. 42) The high concentration of sodium ions in the cells, especially in vessels walls increases their sensitivity to sympathetic mediators. In consequence arterial hypertension develops. Loss of considerable amount of potassium and chlorine ions cause myasthenia and paresis, attack of the skeleton muscular cramps, disorders of myocardial contractive function, nongas alkaloids. The tubules of the nephrones are subject to dystrophic change and lose ability to react with vasopressin. So, poliuria arises, which explains absence of edemas in primary hyperaldosteronism.

In many pathologic conditions (cardiac insufficiency, cirrhosis of the liver, kidney diseases with disorders of kidneys circulation, etc.), excessive production of aldosterone is observed (secondary hyperaldosteronism). Decrease of blood pressure, hypovolemia, and insufficiency of kidney depressor system and increased secretion of rennin by juxtaglomerular cells with the following formation of angiotensin II and III play the main role in development of its mechanism. It is known that cells in the clustered zone of the adrenal glands intensify production of aldosterone under the influence of angiotensin II and III, ACTH (permissive effect), abundance of K^+ and Na^+ deficit in blood plasma. Atrium natriuretical hormone (antagonist of angiotensin II), dopamine and high outcellular Na^+ concentration inhibit secretion of aldosterone.

Second hyperaldosteronism promotes retention of sodium and water in the organism, loss of potassium and chlorine, development of edema, increase of blood pressure.

Adrenogenital Syndrome

Adrenogenital syndrome in a child is a clinical manifestation of congenital hyperplasia of the cortical substance of the adrenal glands.

Arising of the syndrome is connected with hereditary blockade of Cortisol synthesis. Secretion of corticotropin becomes disinhibited which stimulates secretion of androgens of the adrenal glands. The latter has a virilizing effect — appearance and more evident signs of the masculine sex in the intrauterine period. Consequences of hormonal disorders may be different — from mild masculinisation to severe anatomic abnormalities of physical and sexual development.

In boys this pathology cause premature development of the second

sexual signs, girls often are born with pseudogermaphrodism. One of the androgenital syndrome variants in children is characterized by deep disorder of ferments, which participate in biosynthesis of steroid hormones and accompanied by severe disorders of water-electrolyte metabolism (syndrome of salt loss). Without substitutional therapy with corticosteroids children die at early age.

If the hormone synthesis is blocked at the last stage, which is catalizated by 1.1-hydroxilase, the excess of desoxicosterone is formed (steroid with mineralocorticoids properties). In consequence, severe arterial hypertension develops.

Adults and children can have hyperestrogenisation and hyperandrogenisation of the organism in tumor regeneration of net (internal) zone of the adrenal glands cortical substance. Depending on hormone secretion character, women can have development of virilisation, men can have feminization (heterosexual syndrome) or person have premature sexual development (isosexual syndrome).

Dysfunction of the Cerebral

Substance of the Adrenal Glands

Hypersecretion of catecholamines is observed in pheochromocytome — tumor originated from the cerebral substance of the adrenal glands with paroxysmal or stable arterial hypertension or attack of tachycardia, acute pain in epigastrium, profuse sweating. The attack is a result of massive throw out of adrenaline and noradrenaline into blood under the influence of psychical and physical loading and other provocatory effects.

COMPREHENSION CHECK

Try to answer the following questions.

1. How does general adaptation syndrome develop?
2. Characterize disorders of the hypothalamic-hypophysial systems.
3. Describe hyper- and hypofunction of cortical substances of the adrenal glands.

UNIT 29

PATHOPHYSIOLOGY OF THE THYROID AND PARATHYROID GLANDS. PATHOLOGY OF SOME THYROID DISEASES

There are five types of thyroid dysfunctions:

1. Hyperthyroidism (thyrotoxicosis), caused by an excess of thyroid hormone.
2. Hypothyroidism (myxedema), caused by a deficiency of thyroid hormone.
3. Goiter (Basedow's disease), a diffuse enlargement of the thyroid gland, caused by promoted elevation of TSH.
4. Thyroid nodule,, a focal enlargement of a portion of a gland, caused by a benign or malignant neoplasm.
5. Abnormal thyroid functions tests in a clinically euthyroid patient.

The pathogenesis of the most common thyroid diseases probably involves an autoimmune process with sensitization of the host's own lymphocytes of various thyroidal antigens. Three major thyroidal antigens have been documented: thyroglobulin (Tg), thyroidal peroxidase (TPO), and the TSH receptor (TSH-R). Both environmental factors (e.g. viral or bacterial infection or a high iodine intake) and genetic factors (e.g. defect in suppressor T lymphocytes) may be responsible for initiating of autoimmune thyroid disease.

HYPERTHYROIDISM

The main cause of excess production of thyroid hormones are following (Table 17):

Increase of thyroid hormones production, weakening of both thyroxin with thyroxin connected globulin, disorders of the metabolism of the thyroid gland hormones or the increase of sensitivity of the tissues — targets to their influence, lead to development of thyrotoxicosis. The most often manifestation is the *diffuse toxic goiter (Basedow's disease).*

Basedow's disease is characterized by typical syndrome: enlargement of the thyroid gland, exophtalm, increase of heat production, tachycardia, shivering of the fingers, increase of the mental excitability. These and many other pathologic phenomena are conditioned by the toxic action of the exceeding quantity of thyroxin and thriiodtyronine.

The most important etiological factor of thyrotoxicosis for the person is the mental trauma. Infection and overcooling are considered to

be predisposing factors. In abundance of thyroxin and thriiodtyronine, the number of mitochondria in the cells increases, they swell ("the disease of mitochondria"), increase the activity of oxidizing ferments (succinatdehydrogenase, cytochromeoxidase, α-glycerophosphate-dehydrogenase), Na^+, ATP-ase, etc.

Etiological classification	Pathogenetic mechanism
Thyroid hormone overproduction	
Graves' disease	Thyroid-stimulating hormone receptor-stimulating antibody (TSH-R [StimJAb)
Toxic multinodular goiter Follicular adenoma Pituitary adenoma Pituitary insensitivity	Autonomous hyperfunction Autonomous hyperfunction
Hypothalamic disease	TSH hypersecretion (rare)
Germ cell tumors: chorilocarcinoma, hydatidiform mole	Resistance to thyroid hormone (rare)
Struma ovari (ovarian teratoma)	Excess of TRH production HCG stimulation
Metastatic follicular thyroid carcinoma	Functioning thyroid elements Functioning metastases
Thyroid gland destruction	Release of stored hormone
Lymphocytic thyroiditis	Release of stored hormone
Granulomatous (subacute) thyroiditis	Transient release of stored hormone
Hashimoto's thyroiditis	
Other	Ingestion of excessive exogenous thyroid hormone
Thyrotoxicosis medicamentosa, thyrotoxicosis factitia	

Negative nitrogen balance in thyrotoxicosis gives evidence of the predominance of catabolism of proteins. Due to the high disintegration of glycogen in the liver and muscle tissue hyperglycemia is marked. The utilization of glucose in the tissues is accelerated, the activity of gexokinase is increased.

The abundance of the thyroid hormones inhibits the transition of carbohydrates in fats, accelerates disintegration of cholesterol and its utilization of the tissues, intensifies oxidation of the fats in the liver and also increases the sensitivity of fatty tissues to lipolytic action of adrenaline. Due to these changes mobilization of fats from depot arises, explaining why the patients with thyrotoxicosis lose their weight and why hypercholesterinemia and ketonemia occure in these patients.

The thyroid hormones disturb the metabolism of the cardiac muscle. Dystrophic changes in the myocardium, disturbance of atrial-ventricular conductivity, overloading of the left ventricle are revealed. The energetic and plastic maintenance of the cardiac activity, is disturbed. "Thyrotoxic" heart reacts inadequately to cholinergic and adrenergic influences.

HYPOTHYROIDISM. CAUSES AND PATHOLOGICAL MECHANISMS

Etiological factors of hypothyrosis in the people are the congenital defects of biosynthesis of the thyroid hormones. Congenital hypoplasia or aplasia of the thyroid gland, autoimmune and infectious processes in the glandular epithelium in surgical intervention, damage of the gland by thyrostatic preparations, radioactive iodine due to overdosage or allowable medical doses, radioactive pollution of the locality, etc. The most often cause of hypothyrosis is insufficiency of iodine and probably cobalt coming into the organism.

In severe degree of insufficiency of the thyroid gland, congenial or arisen in the early childhood cretinism develops, in the adult people — *myxedema* (hypothyrosis accompanying by mucous edema).

Myxedema is characterized by decrease of metabolism and body temperature, obesity, and immobility. As a result of the increased hydration of the skin and subcutaneous tissue and the high accumulation of hydrophilic mucous substances in them the face becomes puffy with poor mimics, the nose and the lips become thicker. Brittleness of the nails, hear falling out and other trophic disorders are marked. The sexual function gradually subsides, the intelligence decreases, memory is reduced, apathy and sleepiness appear, and in the late period of the disease dementia appears.

The enlargement of the thyroid gland due to iodine insufficiency is known as endemic goiter. This disease is widespread in Alp and other mountain regions of the world, where the salt and water contain little amount of iodine. The deficiency of iodine stipulates decrease of thyroxin and thryiodthyronine synthesis and due to this the production of thyrotropin increases in the pituitary. In its turn it leads to hyperplasia of the thyroid glands, whose mass sometimes reaches some kilograms.

Table 18. Causes and pathological mechanisms

Etiologic classification	Pathogenic mechanism
Congenital	Aplasia or hypoplasia of thyroid gland Defects in hormone biosynthesis or action
Acquired	
Hashimoto's thyroiditis	Autoimmune destruction
Severe iodine deficiency	Diminished hormone synthesis, release
Lymphocytic thyroiditis	Diminished hormone synthesis, release
Thyroid ablation	Diminished hormone synthesis, release
Thyroid surgery	
I^{131} irradiation treatment of hyperthyroidism	
External beam radiation therapy of head and neck cancer	
Drugs	Diminished hormone synthesis, release
Iodine, inorganic	
Iodine, organic (amiodarone)	
Thioamides (propylthiouracil methimasole)	
Potassium perchlorate	
Thiocyanate	
Lithium	
Hypopituitarism	Deficient TSH secretion
Hypothalamic disease	Deficient TRH secretion

Disturbance of Calcitonin Secretion

Calcitonin interacts with receptors in kidneys and bones. This interaction stimulates adenyl cyclase activity and the generation of cAMP. In the kidneys, receptors for calcitonin are localized in the cortical ascending limb of Henle's loop, while in bones, calcitonin receptors are found on osteoclasts.

The main function of calcitonin is to lower serum calcium, and this hormone is rapidly released in response to hypercalcemia. Calcitonin inhibits osteoclastic bone resorption and rapidly blocks the release of calcium and phosphate from bones. The latter effect is apparent within minutes after the administration of calcitonin. This effect, along with the inhibition of resorption, ultimately leads to a fall in serum calcium and phosphate.

Calcitonin accomplishes its antiresorptive effect by acting directly on the osteoclast. Calcitonin blocks bone resorption induced by a variety of

hormones, including PTH and vitamin D. The potency of calcitonin depends on the underlying rate of bone resorption. Calcitonin also has a modest affect on the kidney to produce mild phosphaturia. With prolonged administration of calcitonin, "escape" from its effects occurs.

PATHOPHYSIOLOGY OF SELECTED DISORDERS OF PARATHYROID GLAND

Primary hyperparathyroidism occurs due to excessive production and release of PTH by the parathyroid gland. The mainly cause: adenoma 80-85%, carcinoma — 2-5%, diffuse hyperplasia — 10% (Table 19).

Table 19. Symptoms and signs of primary hyperparathyroidism

Systemic	Weakness Easy fatigue Weight loss Anemia Anorexia Pruritus Ectopic calcifications
Neuropsychiatrie	Depression Poor concentration Memory deficits Peripheral sensory neuropathy Motor neuropathy Proximal and generalized muscle weakness
Ocular	Band keratopathy
Cardiac	Shortened **Q-T** interval Hypertension
Renal	Stones Polyuria, polydipsia Metabolic acidosis Concentrating defects Nephrocaicinosis
Skeletal	Osteopenia Pathologic fractures Brown tumors of bone Bone pain Gout Pseudogout Chondrocalcinosis Osteitis fibrosa cystica
Gastrointestinal	Peptic ulcer disease Pancreatitis Constipation Nausea Vomiting

Secondary hyperparathyroidism — due to a defect outside the parathyroid gland. In patients with chronic renal failure, there are many causative factors that contribute to the often dramatic enlargement of the parathyroid glands. These include decreased 1,25- $(OH)_2D$ production, reduced intestinal Ca absorption, skeletal resistance to PTH, and renal phosphate retention. In most cases of secondary hyperparathyroidism, parathyroid hyperplasia regresses substantially with correcting underlying abnormality.

When the secretion of parathirine increases, the formation and the

activity of the osteoclasts, which realize the resorption of the bone intensifies, their differentiation into the osteoblasts inhibits. They participate in the formation of the bone tissue. The absorption of calcium in the intestine increases, the reverse reabsorption of the phosphate ions in the tubules of the nephrons gets decreased, the formation of the soluble salts of calcium in the bone tissue and insoluble phosphate calcium in different organs especially in the kidneys also increased.

Experimental chronic parathyrosis. In this case we observe osteoporosis, accumulation of the calcium salts in the kidneys, the lungs, the heart and other intestinal organs. The walls of the vessels become thick, and the blood pressure increases. The animals die from anemia as a rule. The origin of hyperparathyrosis in the people is connected with adenoma or hyperplasia of the parathyroid gland. General fibrosis, osteodystrophy develops and its characterized by pain in the muscles, in the bones, articulations, osteomalacia, deformation of the skeleton. Mineral components go out from the bones and accumulate in the muscles and the internal organs. Nephracalcinoses, constriction of the lumen of the tubules of the nephrons or their occlusion by calculi (nephrolithiasis) develop that result in severe renal insufficiency. Due to calcareous de- positon the wall of the magistral vessels hemodynamics and blood supply of the tissues are disturbed.

Hypoparathyroidism

Causes of hypoparathyroidism:

1. Complication of thyroid or parathyroid surgery.
2. Autoimmune.
3. Post- I^{131} therapy for Graves' disease or thyroid cancer.
4. Secondary to iron overload, Wilson's disease.
5. DiGeorge syndrome: autosomal recessive disorder with congenital absence of the parathyroid glands and thymic dysgenesis or agenesis.
6. Hereditary forms of hypoparathyroidism: autosomal dominant or recessive and X-linked recessive.
7. Secondary to magnesium depletion.
8. Tumor invasion (very rare).
9. Hereditary nephrosis, nerve deafness and hypoparathyroidism.

The main kinds of hypoparathyroidism is hypocalcemia, which may lead to different disturbances (Table 20).

Dysfunction of the parathyroid glands results in development of parathyroprival tetany. In the experiment it is reproduced by removal of the glands in dogs and cats. In 1-2 days after the operation the animals become flaccid, they refuse to take food, have thirst, low body temperature, dyspnoe. There is a change of correlation of one-valent (Na, K) and two-valent (Ca, Mg) ions due to reduction of calcium concentration in blood from 2.25-2.99 to 1.0-1.25 mmol/1. As a result sharp increase of neuro-muscular excitability is noticed. There is multiple fibrillar concentration of the body muscles, which are then followed by episodes of clonic convulsions. Clonic convulsions change into tonic ones, opisthotonus comes (sharp bending of the trunk with the head throwing back). Spasm contractions may spread to the inner organs (pylorospasm, laryngospasm). The animals die during one of such episodes.

Table 20. Symptoms ana signs of hypocalcemia

Systemic	Confusion Weakness Mental retardation Behavioral changes
Neuromuscular	Paresthesias Psychosis Seizures Chvostek's and Trousseau's signs Depression Muscle cramping Parkinsonism Irritability Basal ganglia calcifications
Cardiac	Prolonged Q-T interval T wave changes Congestive heart failure
Ocular	Cataracts
Dental	Enamel hypoplasia Defective root formation Failure of adult teeth to erupt
Respiratory	Laryngospasm Bronchospasm Stridor

Simultaneously with hypocalcemia blood has increased contents of non-organic phosphorus. The disturbances of mineral exchange are conditioned by inhibition of resorption of the bone tissue, absorption of the calcium in the intestines and increased reabsorption of phosphates in the tubules of the nephrons.

A definite importance is attributed to the disturbance of desintoxicating function of the liver in the pathogenesis of parathyroprival tetany, feeding of parathyroectomized dogs on meat intensifies tetany due to insufficient disintoxication of products of nitrous

metabolism, in particular, weakened ability of the liver to convert ammonium into urea.

Relative hypofunction of the glands is marked in accelerated growth, pregnancy, lactation and other conditions when the organism requires more calcium and salts of calcium.

Pathogenesis and clinical picture of hypoparathyroidism in the human are close to those observed in the experiment.

Increase of neuro-muscular excitability. Children of 1st and 2nd year of life in combination with rickets may have spasmophilia — periodic spasms of the muscles, arising in the increase of the environmental temperature and other unfavorable influences.

Laryngospasm is very dangerous as it may cause asphyxia and death.

COMPREHENSION CHECK

Try to answer the following questions.

1. Characterize the manifestations of hypo- and hyperthyroidism.
2. Distinguish between primary and secondary hyper and hypoparathyroidism.

UNIT 30

PATHOPHYSIOLOGY OF THE NERVOUS SYSTEM

Disorder of the nervous system activity may appear as a result of the influence of different endogenous and exogenous factors, influencing metabolism, structure and function of the nervous cells of the organism.

First of all it is necessary to mark, that the nervous system and especially its central sections are very sensitive to hypoxia. The brain consumes about 20% of oxygen entering the organism. At a sudden termination of oxygen supply of the brain (inhalation of oxygen-free gaseous mixtures, disturbance of cellular circulation) loss of consciousness comes in 6-7 s, in 15 s normal bioelectric activity of the brain stops. Fool restoration of the brain function in such cases is possible when the duration of circulation standstill does not exceed 5-6 min. If ischemia of the brain continues, longer memory and intellect will be irreversibly disturbed.

It should be marked that different parts of the central nervous system possess different sensitivity to oxygen deficiency. Phylogenetic old structures are more stable to hypoxia.

Pathogenic influence on the nervous system may be produced by such physical factors as ionizing radiation, electric current, noise, vibration, electromagnetic field, mechanical trauma, high and low temperature.

The nervous system function may be disturbed by action of different toxic substances of natural and artificial origin. One can distinguish a large group of the so-called neurotropic poisons which can selectively disturb bioenergic processes in the nervous cells, formation, transportation, excretion and metabolism of neuromediators; influence on permeability of ionic canals in neurons.

The brain is very sensitive to hypoglycemia. Practically all oxygen consumed by the brain is used by oxidation of glucose. At a sharp decrease of the level of glucose in the blood a disturbance of biological currents of the brain takes place. And loss of consciousness may occur. Prolonged hypoglycemia causes irreversible damages to the brain cortex. At more marked hypoglycemia the functions regulated by the truncal mechanisms are disturbed. Disorders of the nervous system activity are observed in the changes of concentration of electrolytes and hydrogen ions in blood.

Starvation, the vitamin starvation in particular, often causes disturbances of the nervous activity.

Influence of aging on the structure and functions of the nervous system is beyond doubt.

With the age atrophy of neurons takes place that leads to the decrease of the brain mass. During this process the decrease of mass of neurons occurs in different speed in different parts of the brain and it starts in different time.

The functions of the nervous system may be disturbed by reflex under the influence of strong and extraordinary actions upon external and internal receptors. Social factors occupy an important place among the reactions which cause the nervous system disturbances. A man possesses the second signal system. With the help of images symbols and notions a model of the surrounding world is created in his imagination. Prolonged or frequent conflict situations which are connected with peculiarities of personality of an individual and with the character of his social environment, organization of society on the whole, conditions of labour and mode of life may lead to an excessive stimulation of emotional centers and disturbances of the higher nervous activity of a man, development of neurotic states, psychic diseases and different psychosomatic disturbances connected with them.

The nervous system pathology may be hereditary. Sometimes affection of the nervous system in hereditary diseases may have a secondary character (e.g. phenylketonuria).

Disturbances of the nervous system activity are possible as a result of development of typical pathologic processes — inflammations, tumors, local disturbances of blood circulation.

Universal mechanisms of disturbances of the neuron functions are the following: loss of ability to maintain the definite quantity of membranous potential by the nervous cell, to generate action potentials and to lead them by processes, to pass excitation from one nervous cell to another one. Decrease of the quantity of interneuronal contacts in the process of some pathologic processes development is possibly one of the significant mechanisms of disturbances of the nervous system functions.

The disturbance of formation, excretion, and disintegration of mediators may be an important link in pathogenesis of many disorders of the nervous system activity. Besides, at present there are many facts that the activity of the nervous system and especially of its higher

sections is defined mainly by substances of the peptide nature (neuropeptides), which are produced both by the nervous and other cells and carry out mediatory and non-mediatory functions. Opiate brain systems the work of which is regulated by endorphins and encephalins are the most studied. However in the brain of the man and animals scores of other oligopeptides were discovered, injections *of which into the* cerebral ventricles or directly into the nervous centers may cause different emotional states and behaviour reactions, influence on elaboration of conditional reflexes, ability to memorize, to study etc. Probably in pathogenesis of disorders of the nervous system functions insufficiency of excessive formation of neuropeptides, change of sensitivity of nervous cells to them may have significance.

Pathology of the nervous system may be as follows:

I. Congenital disorders.

1. Neural tube defects:

a) spina bifida: failure of posterior vertebra arches to close;

b) ancephalopathy.

2. Hydrocephalus — denotes increased volume of cerebrospinal fluid (CSF) within the cranial cavity (ventricles).

3. Fetal alcohol syndrome is associated with excessive maternal alcohol intake during pregnancy. It's characterized by facial abnormalities and developmental defects such as microcephaly, atrial septal defect and other anomalies.

II. Cerebrovascular disease is the most common group of the central nervous system (CNS) disorders; it ranks after heart disease and cancer the third major cause of death in the United States. I

1. Infarction is caused by arterial occlusion from:

a) thrombosis which is most often caused by atherosclerosis;

b) embolism by cardiac mural thrombi vegetations of infect endocardiac valves, clumps of tumor cells, bubbles of air, or droplets of fat.

2. Hemorrhage (intracerebral, subarachnoidal) consists of bleeding into the brain space or subarachnoidal space).

3. Transient ischemic attacks (TIAs) are brief episodes of impaired neurologic functions caused by temporary disturbance of cerebral circulation.

III. Head injuries result from penetrating wounds, which in addition to brain damage can predispose to infection.

IV. Infections.

1. Pyogenic meningitis.

2. Cerebral abscess.
3. Tuberculosis..
4. Fungal infection.
5. Toxoplasmosis.
6. Viral infection (meningoencephalitis and encephalitis). Human immunodeficiency virus (HIV) can cause nervous system dysfunction, may affect the brain, spinal cord, or peripheral nervous system by direct HIV infection.

V. ***Demyelinating diseases*** are characterized by destruction of myelin with relative preservations of axons — multiple sclerosis.

VI. ***Degenerative diseases:***

1. *Alzheimer's disease* — is the most important cause of dementia (progressive dementia, decreased number of neurons in nucleus basalis, generalized cerebral atrophy, granulovascular degeneration), especially affecting temporal and frontal lobes.

2. *Huntington's disease* — autosomal dominant disorder with delay of onset of clinical abnormalities to the age of 30-40. Atrophy, numeral depletion and gliosis of caudatum, putamen and frontal cortex. It causes chorea and athetoid movements, progressive motor deterioration, motor deficits (bradykinesia, akinesia) or abnormal activation of the motor system, resulting in rigidity, tremor, involuntary movements (rapid, jerky — chorea and slow writing movements of the proximal limbs and trunk — in athetosis).

3. *Parkinsonism (paralysis of old age)* usually occurs after the age of 50. There are degeneration of nigral neurons; leads to loss of dopaminergic inhibition and relative excess of cholinergic activity. Remember, dopamine is synthesized by neurons in the substantia nigra.

Universal mechanisms of disturbances of all functions are the following: loss of ability to maintain the definite quantity of membranous potential by the nervous cell due to disturbance in passing excitation from one nervous cell to another one, from one part of the nervous system to another one.

If the nervous system (its components — nerves and others) is damaged so much that its connection with the body of neuron is lost, it degenerates and then the cessation of axoplasmatic flow and transportation of substances of axoplasm occur.

The cessation of the ***moving*** function leads to ***paralyses*** or ***parhesis.*** The pathologic processes and the disturbances of the ***sensitivity*** are called ***hyperesthesia*** (the increase of it), ***hypoesthesia*** (the decrease

of it) and ***anesthesia*** (the lack of sensitivity).

Depending on the character of the lost sensitivity there are distinguished the tactile anesthesia (strictly anesthesia), the analgesia alerga, the thermal one (thermanesthesia) and loss of deep or proprioceptive sensitivity.

If the pathologic process is located in the spinal cord or in the brain, the disorder of sensitivity depends on the disturbance of the ascending pathways. There are two centripetal systems of sensitivity. One of them is called lemnisk and contains the nervous fibers of large diameter which conduct stimuli from the propriorecep- tors muscles, sinews, joints and partially from cutaneous receptors of touch and pressure (tactile receptors). The fibers of this system are included in the spinal cord and pass in the structure of the posterior column into medulla oblongata. From nuclei of the medulla oblongata the medial loop (lemnisk pathway) begins which passes on the opposite side and ends in the posterolateral ventral nuclei of thalamus, neuron of which transmit the obtained information of the somatosensory zone of the cortex of the brain. The second ascending system in the spinothalamic (anterior and lateral) pathway carrying pain, temperature and partially tactile sensitivity. Its fibers go up in the structure of the anterior and lateral funiculi of the spinal cord and terminate in the cells of nuclei of the thalamus (anterolateral system). Rather characteristic changes of sensitivity are observed at cutting of the right or left half of the spinal cord (Brown — Sequard's syndrome): on the side of cutting the deep sensitivity disappears while temperature and pain ones disappear on the opposite side, as the conductive pathways relating to the anterolateral system intersect in the spinal cord. The tactile sensitivity is partially disturbed on both sides. The disorder of the lemnisk system is possible in damage of the peripheral nerves (thick myelinic fibers) and also in various pathologic processes in the spinal cord (disturbance of blood circulation, traumas, inflammation). The isolated damage of the posterior funiculi of the spinal cord occurs seldom, but like other conductive pathways they can be damaged by tumor or during trauma. The disturbance of conductivity in the fibers of the medial loop causes various disorders of sensitivity, manifestation of which depends on the degree of the damage of the system. Thus the ability to determinate speed and direction of motion of the limbs may be lost. The feeling of separate perception of touch simultaneously in two places and also the ability to feel vibration and to evaluate the weight of lifted load are

considerably disturbed. The examine isn't able to determine the shape of subjects touching them and to identify the letters and writing them on the skin he feels only mechanical touch and isn't able to indicate place and force of tactile sensation exactly. Thus the sensation of pain and temperature sensitivity are preserved.

Damage of postcentral gyrus of the cortex of the brain

In the monkeys removes of the postcentral gyrus of the cortex causes the disturbance of sensitivity on the opposite part of the body. In general one considers the character of these disturbances from the knowledge about the functions of the lemnisk system and that such an operation causes lemnisk denervation on the opposite side on which elements of the anterolateral system, however, are preserved. Obviously, the disturbance consists in the loss of the muscular sensitivity. The animal often terminates motion remaining in an inconvenient position for a long time. At the same time the tactile, pain and temperature sensitivity on this side are preserved although their threshold can be increased. In the human the isolated damage of the postcentral gyrus occurs very seldom. For example, sometimes surgeons remove a part of this gyrus for treatment of epilepsy of the cortical origin. In this case circumscribed disorders appear: sensation of the limbs in space, ability to determine the shape of subjects, their size, weight, character of a surface (smooth, rough, etc.) by touch and discriminating sense are lost.

COMPREHENSION CHECK

Try to answer the following questions.

1. Characterize the causes and universal mechanisms of disturbances of different part of the nervous system.
2. What is Alzheimer's disease?
3. Describe parkinsonism and its mechanism.
4. Characterize consequences of motor and sensitive functions of the nervous system.

UNIT 31

NERVOUS TROPHICITY AND DYSTROPHIC PROCESS. PAIN

NERVOUS TROPHICITY AND DYSTROPHIC PROCESS

Nervous trophicity is realised in such action of the nerves on the tissue which results in metabolism changes according to the needs at each given moment. It means that the trophic action of the nerves is closely connected with their other functions (sensitive, motor, secretory) and together with them provides an optimum function of each organ. The first proofs of the nervous influence on trophicity of the tissues were obtained in 1824 by a French scientist Majandy. In experiments on the rabbits he has cut the trigeminal nerve and revealed ulcer in the zone of sensitive denervation (the eye, lip). The trophic disorders develop in any organ if its innervations is disturbed by the intervention of the nerves (afferent, efferent, vegetative) or nervous centers. The medical practice can give a number of facts which also give evidence that the damage of the nervous system (trauma, inflammation) may cause the corresponding damage of ulcer or other disorders in the appropriate zone (edema, erosion, necrosis).

Biochemical, Structural and Functional Changes in the Denervated Tissue

The experience has shown that the pathogenic effects on the peripheral nerve are always accompanied by change of metabolism in an appropriate organ. It concerns carbohydrates, fats, proteins, nucleic acids, etc. There are observed not only quantitative but also qualitative changes. So, myosin in the denervated muscle loses its ATPase properties and glycogen in its structure becomes simple.

The reorganization of the fermentative process is observed. Thus, isofermentative spectrum of lactate dehydrogenase varies for the benefit of LDG_4 and LDG_5, i. e. those ferments which are adapted 1:0 the anaerobic conditions. The activity of such ferments as succinic dehydrogenase decreases. The common tendency of changes of metabolism consists in that it acquires an embryonal character i. e. glycolytic process begins to predominate in while the oxidizing one drops. The power of Krebs cycle is weakened, the output of macroergs decreases, the energy potential is lowered.

In disorder of innervations there are essential morphological changes in tissues. If one speaks about the cornea, skin or mucosa, all stages of inflammation develops. At the same time the removal of infection, trauma, drying doesn't prevent the process but delay its development. Finally ulcer appears which has no tendency to healing. The investigation of a thin structure shows the change of the organelles. Mitochondria decrease in quantity, their matrix is exhibited. Obviously the disorder of oxidizing phosphorilation and Ca-accumulating ability of mitochondria together with energic abilities of the cell are connected with this. The mitotic activity is reduced in the denervated tissues.

As to the functional disorders of development of the neurodystrophic process, the consequences of denervation will be different according to them. For example, the skeletal muscle denervation loses the main functions, their ability to contract. The cordial muscle contracts even in cutting of all extracordial nerves. The salivary gland will secrete saliva, but the character will not depend on a kind of food. A. Henon (1937) established the skeletal muscles deprived of the sympathetic nerves react on adrenaline not less, but more than in the norm; the same muscles separated from the motor (cholinergic) nerves react on acetylcholine more than in the norm. So, the law of denervation was opened, which means the increased sensitivity of denervated structures. In particular it is connected with the capacity of cholinoreceptors which are concentrated in the normal muscles only in the area of myoneural synapses. After denervation membranes of myocyte appear on the entire surface. Now it is known that the singularity of the response of denervated structures consists not only in increase but also in perversion when, for example, instead of relaxation of the vascular muscles, they contract. It is easy to imagine what it will mean, for example, for vessels, for blood circulation. The question is important: co special trophic nerves exist?

F. Majandy at his time assumed that side by side with the sensitive, motor and secretory nerves there are also the special trophic ones, which regulate the tissue nutrition, i. e. assimilating of nutritious material.

Later on I. P Pavlov (1883) in the experiment on animals among the nerves, coming to the heart, found such a branch, which increases the power of systole without any influence on blood circulation. I. P. Pavlov called this nerve "amplifying" and reorganized it to be purely trophic. I. P. Pavlov saw the complete and harmonious heart

innervations in the triple nervous provision: the functional nerves, vasomotor nerves, regulating the supply of the nutritious material and trophic nerves, defining the final utilization of these substances.

L. Orbelli was of the same opinion.

However, the above said doesn't mean that the trophic (sympathetic) nerves have no other influence on the tissue or that the motor (secretory) ones have no influence on metabolism. A. D. Speransky (1935) said that all nerves influence on metabolism, there are no nontrophic nerves — "the nerve is functional just because it is trophic".

Mechanisms of the Trophic Influence of the Nerves

Today nobody doubts that the nerves influence on trophicity: but how is this process accomplished? There are two points of view. Some consider that trophicity isn't an independent nervous function. The nervous stimulus which sets an organ in motion (for example, muscle) changes metabolism in the cell (acetylcholine activates metabolism and ferments, which stimulate increasing permeability). Others think that it is impossible to reduce trophicity to impulsive (mediator) action of the nerve. The new researches have shown that the nerve has a second function, named unimpulsive. Its essence consists of that the flow axoplasm is made as in both sides, and the substances move by process of the neuron, penetrate through synapses and appear in the innervated cells (muscular, etc.). Thus, now it is known that these substances exert a specific action on the effectory cell. The surgical operation when the nerve intended for the red muscle, grows into the white one showed that the radical changes occurred in its metabolism.

The common conclusion is that the trophic action of the nervous system consists of two elements: impulsive and unimpulsive. The later is accomplished by the substances of trophicity, nature of which becomes clear.

Pathogenesis ot Neurogenic Dystrophy

While analyzing the process it is necessary to know that the trophic function is made according to the principle of reflex. And it means that in the analysis of dystrophic process it is necessary to evaluate the value of each link of the reflex, its "contribution" to the mechanism of development of the process.

Obviously, the sensitive nerve plays a special role here. At first, the information of the nervous center about events in the zone denervation

is interrupted. Second, the damaged sensitive nerve is a source of the pathologic information including pain and third, centrifuged influences on the tissue are proceeded from it. It is established that the special substance P (R) disturbing metabolism and microcirculation spreads through the sensitive nerves with axocurrent on the tissue. For example, one can name the experiments of A. D. Speransky with selective damage of centers of hypothalamus. This is accompanied by the appearance of trophic ulcers in various organs. The role of the efferent nerves in dystrophy is that one of their functions (normal) disappears, and other ones (pathologic) occur. The impulsive activity, the development and the action of mediators (adrenaline, serotonin, acetylcholine, etc.) cease the axonic transport of "substances of trophicity" is disturbed or stops; the function (motility, secretion) ceases or is perverted. The process involves genome, the synthesis of ferments is disturbed, and metabolism acquires a more primitive character, the output of macroergs decreases. The membranes and their transport functions are disturbed. The organ with disturbed innervations can become a source of autoantigen. Process is complicated because of neurotrophic changes which involve the disturbance of blood and lymphocirculation, microcirculation. And then hypoxia appears as a result. Therefore, today pathogenesis of neurogenic dystrophy is presented as complex, multifactor process: the nervous system ceases "to control metabolism" in the tissues and after that complex disorders of metabolism, structure and function occur.

PAIN. GENERAL CHARACTERISTICS, NOTIONS

Pain is unpleasant sensation realizing by a special system of the pain sensitivity and the highest sections of the brain related to the psycho-emotional sphere. The system of perception and transfer of the pain signal is also called nociceptive system (nociperceptive). The pain signals cause an adaptive effect — response direct at the elimination of the nociceptive effect of the pain itself if it is severe.

There is also a pathologic pain. The main biological criterion of distinguishing the pathologic pain from the physiological one is its disadaptive and pathologic meaning for the organism.

The pathologic pain conditions the development of the structural and functional changes and impairments in the cardio-vascular system, in the inner organs, in the system of microcirculation, tissue dystrophy,

disturbance of the vegetative reactions, changes in the activity of the nervous, endocrine, immune and other systems.

Modern Theories of Pain

According to the *"gate control"* theory of Malsach and Wall, there is a control mechanism for passing of nociceptive imputation in the system of afferent entrance in the spinal cord. Their control represents "gate" which regulates the activity of T-cells and flow of imputations produced by them, ascending by the pain tracts to the highest of the pain sensitivity. From the point of view of this theory the pathologic pain occurs in insufficiency of the inhibitory mechanisms of the gate control when the uninhibited T- cells may be activated by different stimuli from the periphery and other sources. Constant flow of stimuli from different sources to T-cells with disturbed inhibitory control is a condition of the pathologic pain.

According to the theory of generator and systemic mechanisms of pain (G. N. Kruzhanovsky, 1980), the pathologic pain is caused by formation of generators of the pathologically intensified excitation in the nociceptive system. The generator is an aggregate of hyperactive neuron which may develop self-supporting activity without any additional stimulation from periphery or other sources. Under the influence of the primary generator formed in some part of the nociceptive system of the pain sensitivity are involved into the pathologic process that in their interaction represent new pathodynamic organization with abnormal character of activity producing the pathological pain. It is a pathological algic system (PAS) which is the base for the pain syndrome.

The character of activity of the generator and PAS allows understanding the peculiarities of the pathologic pain, in particular, its attacks and character, preservation and intensification of pain after provocation by single stimulus, spontaneous pain attack without afferent stimulation.

Sources and Mechanisms of the Pathologic Pain

Peripheral sources of the pathologic pain may be tissue receptors (nociceptors) in their intensified constant stimulation, chronically damaged and regenerating sensitive nerves, demyelized fibers, etc. The damaged nerves are quite sensitive to different humoral effects and therefore they become ectopic focus of nociceptive stimulation.

Neuroma plays an especially significant role. Neuroma is a formation of chaotically grown, interwoven sensitive nervous fibers which is formed in unregulated regeneration. Neuroma is quite sensitive to different effects. Therefore pain attacks (causalgias) in neuromas as well as in the nerve damage may be provoked by different factors and changes of the organism conditions. Pains associated with the nerve damage are called neuropathic.

Central mechanisms of the pathologic pain are formation and activity of the generation of the pathologically intensified excitation in some parts of the nociceptive system and PAS, involving different parts of the pain sensitivity system.

The cause of the generator in the dorsal cornua of the spinal cord and nuclei of the trigeminal nerve may be intensified, long stimulation from the periphery. Under these conditions the pain initially of the peripheral character may acquire the character of the central pain syndrome. The generator may appear in significant and stable depolarization of the nociceptive neuron.

The inhibitory insufficiency of the neuron is an obligatory condition for the formation and activity of the generator in any part of the pain sensitivity system.

The cause of the formation of the generator may be partial deafferentiation of the neuron, for example, after cutting the ischiadic nerve or dorsal root. The epileptiformal is registered at first at the deafferented dorsal cornua and then in the nuclei of the thalamus and somatosensory zone of the cortex. The generator may be formed in the dorsal cornua of the spinal cord under the local influence of different convulsants, their nature is of no importance. In all cases there is a pain syndrome with characteristic features.

The inhibition of the generator in the dorsal cornua or the caudal nucleus of the trigeminal nerve by the inhibitory mediators leads to disappearance of the pain syndrome for the time of their action when they are introduced in the area of the generator in microinjection. Anticonvulsants, inhibiting the generator and induced hyperactive PAS, cause slackening or disappearance of the pain syndrome.

PAS is formed from the primary and secondary changed formations of the pain sensitivity system. Under the influence of the primary generator, the functional condition of other parts of the pain sensitivity system is changed, the excitability of their neuron increases and there is a tendency to formation of the neuron population with long pathologic

activity. Secondary generators may be formed in different parts of the pain sensitivity system. PAS also includes structures of the emotional sphere and vegetative nervous system. Stable, ramified, active PAS is a pathophysiological mechanism of severe polymorphic pain syndromes.

Antinociceptive System

Nociceptive system has its physiological, functional antipode — antinociceptive system which controls the activity of the nociceptive system structures. Antinociceptive system consists of various nervous formations related to different parts and levels of the central nervous system, beginning from the afferent entrance in the spinal cord and ending with the brain cortex.

Antinociceptive system plays a significant role in mechanisms of prevention and elimination of the pathologic pain. In excessive nociceptive stimuli, it joins the response and lessens the flow of nociceptive stimulation and intensity of the pain sensation. Thanks to it the pain remains under control and does not become pathologic.

In inadequacy of the antinociceptive system is requires additional and special activations.

Neurochemical Mechanisms of Pain

Functional neurophysiologic mechanisms of the pain sensitivity are realized by neurochemical processes at different levels of the nociceptive and antinociceptive systems.

The peripheral nociceptors are activated under the influence of many endogenic biologically active substances — histamine, substance P, kinines, prostaglandins, etc. The substance P plays an important role in excitability conduction in the primary nociceptive neuron. It is conditioned to be a pain mediator. The direct effect to the stimulating aminoacids and substances causing depolarization or disturbance of neuron inhibition on the dorsal cornua b rings about the formation of the generator and the pain syndrome.

Rather effective endogenic analgetics are opioid neuropeptides. They inhibit the transmitting of nociceptive neurons and activate the neurons of the antinociceptive system, changing the activity of the neuron of the highest section of the brain. The substance P may also cause analgesia and inhibition even of the pathologic pain, activating antinociceptive structures, for example, the dorsal nucleus of the suture.

Of classical neuromediators the analgetic effect has serotonin,

noradrenaline, dopamine, GABA (gamma aminobutyric acid).

Serotonin is a mediator of the antinociceptive system at the spinal level. Noradrenalin is also a mediator of the descending antinociceptive system, it inhibits the activity of the nociceptive neuron of the posterior cornua of the spinal cord and nuclei of the trigeminal nerve. GABA takes part in inhibition of the activity if the nociceptive neurons are at the spinal level.

Treatment Principles in the Pathologic Pain

The main principle of treatment of the pathologic pain is to inhibit the hyperactivity of the nociceptive neuron and generators formed by them and to liquidate PAS, which is the base of the corresponding pain syndrome.

Correction of the basic processes of hyperactivity of the neuron and formed generators may be done with the help of anticonvulsants. The foremost importance is the blockade of Ca^{2+} entry into the nociceptive neuron. It is accomplished with the help of Ca- antagonists.

As the nociceptive and antinociceptive effects are realized at different levels and by several mechanisms it is necessary to use complex pathogenetic therapy. It influences in combination on different parts of the pathologic algic system in order to activate it. Besides, it is important to effect psychoemotional, vascular and other vegetative and tissue components of the pathologic pain. It is also necessary to eliminate the etiologic factor maintaining the pathologic changes in the nociceptive system.

COMPREHENSION CHECK

Try to answer the following questions.

1. Define the trophisity function of the nervous system and dystrophic process.
2. Discuss pathogenesis and manifestation of neurodystrophic changes.
3. What are the sources and mechanisms of the pathological pain?

UNIT 32

PATHOPHYSIOLOGY OF HIGHER NERVOUS ACTIVITY

Pathophysiology of higher nervous activity studies the mechanisms of appearance and development of the pathologic deviation from normal cause of the higher nervous functions of the Human and Animal brain. As for animals we use such a determination as "experimental pathophysiology of higher nervous activity". It means the modeling of some symptoms and syndromes of pathology of the higher functions of human brain or the animals and their studying by the objective methods of investigation, first of all, by the method of the conditioned reflexes. The theoretical theses of pathophysiology of higher nervous activity are based on I. P. Pavlov's doctrine about the conditioned reflexes.

The manifestations of functional pathology of higher nervous activity are various but first of all they include the psychic functions. We can see weakness of analitycal-synthetical activity of the brain, disturbance of long-term and short-term memory, regulation of the emotions and motivations, regulation of general functional condition of the brain, intersemifunctional condition of the brain interhemispherical relations.

As a rule these disturbances are manifested in alimentary sexual, protective group behavior, and they are mostly investigated for characteristics of higher nervous activity. The frequent manifestation of pathology of higher nervous activity is disturbance of cycle of sleep — waking, regulation of the vegetative and somatic functions which in the disturbance of frequency of the cardiac contractions, regulation of the arterial pressure and trophicity of the skin.

There are 3 groups of the causes in the etiology of pathology of higher nervous activity. They are:

1) the causes, which arise as a result of interaction of the organism and environment with prenatal period of life;

2) the genetic causes;

3) the combination of the first and second causes.

There are the functional, posttraumatic and combined pathology of higher nervous activity.

Functional pathology is the disturbances of behavior, which are conditioned by the action of the pathogenic irritants on internal and external receptors.

Posttraumatic pathology of higher nervous activity is the dis-

turbances of behavior, which appear as a result of direct action of pathogenic agent on the brain, for example, in its injury, blood accumulation in the cerebral tissue and tumor of the brain, etc.

Combined (functional and traumatic) pathology is the disturbances, which appear as a result of action both on the receptor system of the organism and on the brain (for example, in radioactive and thermal injury of the head and its mechanical injury, etc.).

The action of pathologic agent induces the primary affection of the brain, its primary disease. And such disturbances are called primary. The disturbances of higher nervous activity induced by other factors, or as a result of another pathology of the organism (infectious disease, non-cerebral localization of tumor, cardio-vascular disease) are secondary ones. As a rule, secondary pathology of higher nervous activity results from astenisation of the nervous system, decrease of its strength for relation to the psychogenic and other actions.

There are two causes for appearance of functional pathology of higher nervous activity. They are:

1) pathogenic agent acts on the receptors by the unconditioned reflex mechanism;

2) pathogenic agent has a signal meaning and acts through the receptors of the brain by the conditioned reflex mechanism.

Thanks to the secondary signal system the functional pathology of higher nervous activity can be stipulated by the verbal action; it means that pathologic agent can influence on the higher parts of the brain through the second (verbal) signal system. The modern notions about the mechanisms of pathology of higher nervous activity base on taking into account the emotions, memory and humoral factors in appearance of pathology.

The Role of the Negative Emotions

They appear under the influence of the pathogenic irritants and can have a long stagnant character. They are promoted by the long delay of external manifestation of negative emotion (the so-called unreactive emotions) accompanied by hormonal and other chemical deviations in blood. They decrease the stability of the nervous system to the pathogenic agent and thus independent self-maintained pathologic system is formed (vicious circle), which desorganizes the activity of other systems. But such pathogenic influence of the negative emotions appears in their long course. At the early stages of their appearance the negative emotions play the biologically positive role and have

characteristics of factor of extreme mobilization of the organism as counteraction to pathogenic agent.

The Role of Memory

The mechanism of the long course of pathological higher nervous activity is difficult and defined by some factors. It is considered that pathologic conditioned reflexes can be formed as a result of fixation of the conditions, which appear in the brain under influence of pathogenic agent in the long-term memory. Another mechanism of arising and maintaining of the pathologic higher nervous activity consists in the formation of the pathologic time connection, which is easily formed under general functional condition of brain.

The general functional condition of the brain changes under the influence of many factors, for example, it decreases as a result of long limitation of the inflow of the ophthalmic, sound, tactile proprioceptive and other stimuli into the brain in changes of the geographical regions, in long hypodynamia. The steadiness of higher nervous activity decreases and the pathologic reactions are especially difficult.

The method of electron microscopia established that the experimental neurosis have the destructive changes in the *neuronal and* glial elements of the neocortex and in the condition apparatus with parallel reparative processes (with the same level of compensation of these disturbed functions).

The biological investigations of the neocortex in animals determined the reversible and irreversible disturbances of the neuromediator system (in the condition of experimental neurosis). The determination of ultrastructural and neurochemical changes in the animal brain in experimental neurosis leads to supposition that neuroses have structural basic. And we can say that any pathology has the structural changes, which we can determine by the adequate methods of its investigation.

Neurosis is a typical form of the disturbances of function of the nervous system, which arises as a result of overstrains and breakdown of higher nervous activity. The pathogenetic base of the necrosis is made by the disturbance of the main nervous processes such as excitation — inhibition namely their strength and balance. The neuroses have such characteristics as the disturbance of VNA, vegetative regulation, movements, and nervous trophicity as well as decrease of general resistance of the organism.

The Principles and Methods of Neurosis Reproduction

The overstrain of the excitation process. *This principle can be realized*

by the using of very strong unconditioned stimulus (the intensive pain, strong sound), long or repeated action of the stimulus, simultaneous action of some different and strong stimuli (conditioned and unconditioned), difficult positive conditioned and non- ordinary stimuli.

The overstrain of the inhibition process. It is caused by sharp increase of the time of elaborated dynamic stereotype differentiation.

The overstrain of movement of the nervous process. In the experiment it is achieved by the transformation of the signal meaning of the conditioned stimuli, disturbance of the dynamic stereotype, "wrong" work of the reflexes (the electric current in the food house at the moment of eating). The modern tendencies of working out of the methods of experimental reproduction of neuroses are directed at the maximal approach of the model with the human neuroses. These methods are: the limitation of "reflex of freedom" (forced fixation of the animal in the apparatus), disturbances of daily meal regimen, light rhythm due to changes of day and night, sexual relations in monkeys, preliminary astenisation of the nervous system under the action of chronic noise, ione radiation, etc.

Types of Experimental Neuroses

Neurosis with predominance of the excitation process (in the weak inhibition process) has continuous, non-adequate agitation, aggressiveness and anger of the animal. It can be transformed in neurosis of the inhibitive type as a result of level-out inhibition.

Neurosis with predominance of the inhibition process (in the weak excitation process) is characterized by development of passive protectional reactions, depression and drowsiness of the animal.

The kinds of neurosis with pathologic movement of the nervous process are following:

a) neurosis with pathologic inertation with development of the phobiae (from Greek *phobos* — fear);

b) neurosis with pathologic lability (the animal makes fuss, continuous actions, increased movement activity).

Circular (cycle) neurosis is characterized by alteration of different above-mentioned types of neuroses.

Such process appears in the animals with the weak and strong type of HNA. The weak type has frustration in the protective inhibition with the development of the passive protective reactions and strong nonsteady type has excitation with the formation of the active searching reactions.

Types of Higher Nervous Activity

Pathophysiology of higher nervous activity includes the studying of the type of higher nervous activity as its main task, the speed of arising of the pathology, its manifestation, level of activation of the protective mechanisms are determined by the individual peculiarities of the nervous system.

The type is the congenital peculiarity of the nervous system and it is reflected in such congenital characteristics as strength, steadiness, mobility of the nervous processes.

According to I. P. Pavlov there are 4 general types of the nervous system:

1) the strong, nonsteady type with predominance of excitation over inhibition;

2) the strong steady type with high mobility of the nervous processes;

3) the strong steady type with low *mobility of* the nervous processes;

4) the weak type with low development of excitation and inhibition.

The pathology of the higher nervous activity appears in animals with the weak type of the nervous system and such animals are the providers of the neuroses. The character of reaction of the nervous system to the pathogenic agent is determinated also by the peculiarities, which were acquired in the process of the individual life.

Now we shall tell about such example of the form of functional pathology of HNA (behavior) as information pathology.

The information pathology represents the different disturbances of the course of the higher functions of the nervous system, and the disturbance of life activity of other systems of the organism which appear under quite long "life" of the brain in the unpleasant conditions of combination of such factors as:

a) volume of information which must be considered for making an important decision;

b) factor of time for making an important decision;

c) level of motivation which determines the importance for making a decision.

The unpleasant variations of combination of these factors are a large volume of information (with making a decision), long deficit of time, high level of behavior motivations.

The general principle of modeling of information pathology is memorizing a great number of the conditioned stimuli and reacting on them

in deficit of time and in high food motivation (strong feeling of hunger). So in the behavior of animal we can see the development of the compensation reactions, so under the action of many conditioned stimuli the animals make their problem easier and stop reacting to one of the signals. But in the conditions of long deficit of time the decrease of the number of the stimuli does stop the development of pathology of HNA. Another mechanism is the development of more common inhibition processes which protect the CNS from further action of the pathogenic factors. Such phase of the protective inhibition is followed by the phase of excitation (intensive animal movement). And it is the compensation of factor of time deficit. It is the time compensation mechanism and under the influence of the pathogenic actions the information pathology develops. In information neurosis we can see such changes of HNA as:

a) frequent or constant mistakes in signal differentiation;

b) sharp decrease of time of keeping the step reactions and short-time memory;

c) the inert processes appear in the brain determining activity with non-adequate meaning with motor hyperkinetic reactions,

The typical disturbances of HNA for humans and animals are noted in the organic injures of the same parts of the brain cortex (frontal lobes). The frontal lobe takes part in the management of the congenital behavior reactions from positions of accumulated experience as well as in concordance of the internal and external motivations. We can see such changes in the patient with pathology of the frontal lobe as absence of motivation, steadfast plans and intentions based on the prognosing with preservation of intellect. The *patient becomes* rude, tactless, frivolous and irritable.

COMPREHENSION CHECK

Try to answer the following questions.

1. What are the main etiological factors which arise disturbances of higher nervous activity?

2. Define the neurosis and give its characteristics.

UNIT 33

DYSREGULATION PATHOLOGY. MULTIPLE ORGAN DYSFUNCTION SYNDROME

According to the modern theories of dysregulation pathology, disturbances of the regulation activity of the organs and their function can lead to exogenous pathogenic conditions, may stimulate further development of this process or cause pathologic processes. There are primary and secondary dysregulation disturbances. At first it appears in any integrative system of the organism (for example, nervous, endocrine, immune) and at last can occur in other organs and systems, so will become multiple organ dysfunction polysystemic pathology.

The main pathological criterion of distinguishing the dysregulation pathology from the physiological one its disadaptive and pathogenic meaning for the organism.

According to the theory of the pathologic pain conditions the development of structural and functional changes and impairments in vascular-cardiac system, in the inner organs, in the system of microcirculation, tissue dystrophy, disturbance of the vegetative reactions, changes in the activity of the nervous, endocrine, immune and other systems. Due to the theory of generator and systemic mechanisms of pain (G. N. Kryzanovsky, 1980) the pathologic pain is caused by formation of degenerators of pathologically intensified excitation in the nociceptive system. The generator is an aggregate of hyperactive neurons which may develop self-supporting activity without any additional stimulation from periphery or other sources. Under the influence of the primary generator formed in some part of the nociceptive system other formation of the system of the pain sensitivity are involved in pathologic process that in their interaction represent new pathodynamic organization with abnormal character of activity producing the pathologic pain. It is a pathologic algic system (PAS), which is base of the pain syndrome.

The character of activity of the generator and PAS allows understanding of the peculiarities of the pathologic pain, in particular, its attacks and character, preservation and intensification of pain after provocation by single stimulus, spontaneous pain attack without afferent stimulation.

MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS)

MODS is a progressive dysfunction of two or more organ systems resulting from an uncontrolled inflammatory response to severe illness or injury. The organ dysfunction can progress to organ failure and death. Although sepsis and septic shock are the most common causes, MODS can be initiated by any severe injury or disease process that activates a massive systemic inflammatory response by the host. Documented clinical infection is not necessary for its development. Other common triggers are severe trauma, major surgery, burns, circulatory shock, acute pancreatitis, acute renal failure, ARDS, persistent inflammatory foci and necrotic tissue.

Today, MODS is the most common cause of mortality in surgical intensive care units. Mortality in MODS is between 45% and 55%, if two organ systems fail. It is higher than 90% when three or more organ systems fail, and it approaches 100% if the failure of three or more organs persists longer than 4 days (Fig. 43).

ADULT RESPIRATORY DISTRESS SYNDROME (ARDS)

ARDS is characterized by pulmonary edema, and is usually acute or subacute. It can quickly produce respiratory failure and death (Fig. 44).

SHOCK

Shock is a condition in which the progress to organ failure and death is observed unless the compensatory mechanisms or clinical intervention reverse the process.

Shock causes many diverse signs and symptoms. The individual may feel sick, weak, cold, hot, nauseated, dizzy, confused, afraid, thirsty and short of breath. Blood pressure, cardiac output and urinary output are usually decreased. Respiratory rate is usually increased (Fig. 45); (Table 21).

Hypovolemic Shock

Hypovolemic shock develops quickly following major burn injury. The severity of burn shock is directly proportional to the extent of the total body surface area (TBSA) that is burned. Burns involving 20% to 40% of TBSA in adults or 8% to 25% of TBSA in children require cardio-vascular support with intravenous fluid. Within minutes of a major burn injury, the capillary bed opens not only in the burn area but also in the entire capillary system. This increased capillary permeability leads to the ensuing hypovolemic shock which is not treated, irreversible shock and death may occur within a few hours.

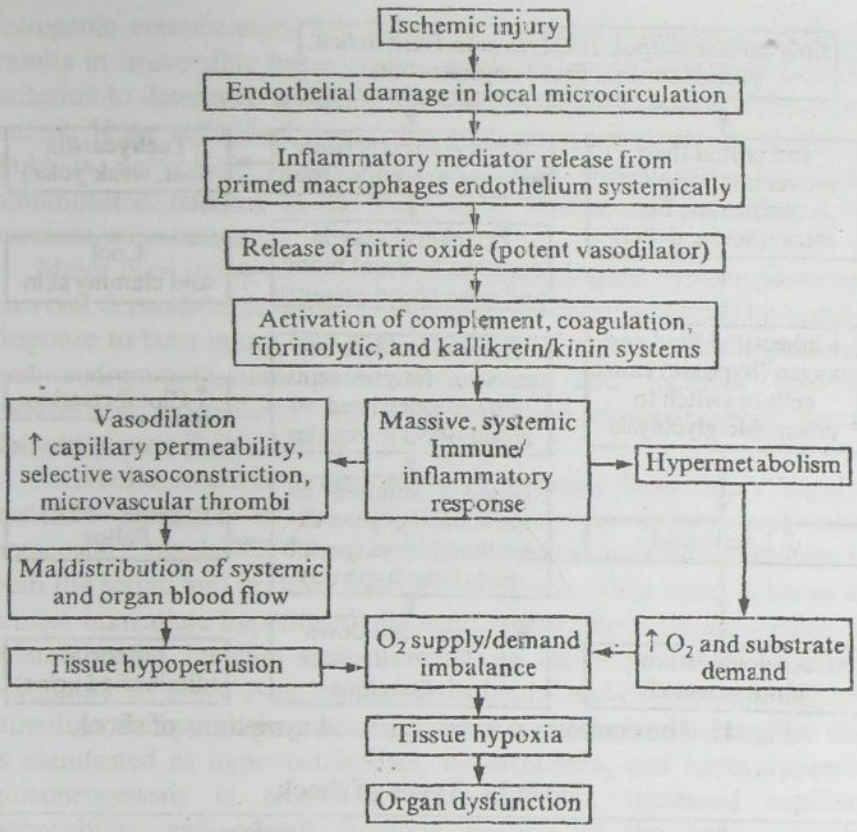

Fig. 43. Pathogenic sequence of MODS

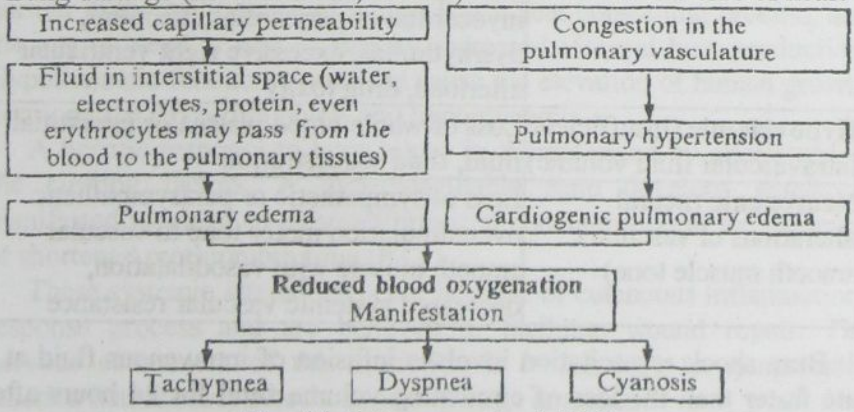

Fig. 44. Pathogenesis of ARDS

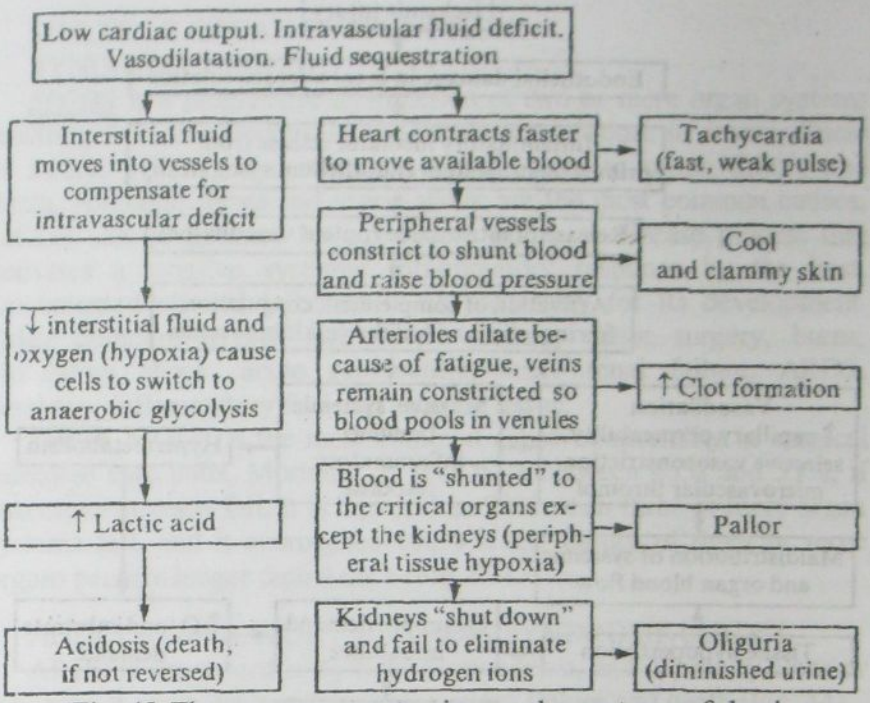

Fig. 45. The common events, signs and symptoms of shock

Table 21. Types of shock

Type	Etiology
Cardiogenic (heart failure)	Myocardial ischemia, myocardial infarction, congestive heart failure, myocardial or pericardial infections, dysrhythmias, excessive right ventricular afterload, drug toxity
Hypovolemic (insufficient intravascular fluid volume)	Loss of whole blood plasma or interstitial fluid, fluid sequestration
Neurogenic (neural alterations of vascular smooth muscle tone)	Loss of sympathetic or parasympathetic overstimulation motor tone to vascular smooth muscle with vasodilatation, decreased systemic vascular resistance

Burn shock resuscitation involves infusion of intravenous fluid at a rate faster than the loss of circulating volume fluid for 24 hours after burn injury. The massive edema associated with burn shock is an

iatrogenic complication, but failure to administer resuscitation fluids results in irreversible hypovolemic shock and death. The most reliable criterion to determine adequate resuscitation of burn shock is the urine output. If the individual doesn't have adequate urine output, sufficient fluid is not being administered. As burn shock ends, the fluid administered remains in the circulating volume and is reflected as increase urine output.

Major burn injury affects the entire physiological system; however, survival depends on its ultimate impact at the cellular level. The cellular response to burn injury involves disruption of transmembrane potential and sodium-potassium pump impairment and includes loss of intracellular magnesium and phosphate and elevated serum lactic dehydrogenase (LDG) levels.

Metabolic reaction to the stress of a major burn injury involve systemic alteration of the sympathetic nervous system and other homeostatic regulation. Catecholamine are found in elevated amounts in both the serum and urine of burned individuals. Burn injury induces an almost immediate hypermetabolic state; rather, the hypermetabolism is related to an increase and resetting of the hypothalamic thermal regulatory set point. A reflex mobilizes neural and/or hormonal afferent stimuli to the hypothalamus and produces a catecholamine response that is manifested as hypermetabolism, hyperthermia, and hyperglycemia; gluconeogenesis is promoted. Vasodilatation, increased capillary permeability and edema facilitate healing of the local area by transporting both heat and glucose preferentially to the wound.

The extensive evaporative water loss may be 20 times as much than normal in the early phase of injury. It is a heat consuming process, and the energy need is met in part by increased visceral heat production. Hypothalamic function alterations cause the elevation of human growth hormone (HGH) serum levels and hypoglycemia.

A hepatic response to burn injury is characterized by alterations in the clotting factors. A hypercoagulable state develops which is manifested by elevated plasma fibrinogen concentration in the presence of shortened prothrombin time (PTT).

These systemic alterations occur because of cutaneous inflammatory response process and are believed to facilitate wound repair. The nervous component of this alteration is in response to sympathetic reaction that releases catecholamine in large amounts.

In individuals surviving burn shock, immunosuppression and in-

creased susceptibility to potentially fatal systemic burn wound sepsis develop. Chemical mediators released during immune response cause peripheral vasodilatation, pulmonary vasoconstriction, increased capillary permeability, and local tissue ischemia in the burn wound. Translocation of microbes and endotoxins across in intestinal wall may be a mechanism of infection leading to septic shock following burn injuries and other major traumas. Natural resistance to infection in burn wounds depends on the nonspecific immune systems and relies on the ability of phagocytic cells to leave the bloodstream, migrate to the site of infection, and ingest and kill microorganisms. The burned individual's serum contains an inhibitor of complement conversion that leads to decreased opsonization of bacteria and less polymorphonuclear neutrophile chemotaxis. Individuals with altered immunocompetence who are burned run an additional risk for complications.

COMPREHENSION CHECK

Try to answer the following questions.

1. What are characteristics of MODS?
2. Explain pathogenesis of ARDS.
3. Name types of shock and give its characteristics.

III. COMPREHENSIVE EXAMINATION

Unit 1:

1. The patient who has been suffering from tumor of the stomach was operated with partly resection of the stomach. What is it after some time?

A. Pathological reaction
B. Typical pathological process
C. Compensatory reaction
D. Disease
E. Pathological state

2. Ischemia (interruption of blood supply) is the most common cause of hypoxic cell injury and necrosis. What is it?

A. Pathological reaction
B. Pathological process
C. Disease
D. Adaptive reaction
E. Pathological condition

3. A victim of the earth quake was rescued from under the ruins. He lost consciousness, his B.P was of 70/35 mm Hg and his pulse was 100 beats/min. what is it?

A. Pre-agony
B. Agony
C. Clinical death
D. Biological death
E. None of the above

4. A patient was admitted to the hospital in a severe state. He lost his consciousness, cannot answer the question and does not react to pain stimuli, his B.P is 30/10 mm Hg, and his pulse is absent. What is it?

A. Pre-agony
B. Agony
C. Clinical death
D. Biological death
E. None of the above

5. Choose-what is the cause and what is the condition of a disease?

A. Mechanical trauma

B. X-ray
C. Malnutrition
D. Oxygen and clean water deficit
E. Streptococcus
F. Narcotics
G. Psychical over tension (stress)

6. All of the following are external group of etiological factors except:
A. Viruses
B. Alcohol
C. Trauma
D. Temperature
E. Heredity

7. The outcomes of the disease can be, except:
A. Recovery (complete or incomplete)
B. Transformation to pathological state
C. Death
D. Returning to the prodromal period

8. Give the most appropriate characteristics choosing from a health and the disease-

A. Constant interaction of an organism with the changeable environmental factor
B. The disturbance of life activity
C. Low human ability to work
D. The most valuable participation in social life
E. Badly adapted to the influence of an extreme factor

a. HEALTH b. DISEASE

9. What is etiology? Choose the most appropriate definition

A. A study of causes of disease and condition facilitating the development of diseases
B. A study of causes of diseases
C. A study of conditions facilitating the development of diseases

10. The specificity of disease is primarily determined by –
A. A cause of disease
B. Condition promoting its development
C. Changes in the reactivity of the body

11. What is pathogenesis? Choose the most appropriate definition.

A. A study of causes and conditions leading to development of a disease
B. A study of typical forms of pathological processes

C. A study of mechanism of onset, development and outcomes of diseases

12. All of the following are the non-specific processes in the pathogenesis of various diseases except

A. Fever

B. Inflammation

C. Thrombosis of blood vessels

D. Hypoxia

E. Synthesis of specific antibodies to an antigen

13. Reactivity of a body involves (choose the most correct answer) –

A. Reveals itself by the reaction of different external factors on the organism

B. It is the ability to form antibodies to irritating agent

C. It is one of the forms of relation and interactions of the organism as a united system with the environment area

14. Indicate the specific process in the pathogenesis of various diseases

A. Proliferation of specific clones of T-lymphocytes

B. Activation of the barrier function of the body

C. Fever

D. Inflammation

E. Edema

15. A boy of 12 years, after returning from school began to grumble about headache, chill, pain, in muscles, loss of appetite. What period of illness are such symptoms are characteristics of?

A. Incubation

B. Latent

C. Prodormal

D. Height of disease

E. Completion

Unit 2:

1. The liquidator of consequences of failure on Chernobyl AES got the dose of ionizing irradiation 6Gr. What changes of leukocytic formula are expected in 10 days?

A. Lymphocytosis

B. Agranulocytosis

C. Leucocytosis

D. Basophilia

E. Eosinophilia

2. In 8 days after the irradiation the ulcero-necrotic changes in the cavity of mouth appeared at a victim the result of blood test are: erythrocytes-3,2 T/l, hemoglobin-6,0 mmol/l, leucocytes -3,2 G/l, trombocytes -90 O/l. what period of bone-cerebral form of acute radiation illness are the described changes significant for?

A. Prodromal
B. Acute radiation reaction
C. Falsely prosperity
D. Extended clinical signs
E. End of illnesses

3. The signs of hemorrhagic syndrome appeared at a patient with radiation illness. What changes in a blood have the deciding value in pathogenesis of this syndrome?

A. Trombocytopenia
B. Lymphopenia
C. Erytropenia
D. Eosinopenia
E. Granulocytopenia

4. A patient got in a hospital in 3 days after influencing of ionizing radiation in a dose 3 Gr. The changes of what functional system are significant in this case?

A. Blood
B. Cardiovascular system
C. Immune
D. Digestion
E. Endocrine

5. After immersion of diver on a depth down, appeared the symptoms of functional violation of the CNS: excitement, euphoria, weakening of attention, professional errors, by toxic action on the neurons of what substance are these symptoms conditioned?

A. Lactate
B. Oxygen
C. Carbonic gas
D. Ammonia
E. Nitrogen

6. An electrician, who broke the safety standards, accidently touched a barbed wire by both hands and perished, what process was the reason of the death?

A. Arrest of sinoatrial node of the heart

B. Depression of the respiration

C. Atrial and ventricular Violation of vagus regulation of the heart

7. A man got in a hospital in 30 days after the influencing of ionizing radiation in dose of 56rey. The changes from the side of what disorders indication of blood system are the main in pathogenesis of violations in this case?

A. Anemia

B. Leucopenia

C. Thrombocytopenia

D. All of the above

E. nothing are present

8. What is false? -Pathogenic effect of natural (lightening) electricity depends on:

A. Permanency (constant, variable)

B. Strength

C. Tension

D. Direction

E. Duration of penetration through the body

F. Reactivity of organism

G. Heredity

9. What direction of electricity through the human body is the most dangerous?

A. Head

B. Kidney

C. Heart

D. Liver

10. When the human is less sensitive to current electric?

A. Under narcosis

B. Tiredness

C. Hypoxia

D. Alcohol intoxication

11. The most resistant to current electric are all the above mentioned except:

A. External epidermal layer

B. Tendons and bones

C. Nerves

D. Blood

F. Cerebrospinal fluid

12. The immediate cause of death in electro trauma is standstill and cardiac arrest. Match the definition with its term.

A. Injury of the respiratory center
B. Ventricle fibrillation
C. Spasm of coronary vessels
D. Spasm of vertebral arteries, briging blood to the respiratory center
E. Injury of the vasomotor center
F. Increase of the nervous vagus tension
G. Laryngospasm
H. Spasm of the respiratory

5. Respiratory standstill
6. Cardiac arrest

Unit 3:

1. What is the probable cause of cell swelling in the early stages of cell injury?

A. High intracellular sodium concentration
B. Increased membrane permeability
C. Cell permeability decreases
D. None of the above
E. A and B are correct

2. All of the following are reversible cell injury except –

A. Intracellular accumulation of sodium ions
B. Increased diffusion of potassium ions out of the cell
C. Depletion of glycogen stores
D. Accumulation of Hydrogen ions
E. Leakage of intracellular enzymes

3. Which of the following intracellular substances are responsible for the cellular protection against oxygen radicals?

A. Vitamin E
B. Thiamin
C. α-tocopherol
D. Ascorbic acid
E. Vitamin A
F. Glutathione
G. Albumin

4. Which of the following cell enzymes contribute to an inactivation of free oxygen radicals?

A. Catalase
B. Cytochrome P-450
C. Superoxide dismutase
D. Glutathione peroxidase
E. Cytochrome oxydases

5. All of the following manifestations of cell injury can be observed in various cell(non-specific), EXCEPT-

A. Protein denaturation
B. Inability to generate action potential
C. Inability to support resting potential
D. Generalized cell swelling
E. Rupture of lysosomes
F. Loss of enzymes
G. Lipid accumulation

6. Membrane proteins possess the following functions, EXCEPT-

A. Structural
B. Antigenic
C. Enzymatic
D. Transported
E. Anti-mutant

7. All of the following are correct, EXCEPT-

A. Coagulative necrosis is connected with denaturation (coagulation) of the protein- occurs primarily in the, kidneys, heart, adrenal glands under ischemia (hypoxia)

B. Liquefaction necrosis can be ischemic injury to neurons and glial cells in the brain by own hydrolytic enzymes due to bacterial infection

C. Caseos necrosis- it is a combination of coagulative and liquefactive necrosis- is commonly seen in tuberculos pulmonary infection

8. Which of the following cell changes are reversible?

A. Karyorrhexis
B. Pycnossis
C. Karyolysis digestion of chromatin
D. Swelling of endoplasmic reticulum

9. Each kind of necrosis is correctly paired, EXCEPT-

A. Coagulation- heart or kidney
B. Liquefaction- spleen or lung

C. Caseos- granulomatous inflammatory sites

D. Fibrinoid- arterial walls

10. All of the following are corect, except-

A. Autolysis- the degradation reactions in dead cells caused by intracellular enzymes

B. Heterolysis- describes similar changes induced by extrinsic factor

C. Apoptosis- the death of single cells within cluster of other cells marked by shrinkage

D. Caseos necrosis- most often result from injured tissues infected by clostridium species.

Unit 4/9:

1. There are no reactions of delayed type hypersensitivity in mice without hairs (nude mice). For this pathology the most possible reason is:

A. Defect of phagocytosis

B. Disorders of hematopoiesis

C. Deficiency of components of complement system

D. Absence of thymus

E. Absence of gamma globulins in blood

2. Transplantation of skin was performed in a patient with wide burns. Graft swelled and changed its color at 8 th. day and was rejected at 11 th.. What cells participate in this process?

A. Erythrocytes

B. Basophils

C. Eosinophils

D. B-lymphocytes

E. T-lymphocytes

3. Deficient content of immunoglobulins was revealed in a patient. What cells of immune systems produce immunoglobulins?

A. Plasma cell

B. T-killer

C. B-lymphocytes

D. T-helpers

E. T- suppressors

4. It is known that plasma cells produce specific antibodies against the antigen. Number of plasma cells increases after introduction of antigen. What cells of peripheral blood serve as precursors of plasma cells?

A. Neutrophils

B. B-lymphocytes
C. Basophils
D. T-lymphocytes
E. Eosinophils

5. Formation of T-helpers is suspended in thymus. What processes of immunogenesis in connective tissue will be violated at first?

A. Phagocytosis of antigens by macrophages
B. Opsonization
C. Conversion of B-lymphocytes to plasma cells
D. Phagocytosis of foreign entities
E. Formation of precursors of T-lymphocytes

6. Transplantation of donor heart was performed in a patient. What conditions have to be observed to prevent transplant rejection?

A. Selection of donor according to HLA
B. Transplantation of bone marrow
C. Transfusion of donors blood
D. Removal of spleen
E. Administration of immunomodulators

7. A patient was operated on for acute purulent appendicitis. He cannot be discharged from the hospital for a long time because of bed healing of postoperative wound. This has diabetes mellitus for many years, repated pyoderma, furunculosis, stomatitis, and gingivitis. What is the reason for decreased immunologic reactivity?

A. Hyperglucemia
B. Hypercholesterolemia
C. Hyperketonemia
D. Hypohydratation
E. Protein metabolism violation

8. Its known that reactivity of the organism is opposed to its resistance during some pathological processes. What pathological process can appear in such situation?

A. Fever
B. Shock
C. Inflammation
D. Posthemorrhage anemia
E. Arterial hypertension

9. Considerable edema of lips appeared in 25-year-old man in a dentist's office some minutes later washing of his mouth with solution of furacillin. Which type of allergic reaction is observed in this case?

A. Immune complex
B. Hypersensitivity of delayed type
C. Anaphylactic
D. Stimulative
E. Cytolytik

Unit 5:

1. Three chromosomes of 21-d pair were revealed by karyotyping of a body. Indicate the phenotypic syndrome of this mutation.

A. Patau's syndrome
B. Edwrd's syndrome
C. Down's syndrome
D. Turner's syndrome
E. Polisomia Y-syndrome

2. Test of amniotic fluid for determination of sexual chromatin showed that fetus's cells include 2 bodies of sexual chromatin (Bar's bodies). What disease was revealed in the fetus?

A. Klinefelter's syndrome
B. Patau's syndrome
C. Down's syndrome
D. Edward's syndrome
E. Trisomy X- syndrome

3. A 2-year-old man complains of headache, failing sight, myasthenia. His height is 2.00 m, weight is 80 kg, he has long extremities, kyphosis. On X-ray examination the skull film showed enlargement of Turkish saddle walls. Sexual chromatin is absent. What pathway is the most possible in appearance of gigantism in young man?

A. Hypersecretion of growth hormone
B. Somatoliberin insufficiency
C. Gonadoliberin insufficiency
D. Testosterone insufficiency
E. Chromosomal mutation

4. A woman addressed the medical-genetic consultation. Short neck with wing shaped skin folds ("sphinx's neck "), broad chest, mammary hypoplasia were revealed on examination. What is the most possible diagnosis?

A. Patau's syndrome
B. Syndrome of "cat's cry"
C. Turner's syndrome

D. Down's syndrome
E. Klinefelter's syndrome

5. Mother's caryotype has 45 chromosomes. There was revealed that it connects with translocation of the 21-d chromosome to the 15-th one. Which disease is more possible will develop in her child if the father's caryotype is normal?

A. Down's syndrome
B. Patau's syndrome
C. Klinefelter's syndrome
D. Morris's syndrome
E. Edwrd's syndrome

6. Sexual chromatin was revealed on examination of the cheek epithelium of a man. Which chromosomal disease is characterized by this symptom?

A. Down's disease
B. Trisomy X-chromosome
C. Turner's syndrome
D. Hypophosphatemic rickets
E. Klinefelter's syndrome

7. A 10-month old baby has fair hair, very white skin and blue eyes. His parents have dark hair. He had normal appearance, but for last three months impairment of cerebral circulation and mental retardation developed in him. The reason of such condition can be:

A. Glycogenose
B. Acute porphyry
C. Hystidinemia
D. Lactosemia
E. Phenylketonuria

8. Daltonism was revealed in a 7-year-old boy on examination. His parents are healthy. But his mother's father had the same anomaly. Which is type of inheritance of inheritance of this anomaly?

A. X-linked dominant
B. Autosomal dominant
C. X-linked recessive
D. Autosomal recessive
E. Partial dominance.....

9. Two types of cell 46XY and 47XY in the equal quantity were revealed during examination of karyotype of the patient. What is the type of inheritance of this anomaly?

A. Monosomia X-syndrome
B. Down's syndrome
C. Normal karyotype
D. Kleinfelter syndrome
E. Patau's syndrome

10. The father of a pregnant woman suffers from gemeralopia. This a X-linked recessive disorder. Her husband's relatives didn't suffer from this disease. What is possibility that her child will suffer from gemeralopia, if it is a boy?

A. 50%
B. 0%
C. 75%

Unit 6:

1. In experiment K.Bernar annoying chorda tympani (branch n.facialis) looked after strengthening of secretion of submandibular gland and after development of arterial hyperemia what is the type of hyperemia after the mechanism of development?

A. Working
B. Reactive
C. Metabolic
D. Neuroparalytic
E. Neurotonic

2. After the forced rapid raising of diver form a depth on a surface started developing the signs of the caisson disease the are: pain in joints, itch of skin, blinking in eye, loss of consciousness. What type of embolism did these symptoms stipulate?

A. Air
B. Gas
C. Fatty
D. Tissue
E. Thromboembolism

3. A plait form extremity of victim was taken off in 2 hours after his imposition on 2 hours patient was dead. The cause of death standed the thromboembolism of pulmonary artery. What disorder of peripheral blood circulation become the reason of embolism?

A. Arterial
B. Vein hyperemia
C. Ischemia

D. Stasis
E. Thrombosis

4. Intravenous introduction of mercury of chloride to the experimental animal entailed formation of mural blood clot. What is the basic pathogenic factor od it's development?

A. Activating of adhesion of thrombocytes
B. Damage of vascular wall
C. Deceleration of blood circulation
D. Diminishment of activity of anticoagulants

5. The superior cervical ganglion of sympathetic trunk is remoted at a rabbit. On the side of the remotion is observing reddening and raising of temperature of skin on the head. What violation of peripheral circulation of blood developed at a rabbit?

A. Neurotonic arterial hyperemia
B. Neuroparalytic arterial hyperemia
C. Metabolic arterial hyperemia
D. Vein hyperemia
E. Stasis

6. At patient with the broken thigh-bone has developed an embolism of small circle of blood circulation what is the type of embolism?

A. Gas
B. Thromboembolism
C. Tissue
D. Fatty
E. Air

7. To the patient with obliterial endarteritis is conducted ganglionarsympathoectomy what type of arterial hyperemia, that arosed up as a result of operation?

A. Reactive
B. Neurotonic
C. Metabolic
D. Working
E. Neuroparalytic

8. A woman of 42 years, with trigeminal neuralgia is complaining about the periodic reddening of the right half of face and neck, feeling of warming and increasing sensitivity of skin. What type of arterial hyperemia is it possible to link the described symptoms with?

A. Reactive
B. Working

C. Neurotonic
D. Neuroparalytic
E. Metabolic

Unit 7:

1. A patient with an acute inflammatory process grumble about headech, pain in muscules and joints drowsiness, fever, a blood-test has shown: leukocytosis, increase of albumens quantity, mainly, globulins what is the mediator of inflammation that stipulate these violation?

A. Interleukin-1
B. Bradykinin
C. Histamine
D. Complement
E. Thromboxane A2

2. A patient has the edema of the right lower half of face. He grumbles about unbearable pulsating pain in a tooth that increases during eating. What is origin of edema during inflammation?

A. Rising of hydrostatic blood pressure
B. Violation of the tophic function of the nervous system
C. Hyperproteinemia
D. Hyperosima blood
E. Alkalosis

3. Caries was complicated by pulpitis at a patient, that was accompanied by unbearable pain. What is the principal reason of pain during the inflammation of pulp?

A. Ischemia
B. Primary alteration
C. Exudation
D. Emigration of leukocytes
E. Proliferation

4. During simulation of inflammation of lower extremity at an animal the temperature of body rose, the number of globulins and leucocytes in a blood increased what are the substances that stipulated development of these reaction of organism during inflammation?

A. Glucocorticoids
B. Interleukines
C. Mineralocorticoid
D. Leukines
E. Somatomedins

5. During microscopic research of punctate from the inflammation at a patient with an abscess are exposed great number of different cell of blood. What cells come first the vessels to fabrics during inflammation?

A. Monocytes
B. Neutrophils
C. Basophils
D. Esinophils
E. Lymphocytes

6. From festering contain of the wound of patient was done a stroke. What cell blood are exposed in it in great amount Romanovsky-Gymse stain?

A. Neutrophils
B. Eosinophils
C. Lymphocytes
D. Reticulocytes
E. Basophils

7. A woman became ill on purulent stomatitis. What are the typical violation in a blood at this state?

A. Monocytosis
B. Lymphocytosis
C. Anemia
D. Leukocytosis
E. Thrombocytosis

8. At a patient with peritonitis festering exudation, which contains plenty of neutrophils, accumulates is an abdominal region. What function is executed by neutrophilic granulocytes at inflammation?

A. Degranulation
B. Prostaglandin secretion
C. Phagocytosis
D. Histamine secretion
E. Local regulation of blood circulation

9. At patient a colloid scar appeared in place of festering inflammation of skin (carbuncle). What stage of inflammation is it directly linked with?

A. Primary alteration
B. Exudation
C. Proliferation

D. Secondary alteration
E. Emigration

10. After a burn in the area of hyperemia and edema of skin the area of necrosis appeared at a patient what mechanism causes strengthening of the destructive phenomena in the focus of inflammation?

A. Primary alteration
B. Secondary alteration
C. Emigration of lymphocytes
D. Diapedesis of erythrocytes
E. Proliferation of fibroblast

11. In the synthesis and selection of mediator of inflammation take part many cells of and connective tissue. What cells does interleukine-1 synthesize in?

A. In macrophage
B. In tissue basophils
C. In lymphocytes
D. In esinophils
E. In thrombocytes

12. In the heart of acute inflammation actively co-operate different cells. Some of them are sources of specific mediator but almost all of them synthesize a great amount of unspecific mediators of an acute inflammation. What cells synthesize unspecific mediators of an acute inflammation?

A. Proteins of complement
B. Kinins
C. Histamine
D. Inteleukines
E. Eicosanoids

13. At a patient with quinsy is exposed change of cellular composition of blood. What violation is characteristic for this state?

A. Neutrophilic leukocytosis
B. Lymphocytosis
C. Anaemia
D. Monocytosis
E. Thrombocytosis

14. At acute inflammation processes the proteins of an acute phase of inflammation are actively synthesized in an organism. What is the main stimulant of their synthesis?

A. Angiotensin -2

B. Immunoglobulins
C. Interferons
D. Histamine
E. Interleukine

15. During puncture of pleural cavity a doctor got a great amount of exudation. Microscopic research of exudat exposed a lot of erythrocytes what lind of exudate is it?

A. Fibrinous
B. Festering
C. Serous
D. Hemorrhagic
E. Mixed

Unit 8:

1. At patient with acute pneumonia a chill appeared with the increase of temperature of body to 39°C, general weakness and dry cough. What mediator possess properties of endogenous progeny?

A. Thromboxane A2
B. Interleukin 1
C. Histamine
D. Serotonine
E. Bradykinin

2. During a day the increase of body temperature of sick changes by the decline of it to the normal level. Such increase of temperature of body is observed periodically in 3 days on fourth. What is the type of temperature curve?

A. Febris intermittent
B. Febris continua
C. Febris recurrens
D. Febris hectica
E. Febris remittens

3. At a patient after supercooling the temperature of body rose to 39,7°C to and fluctuated from 39°C to 39,8°C during 3 days. What is the type of temperature curve at a patient?

A. Febris hectica
B. Febris recurrens
C. Febris continua
D. Febris intermittent
E. Febris remittens

4. Patient with meningitis was on the level body to page 39-40°C for a week. After 8 days under the of antibiotics the temperature has decreased to 36,8°C in 1,5 hours. There were acute hyperemia of skin, profuse sweating, decrease of arterial pressure, and loss of consciousness in him. Which medicine is the pathogenetic remedy?

A. Vasoconstrictor
B. Antibiotics
C. Antipyretics
D. Purogenal
E. Sulfanilamide

5. After being in the room with air temperature 40°C and humidity 80% a patient has been brought to hospital in grave condition. He was unconscious; he had tachypnea, tachycardia, and body temperature 41°C. Reanimation was failed. The patient has died. What is the most possible direct reason of death in this case?

A. Paralysis of the breath center
B. Collapse
C. Coagulation of blood and decrease of volume of circulating blood
D. Dehydration
E. Heart failure

6. Sharp increase of the temperature to 38,7°C was marked in a patient with acute purulent periodontitis. His body temperature has decreased to normal level after opening the pulp cavity. Which type of fever was in the patient?

A. Ephemeral
B. Septic
C. Reccurens
D. Remittent
E. Continua

7. A patient suffers from osteomyelitis of maxilla. His body temperature increases to 40°C and then sharply decreases to 35,6°C every day. Which type of fever curve is characterized by these changes?

A. Continua
B. Intermittent
C. Reccurens
D. Atypica
E. Hectica

8. Body temperature of patient becomes pyretic. Which substances have to act to neurons of thermoregulations for fever development?

A. Interferon
B. Kallidinum
C. Prostaglandins
D. Free radicals
E. Leucotriens

9. Fever in a patient develops in following succession of stages:

A. Incrementi; fastigii; decrementi
B. Incrementii; decrementi; fastigii
C. Fastigii; decrementi; incrementi
D. Fastigii; incrementi; decrementi
E. Decrementi; fastigii; incrementi

10. The temperature of patient with infectious disease increased to 38-39,5°C in day and kept that level about 1 hour, but then it returned to the normal level. Which type of fever is described in case?

A. Continuous
B. Intermittent
C. Remittent
D. Recurrent
E. Atypical

11. The body temperature of a patient with infectious disease increased to 39,5-40,5°C in day and kept that level about 1 hour, but then became normal again. Which disease is characterized by described type of fever?

A. Tuberculosis
B. Influenza
C. Peritonitis
D. Brucellosis
E. Malaria

12. A patient had fever after injection of pyrogenal. His skin has become pale, cold; chill appeared in him, oxygen consumption increased. How do the processes of thermoregulation change in described period of fever?

A. Increase of heat production and decrease of heat loss
B. Decrease of heat loss
C. Heat loss is equal heat production
D. Decrease of heat production and increase of heat loss
E. Decrease of heat production

13. In patient with third stage of fever reaction following manifestations observed: abundant sweating, tachypnea (increase in respiratory rate), decrease of body temperature. What is the mechanism of development of these symptoms?

A. Reduction of shivering thermogenesis
B. Secondary aldosteronism
C. Rise of set point of thermoregulation in hypothalamus
D. Predomination of heat production over the heat loss
E. Peripheral vasodilatation

14. Patient, who has been suffering from malaria, has weakness of heart activity and tachycardia during the stage of heart loss. What is the name of this complication?

A. Infectious-toxic collapse
B. Bacterial shock
C. Hemorrhage collapse
D. Orthostatic shock
E. Hemorrhage shock

15. Adaptation of organism disturbances to decrease of environmental temperature when using medicines alpha-adrenoblokators. Which mechanism is responsible for this?

A. Formation of primary heat
B. Constriction of skin vessels
C. Contractile thermogenesis
D. Sweating

16. After blood transfusion patient complaints feeling of heat, rigor, increase of body temperature to +40°C. Its known the cause of elevation temperature is secretion of endogenous pyrogens. Which cell produce endopyrogens?

A. Erythrocytes
B. Platelets
C. Endotheliocytes
D. B-lymphocytes
E. Macrophages

17. The different types of temperature curve are reported on examination of the infected patients. What other pathological conditions can to the fever?

A. Osmotic hyperhydratation
B. Systemic immune complex diseases
C. Excess production of glucocorticoids

D. Protein starvation

E. Hypohonadism

18. Pallor of the skin, "goose flesh" and increase of oxygen consumption appeared in the patient's skin after injection of pyrogenal. Which stage of fever is characterized by these changes?

A. Stadium incremanti

B. Stadium fastigii

C. The stage of falling temperature by crisis

D. The stage of falling temperature by lysis

19. Acute increase of body temperature, dyspnea, tachycardia, nausea, convulsion, and loss of conciousness developed in a worker, working in the thick uniform in summer. What was the most possible reason of development of those symptoms?

A. Equilibration between heat loss and heat production

B. Decrease of heat production

C. Decrease of heat loss

D. Increase of heat production

E. Increase of heat loss

20. A man in light clothes is staying in a room with air temperature +14 C°. Windows and doors are closed. Which way of heat loss is the most considerable in this case?

A. Evaporation

B. Perspiration

C. Conduction

D. Radiation

C. Convection

21. Experimental mice were kept in a lodge with air temperature 4 C°. Which adaptive reaction supplies its thermal homeostasis?

A. Limitation of heat loss

B. Decrease of oxygen consumption

C. Anabiosis

D. Increase of blood consumption

E. Decrease of oxidation enzyme activity

22. Inclination of the set point of thermoregulation to higher level due to action of IL-1 is in a patient. What is the name of this typical pathological process?

A. Fever

B. Hyperthermia

C. Hypothermia

D. Inflammation
E. Hypoxia

23. The body tempereture of a patient with crupous pneumonia is 39 C°. The difference between the morning and evening temperature of his body didn't exceed 1 C° during 9 days. Which type of the fever curves was that?

A. Continua
B. Hectica
C. Intermittent
D. Hyperpyretic
E. Reccurens

Unit 10:

1. Pain in the heart and joints and pneumonia appeared in a patient three weeks later acute myocardial infection. What is the main mechanism of development of post infarction Dressler's syndrome?

A. Ischemia of myocardium
B. Resorption of enzymes from necrotized area of myocardium
C. Secondary infection
D. Thrombosis of vessels
E. Autoimmune inflammation

2. A patient addressed to a dentist with complaints of redness and edema of mucous membrane of his mouth a month later dental prosthesis. Allergic stomatitis was diagnosed in this patient. What type of allergic reaction by Gell and Cumbs underlies this disease?

A. Cytotoxic
B. Delayed-type hypersensitivity
C. Immune complex-mediated
D. Anaphylactic
E. Simullating

3. Anaphylactic shock developed in a patient with botulism after second injection of antitoxic antibotulinus serum mixture. What is main mechanism of anaphylaxis?

A. Interaction of T-Lymphocytes with mediators
B. Interaction of antigen with IgM
C. Interaction of macrophages with antigens
D. Interaction of antigen with IgE
E. Interaction of T-Lymphocytes with tissue basophils

4. In a 27-years-old man tuberculin test was carried out. Following was observed 24 hours later: infiltration with size of 40x35 mm at the site of injection and hyperemia of skin above it. What group of biologic active substances development of allergic inflammation in this patient?

A. Lymphokines
B. Biogenic amines
C. Prostaglandins
D. Leukotriens
E. Kinins

5. Purulent endometritis developed in a woman after delivery. Treating with antibiotics – inhibitors of murrain synthesis was ineffective. Wide spectrum bactericidal antibiotic was administered to her. 6 hour later temperature rapidly increased up to 40°C with shivering, pains in muscles appeared, BP dropped down to 70/80 mmHg, and oligura developed in this woman. What is the main reason for this condition development?

A. Endotoxic shock
B. Toxic effect of preparation
C. Internal bleeding
D. Anaphylactic shock
E. Bacteremia

6. A 24-years-old patient has edema of face and increase in BP? Which appeared 1.5 weeks later severe streptococcus tonsillitis. The patient has hematuria and proteinuria of 1.2 g/L. Anti-streptococcus antibodies and decrease in content of compliment system components were revealed in patients' blood. Which microvessels do deposits of immune complexes localize in and cause nephropathy?

A. Proximal tubules
B. Glomerule
C. Descendent tubules
D. Loop of Henle
E. Pyramids

7. Nausea, fatigue, stomachache, palpitation, difficult respiration, and skin blisters developed in a patient 25 minutes later injection of antibiotics. What stage of allergic reaction is observed in this patient?

A. Pathochemical
B. Biochemical

C. Pathophysiologikal
D. Immunological
E. Sensibilization

8. Skin tuberculin test was carried out in a patient with chronic lung tuberculosis. Local hyperemia and edema appeared in the site of infracutaneous introduction of tuberculin preparation within 24-28 hours. What cells are effectors in mechanism of this reaction?

A. Neutrophils
B. T-lymphocytes
C. B- lymphocytes
D. Endotheliocytes
E. Smooth muscle cells of microvessels

9. Hyperemia. Sweelling and then necrosis of tissue, their rejection and ulcer (Arthus phenomenon) develop at the rabbit in the place of secondary intracutaneus injection of a substance with strongly pronounced antigenic properties (for example horse serum). What factors play the main role in pathogenesis of this phenomenon?

A. Antibodies presented by IgE
B. Antibodies presented by IgD
C. Antibodies presented by IgA
D. Antibodies presented by IgG and/or IgM
E. Specific T-lymphocytes-effectors

10. Skin rash, itching, swelling and pain in joints, increase in body temperature, and proteinuria appeared in a patient in 5-8 days after use lots of medical serum. Serum sickness was diagnosed. What is the main factor in pathogenesis of this syndrome?

A. Primary systemic accumulation of circulating immuns complexes in the blood
B. Degranulation of mast cells
C. Activation of T-killers
D. Activation of endotheliocytes
E. Cytolysis of blood cells

11. Thyrotoxicosis was diagnosed in a patient. Antithyroid antibodies were found in his blood. Which type of allergic reaction is observed at development of this disease?

A. Immune complex-mediated
B. Stimulating
C. Anaphylactic
D. Cytotoxic

E. Delayed type hypersensivity

12. Hives, itching of the skin, swelling of the skin and mucous membranes, swelling of lymphatic nodes develop in the patient in 9 days after injection of medicinal serum. What disease develops?

A. Pollinosis
B. Serum sickness
C. Schwartzman's phenomenon
D. Overy phenomenon
E. Quincke's edema

13. Dressler's syndrome was diagnosed at the patient 1.5 month later myocardium infarction. It is characterized by pericarditis, pleurisy, and pneumonia. What is the reason for this syndrome?

A. Sensitization of the organism by myocardium antigens
B. Decrease in resistance to microorganisms
C. Activation of saprophytic microflora
D. Intoxication of organism by products of necrosis
E. Release of myocardial enzymes to the blood

14. It is known that bronchial asthma develops by mechanism of immediate hypersensitivity, which includes 3 sequential stages:

A. Immunological, pathochemical, pathophisiological
B. Pathochemical, pathophisiological, immunological
C. Pathochemical, immunological, pathophisiological
D. Pathophisiological, immunological, pathochemical
E. Pathophisiological, pathochemical, immunological

15. A 20-year-old man has injury of the right testicle. What danger does it brings for the left (healthy) testicle?

A. Mimicry of antigens and development of antibody-mediated damage
B. Development of infectious process
C. Development of atrophy
D. Development of hypertrophy
E. No danger

16. Guinea-pigs nephrocytotoxic serum was injected to the rabbit under the experiment. What human disease is modeled in this case?

A. Nephritic syndrome
B. Acute pyelonephritis
C. Chronic renal insufficiency
D. Glomerulonephritis

Unit 11:

1. At a patient a malignant new formation of language is exposed. What features of this tumor allow to deliver it to malignant?

A. Increasing amount of mitotic cells
B. Expansive growth
C. Anaplasia
D. Postitiv effect of paster
E. Infiltrative growth

2. At a patient sick on chronic myeloleukemia developed stomatitis. The research of biopsy material of mucus tunica of mouth cavity exposed its leukocytic infiltration. What property of tumour caused the defeat of mouthcavity?

A. Mutation and transformation
B. Progression and dissemination
C. Metaplasia
D. Continual division

3. In 1910 Raws in the experiment got a sarcoma at chiken by introduction them anticellular filtrate which was got form the sarcoma of sick chickens what method of experimental design was used by an author?

A. Inductions
B. Autotransplantation
C. Heterotransplantation
D. Production

4. The cell of malignant tumour actively product adenocorticotropin. Which form common properties of tumours is this feature linked with?

A. Functional anaplasia
B. Morphological anaplasia
C. Metaplasia
D. Expansive growth
E. Invasive growth

5. From anamnesis of patient with the cancer of lungs is known that during 20 years he smoked out to 30 cigarettes on day. To what group dose belong carcinogens of tobacco smoke?

A. Polycyclic aromatic hydrocarbons
B. Aminonitroside
C. Amines
D. Hydrocyclic hydrocarbons

6. Using product with high maintenance of nitrates may produce cancirogenic substance that are able to entail tumor growth. What group of cancirogens do they belong to?

A. Aflatoxins
B. Polycylclic aromatic hydrocarbons
C. Amines
D. Aminonitroside
E. Nitrosamins

Unit 12:

1. The man 69 years old suffers from chronic intimate insufficiency of left ventricular type. Objectively: cyanosis, short wind, cough with allocation of liquor, periodic asthmas. What type of hypoxia is this?

A. Hemic
B. Tissue
C. Circulatory
D. Exogenic
E. Breathing

2. The man of 36 years complains on cough with allocation of liquor, short wind, headache, the general weakness. Was ill after strong overcooling. Objectively: skin is pale, body temperature 38°C, pulse 91/minute, pressure of 125/65mm.. Under percussion: from the right side above scapula – dullness, auscultation: crepitation. In the blood – neutrophilic leukocytosis. The diagnosis: share pneumonia. What type of hypoxia takes place at the patient?

A. Tissue
B. Hypoxical
C. Circulatory stagnant
D. Circulatory ischemic
E. Hemic

3. The man, approximately, 42 years fell in unconsciousness from the room with a smoke at a fire. What kind of hypoxia has arisen at the victim?

A. Circulatory
B. Hemic
C. Tissue
D. Hypoxical
E. Respiratory

4. The medicolegal expert ascertained death owing to a poisoning cyanides. The reason death was:

A. External breath

B. Transport of a hydrogen with the help malat-aspartase mechanism

C. Transport of oxygen hemoglobin

D. Synthesis of hemoglobin

E. Synthesis of urea

5. What complex of changes of gas structure of blood arises at alveolar hypoventilation?

A. Hypoxemia, hypercapnia, acidosis

B. Hypoxemia, hypocapnia, acidosis

C. Hypoxemia, hypocapnia, alkalosis

D. Hypoxemia, hypercapnia, alkalosis

E. No changes

6. At the climbers who are carrying out an ascention to the Everest, at height of 4,5 kms has above sea level appeared headache, dizziness, short wind. Hypoxia is possible to relate the observable phenomena to what kind?

A. Hypoxic

B. Hemic

C. Circulatory

D. Respiratory

E. Tissue

7. Patient 25 years old has been poisoned with potassium cyanide then, at the phenomenon sharp hypoxia , has come death. What is was a kind hypoxia?

A. Hemic

B. Respiratory

C. Ishemichal

D. Tissue

E. Hemic

8. At diver 24 years old who was carrying out welding works in kesson installation, has appeared strong headache, pains in joints and ears, bleeding from nose and ears, short wind, tachycardia. At inspection in a hospital the diagnosis is "hyperoxycal hypoxia". That from listed it is observed during syndrome of

A. High partial pressure in an alveolar gas mix

B. High contents of oxygen in arterial blood and tissues

C. All from listed – is correct

D. Free-radical oxidation owing to damage of cells, tissues and intercellular matrix

E. System enzimopathies which can lead to a convulsive syndrome of cortical genesis

9. In toxicological department patient 32 years old with a poisoning with aniline paints has arrived, in result of the short wind, tachycardia, dizziness. Laboratory observations expressed cyanosis, Inspection has shown the high contents of methemoglobin in blood. What form of hypoxia is observed?

A. Hemic

B. Cardiovascular

C. Respiratory

D. Tissue

E. Mixed

10. From group of climbers of 4,5 kms which have risen on height, have been urgently delivered in hospital patient ä-42 of years with the phenomena of non-cardiogenic hypostasis, one of heavy complications of mountain illness. What mechanism of this syndrome?

A. Lung venous hypertensia

B. Minus nervous influences on lung parenchyma in the conditions hypoxia

C. Development of neurogenic inflammations

D. Impact of inflammations mediators

E. All forms listed correctly

11. In groups of the climbers, consisting of 3 men 24, 26, 27 years, because of bad adaptation subacute form of mountain illness developed. What from the factors could render a determining role in pathogenic influence on an organism?

A. Decrease of partial pressure of oxygen in inhaled air

B. All forms listed

C. Decompression syndrome

D. High solar radiation

E. Increase of physical loading

12. The woman 36 years with a sharp allergic hypostasis of throat at which the general excitation was marked, the short wind of the mixed type, expansion of pupils, tachycardia, increase the AP, were periodically marked single spasms. What pathophysiological mechanisms can be counted in development of the clinical semiology?

A. All listed
B. Increase of tone of sympathetic nervous system of
C. Excitement of brain cortex
D. Lowering of blood pressure of oxygen
E. Collecting in an organism of carbonic gas

13. The girt 20 years old was taken to the hospital with the phenomena of poisoning with carbonic oxide. What factors play the leading part in pathogenesis poisonings WITH?

A. Hemoglobin dissociation failure
B. Hemic hypoxia because of inactivates Hb and decrease in oxygen capacity of blood
C. Lowering of ability of inactivated Hb to give oxygen
D. All listed
E. Development of tissue hypoxia

14. The group of climbers of 4 persons trained in mountains for rise on height up to 6000 m. At height 3500 m. at them increase the AP was marked, tachycardia, tahypnoe. At two persons euphoria, easing of attention was marked, decrease in intellectual and physical serviceability. To what phase, in view of attributes of hypoxia development, is possible to attribute these pathologies:

A. Neutral phase
B. Phase of full indemnification
C. Phase of incomplete indemnification
D. Phase of indemnification compensatory
E. Critical phase

Unit 13:

1. The nervous and endocrine systems participate in regulation of the basal metabolism. Some of the basic regulators are except

A. Sympathetic nervous system
B. Thyroxin
C. Adrenaline
D. Sexual hormones
E. Somatotropin
F. Aldosterone

2. Pathogenesis of nutritional deficiency diseases depends on all of the following except

A. Neuropsycoatric disorders
B. Food allergy

C. Pregnancy intoxication
D. Cancer therapy
E. Atherosclerosis

3. What is the most common a cause of secondary nutritional deficiency?

A. Interference with ingestion, absorption, utilization (acute gastro-interitis, pepetic ulcers)
B. Neurosis
C. Hypermotility of stomach and intestine
D. Alcoholism or narcomania
E. All of the above are correct
F. None of the above

4. A 3 year old boy was admitted to the children hospital with the following findings: low weight and height, monkey like face, muscle wasting and loss of subcutaneous fat and anemia. The following is likely

A. Marasmus
B. Cretinism
C. Anemia
D. Diabetes mellitus
E. Hereditary abnormalities

5. Each of the following are the characteristics of kwashiorkor disease except

A. Severe edema
B. Scant subcutaneous fat
C. Muscle wasting
D. Growth retardation
E. Fatty liver (due to failure of apoprotein synthesis)

6. Intestinal malabsorption syndromes may result in deficiency of any of the vitamins except

A. A
B. B
C. D
D. E
E. K

7. All of the clinical manifestations are correctly matched with the appropriate vitamin deficiency except

A. Night blindness – vit.A
B. Hemorrhagic phenomenon – vit.K
C. Impaired wound healing – vit.C

D. Osteomalacia – vit. D

E. Cutaneous petechial hemorrhages – vit.E

8. As it is well known medicinal starvation (fasting) is used as a non-specific method of treatment of some of the following disease except

A. Ulcer of stomach

B. Allergy

C. Obesity

D. Hypertension

E. Cutaneous disease

9. Albuminious starvation is more serious, especially in children from the age of 6 months to 3 years of age. What of the following factors play the main role in this case?

A. Ruinously effect on development of the nervous system

B. Depression of the immunity

C. Tendency to edema

D. Muscle wasting of arms and legs

E. Growth failure

10. All of the following are the characterstic of complete starvation except

A. The disturbances of basal metabolism

B. Metabolic acidosis

C. Cachetic edema

D. Atrophy of testes and ovaries

E. Loss of mass of heart till 97%

Unit 14:

1. A patient was admitted to the hospital in comatose state. Accompanying people said that he lost consciousness at training while he was finishing the marathon distance sort of coma is the most possible in this patient

A. Hyperglycemic

B. Hypoglycemic

C. Hypothyroid

D. Hepatic

E. Diabetic ketoacidosis

2. Patient has hyperglycemia, glucosuria, polydipsia, polyphagia and polyuria. What hormone hyposecretion do these changes develop due to?

A. Antiuretic hormone
B. Atriopeptide
C. Glucagon
D. Insulin
E. Cortisone

3. A patient aged 80 complains of increased appetite, thirst, elevated urination, and worsening of general condition after taking some sweet food . What disease is it?

A. Hypercortisolism
B. Hyperthyroidism
C. Hypothyroidism
D. Diabetes insipidus
E. Diabetes mellitus

4. A man aged 38, is under the course of treatment for Schizopherina at in-patient department contents of glucose, ketone bodies, and urea in his blood are normal, Shock therapy with regular injections of insulin has led to development of insular coma, and after that state of patient becomes better. What is the most possible for insular coma

A. Glucosuria
B. Dehydration of tissues
C. Hypoglycemia
D. Metabolic acidosis
E . Ketonemia

5. In worker at the polar station, who has been working there for a long tine, hemorrhage from gums occur, his teeth sway and pull out. What vitamin deficiency leads to these changes?

A. Tocopherol
B. Ergocalciferol
C. Ascorbic acid
D. Folic acid
E. Nicotinic acid

6. A patient, aged 50 complains of increased appetite, thirst and loss of body weight, weakness. At laboratory examination rise of amount of glucose in his blood revealed. What type of cells are injured at this case of this disease development?

A. Lipotropocytes
B. Thyrocytes
C. B-cells of langerhans islets

D. A-cells of langerhans islets
E. Pancreatocytes

7. In patient with constant hypoglycaemia blood analysis does not change after the injection of adrenaline. A doctor supposes hepatic disorder what function disorder is it?

A. Cholestrol formation
B. Excertion
C. Glycolysis
D. Ketogenesis
E. Glycogen deposition

8. A women aged 58 was admitted to the hospital in severe condition. She has confused consciousness; dry skin, hollow eyes, cyanosis and scent of rotten apples from her mouth. At laboratory examination of her glucose in blood – 15.1 mmol/l glucose in her urine-3.5%. What is the most possible reason for this condition?

A. Hyperglycemic coma
B. Hypoglycemic coma
C. Hypovolemic coma
D. Uremic coma
E. Anaphylactic coma

9. A doctor reveals in child symmetric roughness on cheeks, diarrhea and disorders of neural activity. What nutrition factors deficit underlies this condition?

A. Methionine, lipoic acid
B. Lysine, ascorbic acid
C. Nicotinic acid, tryptophan
D. Theronine, Pantathonic acid
E. Phenylalnine, Pangamic acid

10. The most of participants of megellan expedition to America died of avitaminosis. This disease displays as general malaise, subcutaneous hemorrhage, pulling teeth out hemorrhage from gums. What is the name of this avitaminosis

A. Scurvy
B. Pellagra
C. Addison-Birmer's anemia
D. Polyneuritis (beriberi)
E. Rachitis

11. In a women of 52 years old and 125 kg weight, diabetes mellitus develops. It happens due to?

A. Decrease of number of insulin receptors
B. High afiinity binding insulin to synalbumin
C. Reduced cell susceptibility to insulin
D. Increase activity of insulinase
E. Broken insulin synthesis

12. Unconsious patient was admitted to the hospital. He has kussmaul respiration blood pressure 80/50 mmHg, and acetone scent from his mouth. What substances accumulation in organism may lead to these disturbances?

A. Complex carbohydrates
B. Carbonic acid
C. Lactic acid
D. Modified lipoproteins
E. Ketone bodies

13. In patient suffered from diabetes mellitus acidiosis develops due to accumulation of ketone bodies (beta-oxybutyric acid and acetoacetic acid) At this condition pH of arterial blood is?

A. 7.40
B. 7.48
C. 7.56
D. 7.32
E. 7.66

14. A patient 56 years old woman who have been suffering from diabetes mellitus for 6 years complains of compressing pain behind her sternum. What mechanism of heart affection is the most possible in this case?

A. Myocardial dystrophy
B. Microangiopathy of myocardial vessels
C. Macroangiopathy of coronary vessels
D. Myocarditis
E. Vegetative neuropathy of heart

15. Content of glucose in patient's blood is on an empty stomach-4.52 mmol/l in one hour after taking sugar-6.23 mmol/l and in two hours after taking sugar-2.56 mmol/l. These signs are characteristics for?

A. Healthy person
B. Person suffered from insulinoma
C. Person suffered from hidden diabetes mellitus
D. Person suffered from insulin-dependent diabetes mellitus

E. Person suffered from thyrotoxicosis

16. What complication may develop when treating diabetic ketoacidosis with large doses of insulin?

A. Arterial hypertension
B. Leukocytosis
C. Arterial hypotension
D. Hyperkalemia

17. A patient, 40 year old woman, was admitted to the hospital with complaints of weakness, giddiness, hunger, cold sweat and cramps. At examination of the patient distension of pupils of the eyes, weakening of respiration and Bp is 90/50mmHg.Biochemical analysis of her blood shows: general bilirubin is 16.0mmol/L, urea is 4.1m mol/L, creatinine is 98mmol/L, and glucose is 2.0mmol/L. What kind of coma may develop in this patient?

A. Hyperglycemic
B. Hepatic
C. Renal
D. Hypoglycemic
E. At adrenal glands deficiency

18. The Woman B; aged 45,was admitted to the emergency department from a street .At examination of patient following symptoms was reveled; loss of consciousness, loss of reflexes, absence of reflexes from pupil of the eye and sclera, kussmaul respiration ,BP is 70/40mm Hg ,and body temperature is 35degrees Celsius. Biochemical analysis of patient's blood displays: glucose is 22 mmol/L. What kind of coma has developed in this patient?

A. Hypoglycemic
B. Hepatic
C. Renal
D. At adrenal glands deficiency
E. Hyper glycemic

19. Diabetes mellitus develops in animals after injection to them some alloxan. what is the main mechanism of this type of diabetes mellitus ?

A. Selective damage of lambda cells of pancreatic islets
B. Damage of beta and lambda cells of pancreatic islets
C. Formation of antibodies to insulin
D. Selective damage of beta cells of pancreatic islets
E. Gluconeogenesis activation

20. A patient address to a doctor with complaints of constant thirst. Hyperglycemia, polyuria and increased content of 17-ketosteroids in urine were revealed .What is the most probable disease in this case

A. Addison's disease
B. Myxedema
C. Glycogenosis of 1type
D. Insulin dependent diabetes mellitus
E. Steroid diabetes

Unit 15:

1. All of the following hormones stimulate lipolysis except
   A. Adrenalin,nor adrenalin
   B. STH
   C. ACTH
   D. Sexual hormones
   E. Prolactin
2. Which is "good cholesterol"?
   A. Very low density lipoproteins –VLPL
   B. High density lipoproteins-HDL
   C. Low density lipoproteins-LDL
   D. Intermediate density lipoproteins –IDL
3. What is not true

A. The incidence of artherosclerosis is strongly associated with hypercholesterolemia

B. A large atheromatous plaques narrowing the lumen of an artery

C. Atherosclerotic plaques consists of a mixture of fibrous tissue, old fibrin, lipid laden macrophages and cholesterol

D. Increased serum HDL concentration is associated with a decreased risk of atherosclerosis

E. Moncke berg arteriosclerosis is accomplished by narrowing the lumen of an artery

4. Moncke berg arteriosclerosis is marked by all of the following characteristics except
   A. It occurs most often in elderly patients
   B. Calcification occur in the arterial media
   C. Is predominatly seen in radial and ulnar arteries
   D. Significant vascular obstruction occurs
5. As it well known obesity is associated with different syndromes except

A. Atherosclerosis
B. Myxedema
C. Hyperthyroidism
D. Cushing's syndrome (hyperfunction of an adrenal cortex)
E. Hypogonadism

6. Obesity may be connected with the following causes except
A .Brain injury
B. Encephalitus
C. Meningitis
D. Overeating
E. Insulin insufficiency
F. Hereditary predisposition

7. Events in the development of atherosclerotic plaque include all of the following except
A. Accumulation LDL and VLDL
B. Smooth muscle proliferation
C. Calcification
D. D ecreased elasticity
E. Complement activation

Unit 16:

1. A boy, aged 9, with oedemas was admitted to the hospital. What proteins content in blood is decreased in this case?
A. Albumins
B. Protamines
C. Globulins
D. Hemoglobin
E. Hystons

2. Worker of fusing workshop, man of 23 years old, and of 60 kg weight, was admitted to the emergency department. Examination of water-salt exchange in this patient displays: content of general water is 33 liters (55% of body weight), extracellular sector constitutes 28.6% of body weight (17.2 liters), intravascular fluid constitutes 4% of body weight (2.4 liters), and intracellular sector constitutes 26.3% of body weight (15.8 liters). Osmotic pressure of patient's blood is 340 mosm/l; content of sodium in it – 160 mmol/1. Patient's urination is 0.4 liters per 24 hours. Determine the type of dyshydration.
A. Hyperosmolar hyperhydration
B. Hyperosmolar hypohydration

C. There is no dyshydration
D. Isoosmolar hyperhydration
E. Hypoosmolar hypohydration

3. A patient with severe nephropathy accompanied by severe oedema syndrome that; develops as complication. of bronchiectasis. Laboratory examination of this patient displays abundant proteinuria, cylinderuria, distinct decrease of protein content in blood serum, hyperlipidemia, hypokalemia, and other pathological changes. What is the most important link in development of oedemas in this patient?

A. Decrease of oncotic pressure of blood
B. Increase of osmotic pressure of interstitial fluid
C. Increase of hydrostatic pressure of blood
D. Blockade of lymphatic drainage
E. Increase of microvessel permeability

4. A patient has increased osmolarity of urine and decreased urination due to intensive sweating and dehydration. What hormone secretion changes provide compensatory retention of water at first?

A. Antidiuretic hormone
B. Aldosterone
C. Corticosterone
D. Thyroxin
E. Insulin

5. Content of sodium in patient's blood serum, is.100 mmol/L. What does this condition may manifest in?

A. Edemas
B. Arrhythmias
C. Dehydration
D. Heart arrest
E. Tachycardia

6. In a patient, aged 44, thirst develops after burns. What receptors generate impulses that underlie thirst development in this case?

A. Osmoreceptors
B. Pain receptors
C. Thermal receptors
D. Tactile receptors
E. Chemoreceptors

7. Isoosmolar hypohydration has been formed in a patient due to severe diarrhea. What symptoms are characteristic for this disturbance of water exchange?

A. Edematous syndrome
B. Decrease of content of water inside cells
C. Hypovolemic shock
D. Polyuria
E. Arterial hypertension

8. In patient with affection of kidneys hypoosmolar hyperhydration (water poisoning) has developed. What is the main pathogenic factor of this syndrome?

A. Anuria
B. Hypoaldosteronism
C. Polyuria
D. Hypoproteinemia
E. Increase of microvessel permeability

9. Hyperosmolar hypohydration has been formed while prolonged water starvation. Which of following manifestations are typical for this condition?

A. Arterial hypertension
B. Hypoisostenuria
C. Hypothermia
D. Increased salivation
E. Cramps and hallucinations

10. In patient suffered from severe chronic glomerulonephritis retention of isoosmolar fluid in organism and distinct edematous syndrome occur. What is the major factor of edema development in case of glomerulonephritis?

A. Hyperproteinemia
B. Secondary aldoseronism
C. Hypoproteinemia
D. Hypoaldosteronism
E. Arterial hypertension

11. In patients with myeloma content of proteins in blood plasma is increased up to 200 g/1. This leads to redistribution of water between intracellular, interstitial, and intravascular spaces. What direction does water mainly move at in this case?

A. From interstitium to blood vessels
B. From cells to interstitium
C. From interstitium to cells
D. From blood vessels to interstitium
E. From lymphatic vessels to interstitium

12. A patient of 18 years old and of 60 kg weight was admitted to the hospital with signs of hemic hypoxia resulting from poisoning by nitric compounds. Examination of water exchange of this patient displays: general water - 64% of body weight, extracellular fluid - 18%, intravascular fluid - 5%, and intracellular fluid - 46%; osmotic pressure of blood plasma is 250 mosm/1; urination is 0.8 L per 24 hours. Define the type of dyshydration?

A. There is no dyshydration
B. Isoosmolar hyperhydration
C. Isoosmolar hypohydration
D. Hypoosmolar hyperhydration
E. Hypoosmolar hypohydration

13. Edemas at lower extremities occur in a patient suffered from severe heart failure. What is the leading mechanism of edema development in this case?

A. Centralization of blood circulation
B. Lowering of hydrostatic pressure
C. Secondary hyperaldosteronism
D. Orthostatic increase of venous pressure
E. Hypoproteinemia

14. What is the initial link in formation of heart edemas?

A. Increase of vascular permeability
B. Decrease of minute heart volume
C. Activation of renin-angiotensin system
D. Increase of content of aldosteron in blood
E. Increase of secretion of antidiuretic hormone

15. What is the leading factor of edema development in case of nephrotic syndrome?

A. Increase of hydrostatic pressure in capillaries
B. Increase of vascular permeability
C. Hypoalbuminemia
D. Dynamic lymphatic insufficiency
E. Increase of blood volume

16. Patient suffered from cirrhosis of liver was given with 500 ml of 5% glucose solution with medicines. What disturbances of water-salt balance may appear in this patient?

A. Hypoosmolar hyperhydration
B. Hyperosmolar hyperhydration
C. Isoosmolar hyperhydration

D. Hypoosmolar hypohydration
E. There is no dyshydrotation

17 Patient has edema of right lower part of face and pulsing pain in tooth, which intensifies when taking some hot food. Dentist has diagnosed acute pulpitis. What is the leading mechanism of edema development in this case?

A. Disorders of microcirculation in the focus of inflammation
B. Disorders of trophic function of nervous system
C. Hypoproteinemia
D. Hyperosmia
E. Lymphocytosis

18. Toxic lung edema was modeled in rat using solution of ammonium chloride. What is the leading mechanism of edema development in this case?

A. Reducing of colloid-osmotic pressure
B. Rising of venous pressure
C. Increase of vascular permeability
D. Disorders of neural and humoral regulation
E. Intensification of lymphatic drainage

19. A rat was intravenously injected by 10 ml of 40% glucose solution. In 60 min coma develops due to hyperosmolar dehydration in this rat. What is the mechanism of edema development in this case?

A. Loss of water and.salts
B. Reduction of, vasopessin synthesis,
C. Increase of oncotic pressure..of extracellular fluid
D. Increase of osmotic pressure of extracellular fluid
E. Disturbance of acid-base balance

20. Patient has extracellular edema of tissues (dimensions of soft tissues of extremities, liver, and others are enlarged). What parameter of homeostasis decrease do these changes result from?

A. Viscosity
B. pH
C. Hematocrite
D. Oncotic pressure of blood plasma
E. Osmotic pressure of blood plasma

21. At complete starvation (with taking water) generalized edemas develop. What is the leading pathogenic factor in this case?

A. Increase of oncotic pressure of interstitial fluid
B. Decrease of osmotic pressure of blood plasma

C. Decrease of oncotic pressure of blood plasma
D. Increase of osmotic pressure of interstitial fluid
E. Decrease of hydrostatic pressure of interstitial fluid

22. A patient of 30 years old was admitted to the hospital at examination were found: hyperglycemia, ketonuria, polyuria, hyperstenuria and glucosuria. What kind of acid base balance disorders occurs in this case?

A. Gas alkalosis
B. Non-gas alkalosis
C. Metabolic alkalosis
D. Metabolic acidosis
E. Gasalkalosis

23. Acidosis develops in case of severe form of diabetes mellitus. What buffer system components change at first?

A. Bicarbonate
B. Phosphate
C. Hemoglobin
D. Oxyhemoglobin
E. Protein

24. Prolonged convulsions occur in patient suffered from epilepsy. After that following data of laboratory analysis of this patient were received: pH - 7.14, pCO_2 - 45 mmHg, HCO_3^- - 14 mmol/l, Na^+ - 140 mmol/l, Cl^- - 98 mmol/l. What kind of acid-base balance disturbances occurs in this patient?

A. Metabolic kethoacidosis
B. Metabolic kethoacidosis
C. Respiratory alkalosis
D. Metabolic alkalosis
E. There are no disorders of acid-base balance

25. While ascending to mountain in alpinist excitation developed that was replaced with headache, giddiness, breathlessness, and after that apnea occurred. What kind of acid-base balance disturbances occurs in this case?

A. Non-gas acidosis
B. Excretory acidosis
C. Gas alkalosis
D. Non-gas alkalosis
E. Gas acidosis

26. A patient suffered from chronic glomerulonephritis has increasing general malaise, tachycardia with recurrent arrhythmia, confusion, and sleepiness. What kind of acid-base balance disturbance accompanies uremic coma?

A. Non-gas excretory acidosis
B. Non-gas excretory alkalosis
C. Gas acidosis
D. Gas alkalosis
E. Respiratory alkalosis

27. Pregnant woman has toxicosis accompanied by vomiting of 24 hours duration. After that tetany cramps and dehydration develop. What kind of shift of acid-base balance leads to described changes?

A. Gas alkalosis
B. Gas acidosis
C. Non-gas metabolic acidosis
D. Non-gas metabolic alkalosis
E. Non-gas excretory alkalosis

28. A patient suffered from diabetes mellitus was admitted to the hospital because of worsening of his condition. He has general malaise, polyuria, lethargy, and sleepiness, Kussmaul respiration, heart arrhythmia, and acetone scent in expired air are noticed, in this patient. What kind of shift of acid-base balance contributes these symptoms?

A. Gas alkalosis
B. Gas acidosis
C. Non-gas metabolic alkalosis
D. Non-gas metabolic acidosis
E. Non-gas excretory alkalosis

29. A group of alpinists was undergone blood analysis in mountains at height 3000 meters. Following was revealed: decrease of HCO_3^- down to 15 mmol/l (norm is 22-26 mmol/l). What is the mechanism of decrease of HCO_3^- in the blood?

A. Decrease of reabsorption of bicarbonate in kidneys
B. Hyperventilation
C. Intensification of acidogenesis
D. Hypoventilation
E. Reduction of ammoniogenesis

30. pH of blood of patient suffered from diabetes mellitus sets to 7.3. What component of buffer system determination is used to diagnose disorders of acid-base balance?

A. Bicarbonate
B. Oxihemoglobin
C. Phosphate
D. Hemoglobin
E. Protein

31. Buffer capacity of blood decreases in worker as a result of exhausting muscle work. What acid substance income to the blood this may be explained?

A. Alpha-ketoglutaric acid
B. 3-phosphoglycerate
C. Lactic acid
D. Pyruvate
E. 1,3-biphosphoglycerate

Unit 17:

1. A 40-years-old white pregnant female with four children experienced weakness, loss of appetite, and pallor. Her CBC (complete blood count) revealed the following:

Er – 3,0·10$^{T}/_{L}$
Hematocrit – 33%
Hemoglobin (Hb) – 80 g/l

She most likely has

A. Sickle cell anemia
B. Posthemorrhagic anemia
C. Iron deficiency anemia
D. Pernicious anemia
E. None of the above is correct

2. Anemia refers to the deficiency of:

A. Blood plasma
B. Erythrocytes
C. Platelets
D. Hb
E. Both B and D are correct

3. Which symptoms are consistent with aplastic anemia but not with pernicious anemia?

A. Petechia and purpura
B. Pallor
C. Satique
D. Hypoxia
E. Neuropathy

4. The peripheral blood smear of a severaly anemic patients reveals oval macrophages, hyper segmented neutrophils, and decreased platelets. The most lickely cause of the anemia is:

A. A red cell membraine protein defect
B. Vitamin B_{12} or folate deficiency
C. Marrow hyperplasia
D. Iron deficiency
E. Marrow hypoplasia

5. Ineffective erythropoiesis is characteristic of which one of the following conditions?

A. Hereditary spherocytosis
B. Erythroblastosis fetalis
C. B-Thalassemia major
D. Anemia of chronic disease
E. Sickle cell anemia

6. A 25-year-old African-American man with a history of severe life-long anemia requiring many transfusions has nonhealing by ulcers and recurrent periods of abdominal and chest pain. What is it?

A. Sickle cells anemia
B. Increased erythrocyte osmotic fragility
C. Anisocytosis
D. Teardrop-shaped cells
E. Decreased erythropoietin

7. In adult patients with sickle cell anemia very often occur repeated episodes of splenic infarction. The spleen in this patient would be expected to be:

A. Enlarged
B. Shrunken
C. Normal sized

8. A man lives in mountains within 10 years. What changes of indices of blood test may be found out in him?

A. Increased of Er number
B. Decreased HB content
C. Decreased of color index value
D. Decreased in reticulocytes count
E. Appearance erythroblast in blood

9. Individuals at risk for Fe-deficiency anemia may include all of the following except

A. Those having undergone a gastroectomy

B. Those with neoplastic disease
C. Those with minor chronic blood loss
D. Those with hypoaciditas gastritis
E. Those with massive acute blood loss

10. What kind of disorders of total blood volume appears in case of absolute erythrocytosis?

A. Polycytemic hypervolemia
B. Oligocytemic hypervolemia
C. Oligocytemic hypovolemia
D. Simple hypervolemia
E. Simple hypovolemia

11. Anemia, leuko- and thrombocytopenia, color index-1.3, presence of megaloblasts and megalocytes were determined in the laboratory analysis of blood of a patient a year later after he was operated on for subtotal resection of the stomach for the ulcer of lesser curvature of the stomach. What factor deficiency results in these changes?

A. Gastromucoprotein
B. Gastrin
C. Pepsin
D. Chlorine hydrate
E. Mucin

12. Amino acids replacement in alpha and beta chains of hemoglobin takes place in a number of hemoglobinopathies. Which of them is typical for HbS (sickle-cell anemia)?

A. Glycine to serine
B. Aspartate to lysine
C. Methionine to histidine
D. Glutamate to valine
E. Alanine to serine

13. Hereditary microspherocytic hemolytic anemia (Mincovsky-Shoffar disease) was diagnosed in a woman aged 34. What mechanism caused hemolysis of erythrocytes in the patient?

A. Enzymopathy
B. Hemoglobinopathy
C. Autoimmune impairment
D. Membranopathy
E. Hypoplasia of bone marrow

14. Megaloblastic anemia was diagnosed in a patient. What substance deficiency may use the development of this disease?

A. Cyanocobalamin
B. Cholecalciferol
C. Magnesium
D. Glycine
E. Copper

15. Three years ago a managed 45 was operated on for stomach resection. After the operation the content of erythrocytes in the blood is 2.0×10^{12}, Hb 85 g/l, color index – 1,27. What vitamin absorption is impaired that causes the change of erythropoiesis?

A. C
B. P
C. A
D. B_6
E. B_{12}

16. A patient, carrier of hereditary sickle-cell erythrocytes anomaly, had pneumonia accompanied by hemolytic crisis and development of anemia. What is the main cause of hemolytic crisis in this case?

A. Hyperoxia
B. Heterozygosis HbS
C. Mutation of structural gene
D. Hypoxia caused by pneumonia
E. Blood osmolarity change

17. Examining the oral cavity of a patient, a dentist paid attention to the presence of inflammatory-dystrophy process in the mucous membrane (Gunter's glossitis, atrophic stomatitis). Blood analysis revealed hyperchromic anemia. What factor is a cause of this disease?

A. Hypovitaminosis B_6
B. Hypovitaminosis A
C. Increase of stomach juice acidity
D. Hypovitaminosis B_1
E. Hypovitaminosis B_{12}

18. A female patient complains of malaise, weakness, breathlessness, rapid fatigability, and dizziness. Her blood test data: erythrocytes – 1.8×10^{12}/L, Hb – 80g/L, leukocytes – 3.2×10^{9}/L, color index – 1.5. Anisocytosis, poikilocytosis, megaloblasts, megalocytes were found in smear. What is the possible diagnosis?

A. B_{12}-deficiency anemia
B. Posthemorragic anemia

C. Acute leukemia
D. Fe – deficiency anemia
E. Hemolytic anemia

Unit 18:

1. A patient, who was exposed to ionizing radiation, has panmyelophtisis and secondary infection. All of the following are characteristic of panmyelophtisis except

A. Agranulocytosis
B. Anemia
C. Thrombocytopenia
D. Lymphopenia
E. Eosinophilia

2. A patient with leukemia has general number of leukocytes $180 \cdot 10^9/_L$. What kind of leukemia does in these case?

A. Leukemic
B. Leukopenic
C. Subleukemic
D. Aleukemic

3. Polycythemia vera is associated with all of the following findings except

A. Erythrocytosis
B. Leukocytosis
C. Thrombocytosis
D. Increased erythropoietin
E. Splenomegaly

4. Complete blood test in 40-year-old male showed the following:

Hb = 75 $g/_L$
Er = 2,5 $^T/_L$
L = 2 $^G/_L$
Platelets = 18 $^G/_L$
Monocytes = 1%
Myeloblasts = 91%
E = 1%
Band form neutrophils = 1%
Segment neutrophils = 30%
Lymphocytes = 3%

The physical examination showed:

- skin to pale with petechiae
- hemorrhage of mucous in the oral cavity
- Hepato-lienal syndrome
- Enlargement of lymphoid glands in all groups

What is the disease?

A. Acute lymphoid leukemia
B. Chronic lymphoid leukemia
C. Acute myeloid leukemia
D. Chronic myeloid leukemia
E. Cancer of the liver

5. A 38-year-old female was brought to physician. The physical examination showed enlargement of lymphoid glands in all groups. The spleen and liver were also enlarged. The skin is pale with petechiae, hemorrhage of mucous in the oral cavity.
CBC: Hb = 80 g/l, Er = 2,5 $^{T}/_{L}$, L = 100 $^{G}/_{L}$, Plateletes 18 $^{G}/_{L}$, Lymphoblasts = 60%, Lymphocytes 35%.
Analyze the blood test and make up conclusion:

A. Acute lymphoid leukemia
B. Chronic lymphoid leukemia
C. Acute myeloid leukemia
D. Chronic myeloid leukemia

6. Which of the following substances may stimulate production of the colony stimulating factors in bone marrow? (not only one right answers)

1. IL-1
2. TNF
3. Epinephrine
4. Glucocorticoids
5. Serotonin
6. Thrombin

7. Mechanism of the redistribution leucopenia are: (not only one right answers)

1. Suppression of leukopoiesis
2. Increased margination of leukocytes in the vascular bed
3. Increased extravasation of leukocytes tissues
4. Increased leukocyte destruction in the vascular bed
5. Low rate of L released from the marrow storage pool
6. Increased L destruction by the spleen

Unit 19:

1. Which finding would be LEAST expexted in disseminated intravascular coagulation (DIC)?

A. Increased fibrin degradation products
B. Prolonged activated partial thromboplastin time

C. Prolonged prothrombin time

D. Prolonged thrombin time

E. Thrombocytosis

2. A 23-year-old female pathology student was found to have a prolonged bleeding time (BT) and a prolonged activated partial thromboplastin time. Her platelet count was normal. These findings are strongly suggestive of:

A. Classic hemophilia

B. Thrombasthenia

C. Congenital afibrinogenemia

D. Von Willebrand disease

3. Which of the following defect is associated with hemophilia?

A. Deficiency of Hb S

B. Deficiency of Hb A

C. A defective gene in the X-chromosome

D. A defective gene of Y-chromosome

4. A 25-year-old man has a lifelong hemorrhagic diathesis. The PT (prothrombin time) and bleeding time are normal, but the APTT (activated partial thromboplastin time is prolonged). The most likely cause of the bleeding disorder is:

A. Factor VIII deficiency

B. Factor IX deficiency

C. Factor VII deficiency

D. A platelet functional disorder

E. Von Willebrand's disease

5. Characterize what is disease if hemogram those of the following:

General amout of L – 260G/l , Thrombocyte 80,0G/l, Er – 3,0 $T/_L$ hemorrhagic syndrome presents

Leucogram:

E	B	Neutrophils				L	M
		m	meta	band	segment		
12	10	40	0	1	17	12	8

Index of a shift to neutrophils less, than norm

6. A 27-year-old male patient has hemorrhage after injury of vessel that lead to formation of friable thrombi. What coagulation factor deficiency has led to this disorder?

A. II (prothrombin)

B. III (thromboplastin)
C. VII (proconvertin)
D. XII (Hageman's factor)
E. XIII (fibrin stabilizing factor)

7. Hemophilia B was diagnosed in a child who has hemorrhagic syndrome. This type of hemophilia results from absence of:

A. Coagulation factor IX (Christmas's factor)
B. II (prothrombin)
C. VIII (antihemophilic globulin)
D. XI (thromboplastin)
E. XII (Hageman's factor)

8. It is known that thrombus undergo some changes after its formation. What sort of thrombus formation is the most dangerous for a patient?

A. Aseptic lysis
B. Septic lysis
C. Organization without recanalization
D. Organization with recanalization
E. Calcification of thrombus

Unit 21/22/23:

1. Thrombosis of coronary artery has caused the myocadial infarction development what mechanism oft he impairment dominant in this disease?

A. Electrolyte-osmotic
B. Acidotic
C. Protein
D. Lipid
E. Calcic

2. Acute cardiac insufficiency appeared in a patient with arterial hypertension due to hypertensive crisis what mechanism of cardiac insufficiency is the main in this case?

A. Overload of heart by resistance
B. Absolut coronary insufficiency
C. Relative insufficiency
D. Overload of heart rush of blood
E. Myocardial impairment

3. A patient aged 59 was hospitalized at cardiological department in a sever state with the diagnosis of acute myocardial

infarction of the posterior wall of the left ventricle and septum and starting pulmonary edema. What is the primary mechanism causes the development of pulmonary oedema in the patient?

A. Pulmonary arterial hypertension
B. Left ventricular failure
C. Pulmonary venous hypertension
D. Hypoxemia
E. Decrease of alveolocapillary diffusion of oxygen

4. Patient aged 18 complain of general weakness, quick fatigability, depressed mood she has asthenic type of constitution. Pulse 68 · per min AP-90/60mm hg primary neurocirculator arterial hypertension was diagnosed. What is the main factor of decreasing of arterial pressure in a patient?

A. Decreas of minute volume of the blood
B. Decreas of cardiac output
C. Decreas of the tension of resistant vessels
D. Hypovolemia
E. Deposition of the blood in the vines of systemic circulation

5. A patient has stable and marked increase of arterial pressure increased extracellular volume of fluid, increased content of NA+ and decrease of K+ in the blood, positive effect of saluretic. What is the mechanism hypertension development in a patient?

A. Mineralocorticoid
B. Renin-angiotensine
C. Renovascular
D. Reflexogenic
E. Centr-ischemic

6. While climbing upstairs on the 5th floor a patient has got an increased arterial pressure. The cause is the increase of?

A. Minute volume of the blood
B. The number of functioning capillaries
C. Content of ions in blood plasma
D. Viscosity of the blood
E. Circulating volume of the blood

7. In making correct diagnosis of myocardial infraction the main role belongs to enzymodiagnosis. What enzyme content blood level definition is the most important during the first 2-4 hours after infraction?

A. Aldolase

B. Lipoprotein lipase
C. Alanine aminotranspherase
D. Creatin phosphokinase
E. Acetylcolinesterase

8. On ECG analysis was determind sinus rhythm, regular, interval RR -0.58 sec, location and duration of other intervals, waves and segment are not changed. Call the type of arrhythmia?

A. Sinus tachycardia
B. Sinus bardycardia
C. Idioventricular rhythm
D. Sinus arrhythmia
E. Ciliary arrhythmia

9. One of the most dangerous in pathogenesis of myocardial necrosis is the further increase of the zones of necrosis, dystrophy and ischemia. The important role in this belongs to the increase of the oxygen use by myocardium. What substance contributes to this process?

A. Chlorine ion
B. Cholesterol
C. Catecholamine
D. Acetylcoline
E. Adenosine

10. The functioning of separate parts of conductive system is stopped on the isolated heart by actions of cooling. What structure is cooled if the contraction stopped at first, but then they with a rate 2 times slower then initial one?

A. Sinoatrial node
B. Purkinji`s fibres
C. Limbs of His` bundle
D. Atrioventricular node
E. His` bundle

11. A patient with chronic glomerulonephritis has odema AP-210/100 mm Hg the rate of heartbeat is 85 per minute the borders of the heart are dilated. What is the leading mechanism in the development of arterial hypertension?

A. Increase of sympathetic system activity
B. Hyperfunction of the heart
C. Activation of renin-angiotensin-aldosterone system
D. Increase of circulating volume of the blood
E. Increase of vasopressin output

12. The patients ECG shows that interval RR=1.5 sec. heart rat -40 per min. What is the pacemaker of the heart?

A. Left limb of His` bundle
B. Sinus nod
C. His`bundle
D. Right limb of the His bundle
E. Atrioventricular nod

13. Pulmonary odema developed in a patient with hypertonic crisis. What is the main factor in the pathogenesis of his state?

A. Increase of arterial pressure
B. Permeability increase of the vessels of pulmonary circulation
C. Increase of hydrostatic pressure in the capillary of the lung
D. Resistability increase of the lung vessels
E. Decrease of oncotic pressure of blood

14. During the examination of blood for activity of AsAT and AIAT in the patient who complained of pain in the chest and in upper in part of the abdomen , the following result were received activity of AsAT 2 time higher than AIAT activity what disease dose the patient have?

A. Acute infection hepatitis
B. Acute pancreatitis
C. Myocardial infarction
D. Chronic hepatitis
E. Cirrhosis of the liver

15. Redistribution of organ blood supply took place in a young man, aged 20 during the load. What organ did the blood flow increase in most of all?

A. Brain
B. Kidneys
C. Liver
D. Skeletal muscles
E. Heart

16. Clinical manifestation of pulmonary oedema appeared in a patient with left ventricular failure. Which of the pathogenic mechanisms is the primary in such pathology?

A. Hydrodynamic
B. Congestive
C. Colloid-osmotic
D. Lymphogenous

E. Membranogenous

17. A patient has cyanosis enlargement of the liver, oedema of the lower extremities due to the right ventricular failure. What is the cause of right ventricular failure development?

A. Cardiogenic cirrhosis of the liver
B. Functional shunting in lungs
C. Hypercatecholaminemia
D. Increase of venous pressur
E. Hypotension of pulmonary circulation

18. A woman aged 25, complains of constant pain in the heart area, breathlessness on movement general malaise. Objectively: skin is place and cold, acrocyanosis, pulse -96/min AP-105/70 mm Hg. heart border's shifted 2 cm left. The first sound is weakened over the apex of heart, there is systolic murmur over the apex. Diagnosis is mitral insufficiency. What is the cause of the blood circulation failure?

A. Myocardial overload by increased blood volume
B. Myocardial overload by increased of resistance of blood outflow
C. Mayocardial failure
D. Volume decreased of circulating blood
E. Volum increased of vasvular bed

19. 1500 ml of different solution were given intravenously to a patient with acute myocardial infarction on 8 hours. Also oxygen inhalation were give. Death occurs due to pulmonary oedema. What was the cause of the pulmonary oedema?

A. Overload of the left ventricle by the volume
B. Decrease of oncotic pressure due to hemodilution
C. Allergic reaction
D. Neurogenic
E. Oxygen inhalation

20. Function hypertrophy of the left ventricle of the heart has developed in a sportsman ages 20, due to constant physical load. What morphofunctional process has lead to hypertrophy?

A. Increase of cell size and number of contractile organells
B. Increase of fibroblast number
C. Increase of the number of conductive cardiomyocytes
D. Increase of the amount of connective tissue
E. Increase of the amount of fat tissue

Unit 24/25:

1. At a patient with chronic inflammation of submandibular gland the hyposalivation is observed. Violation of incretion of what substance can we observe here?

A. Parathormone
B. Calcitonin
C. Parotin
D. Glucagon
E. Somatostatin

2. Poisoning by the phosphoorganic substances entailed the protracted strengthening of salivation at a patient. What can be the result of hypersalivation in this case?

A. Dehydration hyposmolar
B. Hyperhydration hyposmolar
C. Violation of digestion in a stomach
D. Improvement of digestion in a stomach
E. Delay of evacuation of chyme from a stomach in an intestine

3. A man delivered in a hospital with acute pancreatitis, which was complicated by shock. What is the basic mechanism of development of pancreatitis shock?

A. Stimulation of pancreatic secretion.
B. Entry of activated proteases in blood.
C. Violation of outflow of pancreatic juice.
D. Decrease of incretion of insulin.
E. Rise of arterial pressure.

4. At a patient of 38 years that transmitted hepatitis and continues to use an alcohol, the signs of cirrhosis of liver developed. They are ascites and edemata of lower extremities. What changes of composition of blood are deciding in development of hepatic edemata?

A. Hypoglycemia
B. Hyper-, dislipemia
C. Hyperkalemia
D. Hypogammaglobulinemia
E. Hypoalbuminemia

5. Patient with an endemic goitre appealed to the doctor with complaints on suppuration from gingival pockets and loosening of teeth. What is the basic factor of development of periodontitis?

A. Hypersalivation
B. Stress influence
C. Endocrine violations
D. Disturbance of swallowing
E. Deficient nutrition

6. A patient with the alcoholic cirrhosis of liver grumbles about general weakness and asphyxia. The decline of arterial pressure, ascytes, expansion of superficial veins of front wall of stomach, splenomegaly, are exposed. What violation of hemodynamics is observed at a patient?

A. Heart insufficiency
B. Insufficiency of the left ventricle of heart
C. Insufficiency of the right ventricle of heart
D. Collapse
E. Portal hypertension

7. At a patient after poisoning by mushrooms appeared the yellow coloring of skin and sclers, dark color of urine. What pigment causes coloring of urine at a patient with hemolytic jaundice?

A. Conjugated bilirubin
B. Unconjugated bilirubin
C. Urobilin
D. Verdoglobin
E. Biliverdin

8. For the design of gastric ulcer atofan was entered in the gastric arteries of an animal, which causes it's sclerosis. What mechanism of damage of mucus membrane of stomach is conducting in this experiment?

A. Disregulative
B. Neurodystrophy
C. Mechanical
D. Ischemic
E. Neurohumoral

9. A patient aged 57 was admitted to a clinic with suspicions on Zollinger-Ellison syndrome. What impairment of secretory gastric function is the most possible?

A. Hyperacid hyposecretion
B. Hyperacid hypersecretion

C. Achylia

D. Hypoacid hypersecretion

10. A patient aged 35 with ulcerons disease had a rejection of antral portio of the stomach. What gastro-intestional hormone secretion will be impaired due to operation?

A. Gastrin

B. Secretion

C. Neurotensin

D. Histamine

E. Cholecystokinin

11. A patient has a stone in the common bile duct. The impairment of what digestive process is observed in this case?

A. Digestio of carbohydrates

B. Absorption of carbohydrates

C. Digestio of fats

D. Absorption of proteins

E. Digestio of proteins

12. Spasmodic pains in the abdomen and repeated diarrhea in a healthy person 3-5 hours later after taking meals. This was preceded by nausea and vomiting, general weakness, loss of appetite. What is the most possible cause of this case?

A. Chronic pancreatitis

B. Food intoxication

C. Enterocolitis

D. Hyperacid state of the stomach

E. Chronic gastritis

13. A patient had been taking antibiotics of a wide spectrum of action for asking period of time that caused decrease of appetite, nausea, and diarrhoea with saprogenic smell. What is the side effect of treatment?

A. Direct irritative action

B. Hepatotoxic action

C. Allergic reaction

D. Nephrotoxic action

E. Dysbacteriosis

14. On examination of a patient suffering from acute pancreatitis increased amount of chylomicrons was determined in the blood. What enzyme activity is sharply decreased in this pathology?

A. Lipoproteinlipase
B. Pancreatic lipase
C. Pancreatic phospholipase
D. Tissue triglyceride lipase
E. Tissue diglyceride lipase

15. The analysis of gastric juice of an elderly man who complained of unmotivated weakness, sickness, absence of appetite showed achylia, achlorhydrea, presence of lactic acids and coagulated blood, decreased of pepsin secretion. What disease causes such clinical-laboratory symptoms?

A. Cancer of the stomach
B. Chronic gastritis
C. Chronic pancreatitis
D. Cavitary Maldigestion
E. Acute gastritias

Unit 26:

1. In inflammatory process colloidal properties of bile are impaired in gall bladder and this result in the formation of gallstones. The crystallization of what substance is the main cause of the formation

A. Cholesterol
B. Urate
C. Chloride
D. Oxalate
E. Phosphate

2. Flabby contraction of gall bladder was revealed In a woman aged 55 after introducing some of vegetable oil into duodenum. What hormone insufficiency with such state?

A. Gastrin
B. Cholecystokinin
C. Enterogastrin
D. Vip
E. Pancreozymin

3. A patient aged 25 has a diagnosis of chronic hepatitis. A patient has lost 10 Kg of his body weight for 2 months. Objectively: the skin is dry, desquamative, and pale with yellowish colour, small punctate hemorrhages on the skin, stomatorrhagia. The impairment of what hepatic function do petechial hemorrhage and stomatorrhagia prove?

A. Glycogen synthetic
B. Chromogenic
C. Detoxicative
D. Depositing
E. Protein synthetic

4. On examination bile congestion in the liver and cholelitiasis were revealed in a patient. Point out the main component of cholelitiasis in this state?

A. Calcium bilirubinate
B. Triglycerides
C. Protein
D. Mineral salts
E. Cholesterol

5. What kind of jaundice is characterized amount of direct bilirubin in the blood, appearance of bilirubin in urine, acholic stool?

A. Obstructive
B. Hemolytic
C. Parenchymatous

6. Residual nitrogen and urea were determined in the patient`s blood analysis. The amount of urea in the residual nitrogen is considerably reduced. What organ disease is characterized by this analysis?

A. Intestine
B. Kidney`s
C. Stomach
D. Liver
E. Heart

7. A patient complains of general of weakness, boring pain in the abdomen, bad appetite, suspicion on jaundice. Blood serum contains 77.3 mcmol/L of total bilirubin and 70.76 mcmol/L of conjugative bilirubin . what the most possible type of jaundice?

A. Acute hepatitis
B. Mechanical jaundice

C. Parenchymatous jaundice
D. Hemolytic jaundice

8. In 70 `s the scientists determined that the cause of severe jaundice in newborns was the impairment of binding of bilirubine in hepatocytes. What substance is used for the formation of conjugate?

A. Pyruvic acid
B. Uric acid
C. Glucoronic acid
D. Sulphuric acid
E. Lactic acid

9. A manged 38 with ecteric skin has anemia, enlarged spleen, hyperbilirubinemia, urobilinuria, hypercholic stool. What condition are these changes typical for?

A. Subhepatogenous jaundice
B. Cellular-hepatogenuos jaundice
C. Gilbert`s syndrome
D. Suprahepatogenous jaundice
E. Syndrome of hepatic insufficiency

10. Which of The factors plays the leading role in the development of encephalopathy in hepatic insufficiency?

A. Hypoproteinemia
B. Hypofibrinogenia
C. Hyperbilirubinemia
D. Increase of toxic substances in the blood
E. Hyperaldosteronism

Unit 27:

1. Two weeks after recovery from a severe streptococcal angina, a 15 year old girl is seen because of the acute onset of periorbital edema oliguria, hematuria, nausea and head ache. The most likely diagnosis is

A. Post streptococcal glomerulonephritis
B. Nephrotic syndrome
C. Amyloidosis of kidney
D. Focal segmental glomerulosclerosis
E. Rapidly progressive glomerulo nephritis

2. What is not quantitative disorders of renal insufficiency?

A. Oliguria
B. Polyuria
C. Anuria
D. Nicturia
E. Pollaciuria
F. Glucosuria

3. What is not qualitative disorders of renal insufficiency?
A. Proteinuria
B. Hematuria
C. Lipiduria
D. Glucosuria
E. Oliguria

4. An individual has an elevated blood level of urea and creatinine because of complete calculi blockage of one ureter. This is referred to as:
A. Pre renal disease
B. Intra renal disease
C. Post renal disease
D. Preclampsia
E. Hypercalcemia

5.A 26 year old woman with a butterfly rash, massive arthralgia, proteinuria, oliguria was hospitalized with diagnosis lupus nephropathy(is the renal component of systemic lupus erythrematosus-SLE) what is the type due to classification of the world health organization(WHO) presents?
A. Type 1 (observable renal disorders)
B. Type 2 (focal mesangial form)
C. Type 3 (focal proliferative form)
D. Type 4 (diffuse proliferative from)
E. Type 5 (membranous type)

6.All of the following can lead to (CR) chronic renal insufficiency except
A. Glomerular
B. Tubular disease
C. Dm(diabetes mellitus)
D. Gout
E. Acute pneumonia

7.the narrowing of afferent glomerular renal arteriole caused the decrease of diuresis. The cause of this is a decrease of:

A. Reabsorption of glucose

B. Effective filterable pressure

C. Reabsorption of ions

D. Reabsorption of urea

E. Reabsorption of water

8.A man aged 32 has been ill with chronic glomerulonephritis for 4 years. He was hospitalized with the sign of anasarca. AP-185/105 mmHg. Blood analysis shows: Hb-110gm/l:erthrocytes-$2.6x10^{12}$/l: leucocytes-$9.5x10^{9}$/l: residual nitrogen-32 mmol/l: total protein-50 gm/l. What change points out glomerulonephritis with nephrotic syndrome?

A. Anemia

B. Arterial hypertension

C. Hypoproteinemia

D. Hyperzotemia

E. Leukocytosis

9. Edemas appeared in a patient after streptococcus infection. The urinalysis was made and allowed to make a diagnosis of acute glomerulonephritis. What pathologic changes in urine confirm the diagnosis?

A. Fresh erythrocytes

B. Protein only with low molecular mass (up to 40000)

C .Increased excretion of sodium

D. Protein with high molecular mass and lixiviated erythrocytes

E. Leukocyturia

10. What pathology of kidney is characteristic for non-massive proteinuria?

A. Nephritis syndrome

B. Urethritis

C. Chronic renal failure

D. Acute renal failure

E. Nephrotic syndrome

11. After poisoning by salts of heavy metals a patient had glucosuria without hyperglycemia, polyuria, natriuresis, non-gas acidosis, urine pH=5.8 , Which of the structure is damaged?

A. Nephron tubules

B. Nephron glomeruli
C. Nuclei of hypothalamus
D. Adrenal cortex
E. B-cells of Langergans Islands

12. A patient with chronic renal disease is edematous, and his BP is 210/100 mm Hg. What is the main link in pathogenesis of arterial hypertension of this patient?

A.proteinuria
B. Hematuria
C. hyperazotemia
D. Increase of circulatory blood volume
E. Activation of renin-angiotensin system

Unit 28:

1. Which is not a characteristic of stress syndrome?
   A. Adrenal atrophy
   B. Atrophy of the thymus
   C. Anemia
   D. Bleeding gastrointestinal ulcers
   E. Shrinkage of lymphatic organs
2. Which characterizes the alarm stage?
   A. Increased lymphocytes
   B. Increased sympathetic activity
   C. Eosinopenia
   D. Increased parasympathetic activity
3. Glucocorticoids would be highest during the stage of:
   A. Exhaustion
   B. Alarm
   C. Resistance
4. Long-term corticosteroid therapy may cause. Which of the following?
   A. Delayed wound healing
   B. Osteoporosis
   C. Peptic ulcers
   D. Hyperkalemia
5. Match the circumstance the hypersecretion a) of Aldosterone, b) of Glucocorticoids

A. Increased cardiac output
B. Hyperglucemia
C. Hypernatremia
D. Basal metabolic race increases
E. Water retention increases
F. Inhibits inflammatory response
G. Promotes exsudate phase of inflammation
H. Inhibits allergic processes

6. The production of cortisol in response to stress can be initiated by:

A. Hypothalamus, anterior pituitary, adrenal cortex
B. Hypothalamus, sympathetic nerve fibers, cortex
C. Hypothalamus, sympathetic nerve fibers, adrenal medulla
D. Brain cortex-hypothalamus-CRF-anterior pituitary, adrenal cortex

7. Severe stress results in all except:

A. Hypertrophy the cortex of adrenal glands
B. Shrinkage of the thymus
C. Shrinkage of lymphatic organs
D. Ulcers in stomach and duodenum
E. Increased immune reactivity

8. Which of following hormones has got permission effect on epinephrine (norepinephrine)?

A. Glucocorticoides
B. Mineralcorticoides
C. Insulin
D. Thyroid hormones

9. What is not true?

A. Epinephrine increases blood sugar
B. Epinephrine elevates blood pressure
C. Epinephrine stimulates heart work
D. Epinephrine don't exhaustion if stress contiues for a long time

10. What is not of diseases of adaptation?

A. Atherosclerosis
B. Diabetes mellitus
C. Infarction of the heart
D. Gigantism
E. Impotence

11. Liquidator of an accident at Chernobilskaya AES began complaining of increased excitability, nervousness, heartbeat, decrease of body weight, constant weakness, body tremor, feeling of fever, bad heat endurance. What gland hyperfunction may be the cause of such state?

A. Thyroid gland
B. Adenohypophysis
C. Adrenal gland
D. Medulla of adrenal gland
E. Parathyroid gland

12. Muscular weakness, adynamia, decrease of body temperature, hypoglycemia, developed in a dog after two-sided resection of adrenal gland. What other manifestation of adrenal insufficiency may be noted?

A. Lymphopenia
B. Arterial hypotension
C. Increase of glycogen synthesis
D. Hypernatriemia
E. Hypokalemia

13. A woman complains of increased irritability, perspiration, weakness, loss of body, weight, tremor of extremities, increased heartbeat rate, and exophthalmia. What metabolic impairment in the organism accompanies this disease?

A. Increase of adenosine triphosphoric acid synthesis
B. Decrease of organism sensitivity to hypoxia
C. Weakening of phospholipase activation
D. Increase of basal metabolism
E. Decrease of cholesterol lysis

14. A patient who suffered from severe thyrotoxicosis had been operated on for strumectomy after that weakness, sensitivity to cold, increase of body weight, paleness and dryness of skin developed. What are the other manifestations of hypothyrosis?

A. Inhibition of CN S activity
B. Tachycardia
C. Increase of basal metabolism
D. Increase of intestinal peristalsis
E. Decrease of tolerance to carbohydrates

15. In case of hypercortisolism – Cushing's disease – the

following changes in the organism take place:

A. Development of cachexia

B. Impoverishment of the liver with glycogen

C. Hyperglycemia

D. Hypotension

E. Lymphocytosis

16. A patient was admitted to the hospital with complaints of loss of weight, quick fatigability, darkening of skin. His heart sounds are dull. What are the other manifestations of adrenal insufficiency?

A. Lymphopenia

B. Adynamia

C. Arterial hypertension

D. Increase of minute blood volume

E. Increased appetite

17. A patient admitted to the hospital complains of quick, fatigability, loss of weight, hyperpigmentation of the skin. Her heart sounds are dull. She has pulse rate – 96 beats per minute and BP – 90/50 Hg. What metabolic impairments are observed in hypocortisolism?

A. Hyperkalemia

B. Increase of glycogen synthesis

C. Hypernatremia

D. Hyperhydration

E. Hypoglycemia

18. The, manifestations of hypoparathyrosis developed in a patient after strumectomy. What changes in the organism are observed in this case?

A. Hypophosphatemia

B. Resorption of bone tissue

C. Acidosis

D. Hypocalcemia

E. Decrease of neuromuscular excitability

19. Small height, disproportional development of the body, and insufficient mental development were found in a boy of 10 during examination. What hormone deficiency caused these changes?

A. Thyroxin

B. Parathormone

C. Thyrocalcitonin
D. Adenocorticotropic hormone
E. Oxytocin

20. With the help of indirect calorimetrical measurement it was determined that the basal metabolism of the patient was 40% lower than the proper, one. What endocrine gland hypofunction is the cause of described changes?

A. Adrenal glands
B. Thyroid gland
C. Epiphysis
D. Thymus
E. Pancreas

Unit 29:

1. What changes in adult organism may be evoked by hypersecretion of growth hormone?

A. Intensification of lipolysis
B. Development of diabetes mellitus
C. Intensification of urea production
D. Reduction of transport of amino acids to the cell
E. Increase in content of calcium in blood

2.A 40 years old patient complaints of decreased capability of working, sleepiness, sensitivity to cold, fragility and coming out of hairs, dryness of skin, and edema of face and extremities. There is no formation of pit under the pressing at the anterior surface of patient's calves. patient has slow tendon reflexes and bradicardia. What infringement do these changes result from?

A. Vitamin deficiency
B. Adrenal insufficiency
C. Hypoparathyroidism
D. Hypothyroidism
E. Iron deficiency

3. Influence of unfavorable psycho-emotional factor upon a patient results development of non –specific pathological process, which course consists of 3 stages anxiety reaction;2)stage of resistance;3)stage of exhaustion. This process involves system hypothalamus-pituitary-adrenal cortex. What is the name for this process?

A. Stress
B. Parabiosis
C. Adaptation
D. Compensation
E. Dominance

4. A doctor suspects the hypothyroid goiter in a patient with enlarged thyroid gland .What sign has a decisive importance for establishing the diagnosis?

A. Decrease of basal metabolism
B. Bradicardia
C. Edemas
D. Arterial hypotension
E. Hypodynamism

5.Arterial hypotension, muscular weakness, and periodic convulsions appear in the patient with hepatic cirrhosis. Content of sodium is increased and content of potassium is decreased in patient's blood. What kind of endocrine disorders underlies this symptoms?

A. Primary hyperaldosteronism
B. Hypopituitarism
C. Secondary hyperaldosteronism
D. Hyperpituitarism
E. Hypoaldosteronism

6.Prolonged intake of mineralocorticoid led to development of muscular weakness in a patient. What gives rise to these symptoms ?

A. Hyperkalemia
B. Hypokalemia
C. Hypernatremia
D. Hyponatremia
E. Hypervolemia

7. What hormone increased secretion causes becoming thin at the period of enhanced growth?

A. Progesterone
B. Prolactin
C. Glucagon
D. Growth hormone
E. Insulin

8.What kind of endocrine disorders lead to obesity?

A. Hypogonadism
B. Hypofunction of adrenal glands
C. Hyperparathyroidism
D. Hypercortisolism
E. Hyperaldosteronism

9.50-years-old female patient ,who has operated on thyroid gland for diffuse toxic goiter ,begins complaining that she is spiritless and slow, has fast fatigability, increased working ability, sleepiness, worsening of memory and increasing of body weight. At examination the patient has dry skin ,edematous face, and striped nails with broken edges. What is your assumable diagnosis?

A. Myxedema
B. Cushing's disease
C. Acromegaly
D. Obesity
E. Thyrotoxicosis

10.A 25-years-old male patient ,who endured influenza, complains of increased thirst(he drinks 5 to 6 litres of water daily),frequent abundant urination ,and loss of body weight. Patient has dry mucous membranes and dry skin with reduced turgor. Urinolysis of this patient displays ;urine is colourless, its specific gravity -1.000-1.004,leukocytes and erythrocytes -1 to 2 in field of vision. What pathology doses this patient displays suffers from?

A. Conn's disease
B. Diabetes mellitus
C. Diabetes insipidus
D. pheochromocytoma
E. secondary hyperaldosteronism

Unit 30:

1. At a patient after traumatic cutting of sciatic nerve appeared the trophic changes of skin. What is the basic mechanism of it appearance?

A. Phagocytosis of nervous endings
B. Phantomic pain
C. Stopping of axoplasmatic current
D. Destruction of myelin membrane
E. Damage of intercepts Ranvie

2. As a result of injuring at a patient were deleted thyroid glands. Clinically it showed up in a languor, thirst and acute increase of neuromuscular excitability. With violation of exchange of what substance is it linked?

A. Calcium
B. Manganese
C. Chlorine
D. Molybdenum
E. Zinc

3. At a man of 35 years after a car failure the massive trauma of lower extremities is exposed without considerable external loss of blood. A victim stays in excited spirits. What component of pathogeny of traumatic shock at a patient is conducting and does need immediate correction?

A. Internal hemorrhage
B. Pain
C. Internal loss of plasma
D. Intoxication
E. Violation of function of organs

4. At a woman of 68 years after a stroke the motions in overhead and lower right extremities are absent. Tone of muscles of these extremities and reflexes in them are promoted. Pathological reflexes are present. What paralysis is it?

A. Extrapyramid
B. Paraplegic
C. Peripheral
D. Central
E. Miastenic

5. At patients with epilepsy appeare the centers in the cortex of cerebrum, that functionate on principles of pathological determinants. What is in basis of mechanism of forming of these centers?

A. Outboundary
B. Phenomenon of falling out
C. Formation of generator of the pathologically increased excitation
D. Overexcitation
E. Parabiosis

6. In the experiment at the collision of food and defensive reflexes an animal had a neurosis with the defeat of internal organs. Development of what illnesses can be directly related to the neurosis?

A. Itsenko-Kushing disease
B. Diffuse glomerulonephritis
C. Stomach ulcer
D. Hepatitis
E. Anemia

7. At a woman who is ill on myasthenia, there were disorders of breathing, that need application of artificial ventilation of lungs. What type of insufficiency of breathing developed at this sick?

A. Obstructive
B. Centrogenic
C. Thoracodiaphragmatic
D. Neuromuscular
E. Restrictive

8. Patient of 43 years, 4 months ago transmitted the traumatic amputation of the lower left extremity. Now he grumbles about feeling of presence of the amputated extremity and permanent, strong, sometimes unendurable pain in it. What is the type of pain?

A. Phantom
B. Causalgia
C. Neuralgia
D. Thalamic
E. Reflex

9. After a car catastrophe at a patient the trauma of middle third of shoulder is diagnosed with the incomplete rupture of middle nerve. Except for motive and sensory disorders below from the place of trauma, a patient grumbles about acute, burning, unendurable pain. What is the type of pain?

A. Somatic
B. Projection
C. Eccentric
D. Phantom
E. Causalqia

Unit 31:

1. Part of cerebrum was deleted in the experiment, as a result asynergy and dysmetria developed at an animal. What department of cerebrum is remote at an animal?

A. Midbrain
B. Frontal part
C. Parietal part
D. Cerebellum
E. Reticular formation

2. At a patient which grumbles about pain in the area of left shoulder-blade, the heart attack of myocardium is diagnosed. What is the type of pain?

A. Phantom
B. Visceral
C. Eccentric
D. Primary (protopathic)
E. Secondary (epicrytic).

3. Neurosis is characterized by following traits except:

A. Asthenisation of the high nervous system (loss of memory rapid tiredness of intellectual activity)
B. Vegetative disorders (tachycardia, bradycardia)
C. Disorders of sensation
D. Dystrophic ulcer of the legs, stomach
E. Cardiac hypertrophy

4. How does the disturbance of integrative function of CNS manifest?

A. Weakness of analytical-synthetical function of the brain
B. Disturbance of long-term and short-term memory
C. Disturbance of regulation of the emotions and motivations
D. Disturbance of the sleep-waking cycle
E. A, B, C are correct
F. All of the above are correct

5. As it is well-know, that neurodystrophic changes in tissue or organs are depend on such nerves:

A. Afferent (motor)
B. Efferent (sensitive)

C. Vegetative nervous system
D. Cortex of the brain
E. All of the above are correct
F. A, B, D are correct

6. Why the nervous system will be able to cease "to control metabolism" in the tissue (or organ)?
A. Due to hypoxia
B. Mechanical damage of the peripheral nerves
C. Trauma of a brain cortex
D. Microcirculatio disorders in hypothalamus
E. All of the above are correct

7. What are the characteristic of Alzheimer's disease (AD)?
1. Defects on chromosomes 14, 19, 21 (early-onset Familial AD)
2. Aggregation and precipitation of insoluble amyloid or senile in brain tissue and blood vessels
3. Late-onset FAD's dementia
4. Appearing antibrain antibody (autoimmune mechanism)
5. Decreasing oxygen and glucose transport to brain cells
6. Impairment of the hemato-encephalic barrier and nerves impulses transmission

8. All of the following excitory neuromediators except:
A. Dopamine
B. Enkephalin
C. Epinephrine
D. Endorphins
E. GABA (gamma-aminobutyric acid)

9. All of the following classical neuromediators except
A. Acetylcholine
B. Serotonin
C. Histamine
D. Epinephrine
E. Prostaglandin

10. The disturbances of the higher mental activity, development of neurotic state, mental diseases and different psychosomatic disturbances depend on:

A. Peculiarities of personality of individuals
B. Character of their social environment
C. Organization of society on the whole
D. Working conditions and way of life
E. All of the above are correct
F. A and D are correct

Unit 32:

1. Which contains the thalamus and hypothalamus?
A. Diencephalon
B. Cerebrum
C. Medulla oblongata
D. Brain stem

2. All of the following disease (syndrome) is accompanied by progressive dementia except
A. Alzheimer disease
B. Wernicke disease (alcohol encephalopathy)
C. Pick disease (hereditary cerebral atrophy)
D. Phenylketonuria
E. Parkinson's disease

3. A 20-years-old female has been admitted to hospital with complains of poor appetite, frequent headaches, occasionally, "losses of voice", vision, hearing, memory. According to her history in her childhood she was nervous, sensitive, fastidious, cry-baby. The symptoms appear after very difficult examine session at the University. Where the patients occupation requires considerable intellectual and physical efforts.
What form of the nervous system pathology developed in this patient?
A. Psychostenia
B. Hysteria
C. Neurosthenia
D. Neurodystrophy
E. Paresis

4. All of the following diseases may have association with neurosis except
A. Peptic ulcer
B. Essential hypertension

C. Diabetes mellitus
D. Eczema
E. Glomerulonephritis

5. The most common complication of alcohol and narcotic abuse include all of the following except:
A. Chronic hepatitis
B. Cirrhosis of the liver
C. Chronic pancreatitis
D. Cardiomyopathy
E. Athrosclerosis

6. All of the following are related to hyperkinesis except:
A. Hemiplegia
B. Tremor
C. Chorea
D. Myoclonia
E. Tic

Unit 1.The subject, methods and aim of Pathophysiology. The general teaching about diseases, etiology and pathogenesis:

1 – E; 2 – A; 3 – B; 4 – C; 5 – A. the causes 1,2,5 and 6; 6 – B. a condition 3 and 4 6 – E; 7 – D;8 – a) health D, b) disease B,C and E; 9 – A; 10 – A; 11 – C; 12 – E; 13 – C; 14 – A; 15 – C.

Unit 2. Pathogenic effect of environment factors:

1 – B; 2 – D; 3 – A; 4 – A; 5 – E; 6 – A; 7 – D; 8 – G; 9 – A; 10 – A; 11 – F; 12– Respirathorystandill: A,G,H Cardiac arrest: B,C,D,E,F.

Unit 3. Cellinjury:

1– E; 2– E; 3– A,C,D,E,F; 4– A,C,D; 5– G; 6– E; 7– B; 8– D; 9– B; 10– D.

Unit 4/9. Reactivity. Immunity:

1– D; 2– E; 3– A; 4– B; 5 – C; 6– A; 7– E; 8 –E; 9– C.

Unit 5. Role of heredity and constitution in pathology:

1– C; 2 – E; 3–A; 4– C; 5– A; 6– E; 7 –E; 8– C; 9– D; 10– A.

Unit 6.Typical pathological processes pathophysiology of peripheral circulation of blood:

1 – E; 2 – B; 3 – E; 4 – B; 5 – B; 6 – D; 7 – E; 8 – C.

Unit 7.Inflammation:

1 – A; 2 – A; 3 – C; 4 – B; 5 – B; 6 – A; 7 – D; 8 – C; 9 – C; 10 – D; 11 – A; 12 – E; 13 – A; 14 – E; 15 – D.

Unit 8 Pathophysiology of thermoregulation, fever:

1– B; 2– A; 3– C; 4– A; 5– A; 6– B; 7– E; 8– E; 9– A; 10– A; 11– A; 12– A; 13– A; 14– A; 15– A; 16– E; 17– A; 18– A; 19– C; 20– C; 21– C; 22– A; 23– A.

Unit 10. Allergy:

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

Unit 11. Tumors:

1 – E; 2 – B; 3 – A; 4 – C; 5 – A; 6 – E.

Unit 12.Hypoxy:

1– C; 2– B; 3– E; 4– C; 5– A; 6– A; 7– D; 8– C; 9– A; 10– E; 11– B; 12– A; 13– D; 14– D.

Unit 13.The disturbances of energy, protein and basal metabolism. Starvation:

1– F; 2– E; 3– E; 4– E; 5– B; 6– B; 7– E; 8– A; 9– A; 10– E.

Unit 14.Pathophysiology of metabolism Diabetes mellitus:

1 – B; 2 – D; 3 – E; 4 – C; 5 – C; 6 – C; 7 – E; 8 – B; 9 – C; 10 – A; 11 – A; 12 – E; 13 – D; 14 – C; 15 – B; 16 – D; 17 – D; 18 – E; 19 – D; 20 – E.

Unit 15. Pathophysiology of lipidmetabolism (atherosclerosis):

1– E; 2– B; 3– E; 4– D; 5– C ; 6– E; 7– E.

Unit 16.Pathophisiology of water-electrolite metabolism. Acid-base imbalance:

1 – A; 2 – B; 3 – A; 4 – A; 5 – C; 6 – A; 7 – C; 8 – A; 9 – E; 10 – B; 11 – A; 12 – D; 13 – C; 14 – B; 15 – C; 16 – A; 17 – A; 18 – C; 19 – D; 20 – D; 21 – C; 22 – D; 23 – A; 24 – B; 25 – E; 26 – A; 27 – E; 28 – D; 29 – B; 30 – A; 31 – C.

Unit 17. Red blood cells pathology:

1 – C; 2 – E; 3 – A; 4 – B;

5 – C – Ineffective erythropoiesis, red cell destruction in marrow prior to red cell release, is a major characteristic of β-thalassemia major and is caused by aggregation of excess α-chains;

6 – A;

7 – B – Repeated splenic infarction lead to a fibrotic, shrunken spleen (autosplenoectomy) in adult patients with sickle cell anemia;

8 – A; 9 – E; 10 – A; 11 – A; 12 – D; 13 – D; 14 – A; 15 – E; 16 – D; 17 – E; 18 – A

Unit 18. White blood cells pathology:

1 – E; 2 – A; 3 – D (Polycythemia vera is a clonal proliferative

disorder characterized by a decrease in erythropoietin concentration) ; 4 – C; 5 – A; 6 – 1, 2; 7 – 2, 3, 5

Unit 19. Hemostasis Answers Coagulant and anticoagulant system:

1. E – DJC is characterized by widespread clotting with consumption of platelets. Thus thrombocytopenia, not thrombocytosis, due to prolongation of the protrombin time (extrinsic pathway of coagulation), activates partial thromboplastin time (a measure of the extrinsic pathway of coagulation) and thrombin time (a measure of the fibrinogen concentration). Activates the fibrinolytic system, with degradation of both fibrin and fibrinogen, and is therefore marked by increased fibrin and fibrinogen degradation products.

2. D – Von Willebrand disease (congenital deficiency of von Willebrand factor) is characterized by defective platelet adhesion, results in a prolonged BT even though the platelets are normal. The activated thromboplastin time is also prolonged because of a secondary deficiency of factor VIII, which normally circulates in a complex with von Willebrand factor and is unstable when von Willebrand factor is deficient.

3 – C; 4 – A; 5 – Leukosytic myeloid leukemia with anemia and thrombocytopenia; 6 – E; 7 – A; 8 – B.

Unit 21/22/23. Cardiovascularpathology:

1 – E; 2 – A; 3 – B; 4 – C; 5 – A; 6 – A; 7 – D; 8 – A; 9 – C; 10 – A; 11 – C; 12 – B; 13 – C; 14 – C; 15 – D; 16 – B; 17 – E; 18 – A; 19 – A; 20 – A.

Unit 24/25. Pathophysiology of the system of digestion in an oral cavity and stomach:

1 – C; 2 – C; 3 – B; 4 – E; 5 – C; 6 – E; 7 – C; 8 – C; 9 – B; 10 – A; 11 – C; 12 – B; 13 – E; 14 – A; 15 – A.

Unit 26. Pathologyoftheliver:

1 – A; 2 – B; 3 – E; 4 – E; 5 – A; 6 – D; 7 – C; 8 – C; 9 – D; 10 – D.

Unit 27. Pathophysiology of the kidney:

1 – A; 2 – F; 3 – E; 4 – C; 5 – D; 6 – E; 7 – B; 8 – C; 9 – D; 10 – A; 11 – A; 12 – E.

Unit 28.Pathophysiology of the hypothalamic hypophysial system. Stress and GAS:

1 – C; 2 – B; 3 – C; 4 – C; 5a – C, E, G; 5b – A, B, D, F, H; 6 – D; 7 – E; 8 – A; 9 – D; 10 – E; 11 – A; 12 – B; 13 – D; 14 – A; 15 – C; 16 – B; 17 – E; 18 – D; 19 – A; 20 – B.

Unit 29: Payhophysiology of endocrine system:

1 – B; 2 – D; 3 – A; 4 – A; 5 – C; 6 – B; 7 – D; 8 – A; 9 – A; 10 – C.

Unit 30. Pathophysiology of the nervous system:

1 – C; 2 – A; 3 – B; 4 – D; 5 – C; 6 – C; 7 – D; 8 – A; 9 – E.

Unit 31. Pathophysiology of the nervous system:

1 – D; 2 – C; 3 – E; 4 – F; 5 – E; 6 – E; 7 – 1, 2, 3, 4, 5, 6; 8 – E; 9 – E; 10 – E.

Unit 32. Pathophysiology of the nervous system:

1 – A; 2 – E; 3 – A; 4 – E; 5 – E; 6– A.

ACTH adrenocorticotropic hormone
AD Alzheimer's disease
ADH antidiuretic hormone
ADP adenosine diphosphate
AIDS acquired immune deficiency syndrome
ALL acute lymphoblastic leukemia
AMegL acute megakaryoblastic leukemia
AML acute myelogenous leukemia
AMML acute myelomonocytic leukemia
AMoL acute monoblastic leukemia
AMP adenosine monophosphate
ANLL acute nonlymphoblastic leukemia
ANS autonomic nervous system
APL acute promyelocytic leukemia
APUD amine precursor uptake decarboxylation
ARDS adult respiratory distress syndrome
ARI acute renal insufficiency
ASK antistreptokinase
ASO antistreptolysis-0
AST aspartate aminotranferase
ATP adenosine triphosphate
AV atrioventricular
AVP arginine vasopressin
AZT azidothymidine
B basophil
BAS biologically active substances
BH_4 tetrahydrobiopterin
BOP blood oncotic pressure
BUN blood urea nitrogen
CAD coronary artery disease
cAMP cyclic adenosine monophosphate
CBC complete blood count
CD cluster of differentiation (proteins)
CHF congestive heart failure
CHP capsular hydrostatic pressure

CLL chronic lymphocytic leukemia
CML chronic myelogenous leukemia chronic myeloblastic leukemia
CNS central nervous system
COPD chronic obstructive pulmonary disease
CPK creatine phosphokinase
CRF chronic renal failure
corticotropin releasing factor
CVA cerebral vascular accident
DIC disseminated intravascular coagulation
DKA diabetic ketoacidosis
DNA deoxyribonucleic acid
E eosinophils
EBV Epstein-Barr virus
ECF extracellular fluid
ECG electrocardiogram
EL erythroleukemia
EP endogenous pyrogen
ERV expiratory reserve volume
Fab antigen-binding fragment
FAD flavin adenine dinucleotide familial Alzheimer's disease
Fc crystalline fragment
FDP fibrin degradation products
FMN flavin mononucleotide
FRC functional residual capacity
FSH follicle-stimulating hormone
G1 centrioles replicating phase of a cell cycle
G2 final growth phase of cell before mitosis
GAS general adaptation syndrome
GBHP glomerular blood hydrostatic pressure
GDM gestational diabetes mellitus
GH growth hormone
GIP gastrointestinal peptide
GIT gastrointestinal tract
GMP guanosine monophosphate
GTP guanosine triphosphate
HDL high density lipoprotein
hGH human growth hormone

HHNKS hyperosmolar hyperglycemic nonketonic syndrome
HIV human immunodeficiency virus
HLA human leukocyte antigens
HLV-III human T-lymphotropic virus type III
HPA hypothalamic-pituitary-adrenal
IC inspiratory capacity
ICAM intracellular adhesion molecules
ICF intracellular fluid
IDDM insulin-dependent diabetes mellitus
IDL intermediate density lipoproteins
IF inhibiting factor
Ig immunoglobulin
IGT impaired glucose tolerance
IL interleukin
INF interferon
IRV inspiratory reserve volume
ITP immune thrombocytopenia
IVBC intravascular blood clotting
L lymphocyte
LAV lymphadenopathy virus
LDH lactic dehydrogenase
lactate dehydrogenase
LDL low density lipoprotein
LH luteinizing hormone
Lp lipoprotein
LPS lipopolysaccharides
M monocyte
mitosis phase of a cell cycle
MBV minute blood volume
MHC major histocompatibility complex
MIP macrophage inflammatory protein
MODS multiple organ dysfunction syndrome
MSH melanocyte-stimulating hormone
NAD nicotinamide adenine dinucleotide
NFR net filtration pressure NIDDM non-insulin-dependent
diabetes mellitus
NK natural killer (cell)

NSAID	nonsteroidal anti-inflammatory drug
PAS	pathological algic system
PG	prostaglandin
PT	prothrombin time
PMN	polymorphonuclear neutrophil
PTH	parathyroid hormone
PTT	partial thromboplastin time
PV	polycythemia vera
qBH_2	quinonoid dihydrobiopterin
RBC_S	red blood cells
RH	release hormone
RNA	ribonucleic acid
S	synthesis phase of a cell cycle
SA	sinoatrial
SCID	severe combined immune deficiencies
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIADH	syndrome of inappropriate secretion of ADH
SLE	systemic lupus erythematosus
STH	somatotropic hormone
T3	triiodothyronine
T	thyroxine
TBSA	total body surface area
TBW	total body water
T1 c	cytotoxic T-cell
T-cell	thymocyte derived cell
TD	tidal volume
Th	T-helper cell
TLC	total lung capacity
TNF	tumor necrosis factor
Ts	suppressor T-cell
TSH	thyroid-stimulating hormone
TTH	thyrotropic hormone
TTP	thrombotic thrombocytopenic purpura
vc	vital capacity
VLDL	very low-density lipoproteins

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Бібліотека студента-медика

Провідний редактор серії
В. М. Попов
Художнє оформлення серії
О. А. Шамшуріна

Навчальне видання

Гоженко Анатолій Іванович
Гуркалова Інна Павлівна

ПАТОФІЗІОЛОГІЯ

Підручник

Англійською мовою

Провідний редактор ***В. М. Попов***
Редактор ***Р. В. Мерешко***
Художній редактор ***О. А. Шамшуріна***
Технічний редактор ***С. С. Ракул***
Коректор ***О. М. Фащевська***
Поліграфічні роботи ***І. К. Каневський***

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