# GENERAL PATHOPHYSIOLOGY

***Self-study methodical instructions for international students (majoring in «Medicine» and «Dentistry»)***

**МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ**
**Харківський національний медичний університет**

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***(majoring in «Medicine» and «Dentistry»)***

# ЗАГАЛЬНА ПАТОФІЗІОЛОГІЯ

***Методичні вказівки***
***для самостійної позааудиторної підготовки іноземних студентів***
***(спеціальність «Медицина» та «Стоматологія»)***

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# Subject plan
# practical lessons on pathological physiology
# General Pathology

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2. Harsh Mohan: *Textbook of Pathology* 3rd ed., Jaypee Brothers Medical Publishers ltd, Delhi, India, 1998.
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**PRACTICAL LESSON № 1**
**Topic: SUBJECT AND OBJECTIVES OF PATHOPHYSIOLOGY. METHODS OF PATHOPHYSIOLOGICAL STUDIES. MAIN STAGES OF PATHOPHYSIOLOGY DEVELOPMENT**

**Relevance of the topic.** Pathological physiology – is the science that studies the functional changes in the ill human or animal organisms. It studies the most general laws of the origin, development, clinical course, and outcome of the disease. The main method of investigation in pathophysiology is an experiment by which certain types of animal models of disease, deteriorations of organs, and systems are reproduced for the study of the basic laws of human diseases. Thus, the experiment is the primary pathophysiological research method.Overall Objective – is to be able to determine the nature of the pathophysiological experiment, its features and value in medicine.

**For this it is necessary to be able to (specific objectives):**

1. Enumerate and briefly describe the main stages of the pathophysiological experiments and the main criteria for the selection of animals in experiments.
2. Compose a plan of the pathophysiological experiment and choose the kind of laboratory animal according to its purpose.
3. Estimate the ratio of the experiment with the method of clinical observation

**Required to achieve the learning basic knowledge-skills.**

**To be able to:**

1. Enumerate the main types of experiments.
2. Outline the acute and chronic experiments and evaluate their strengths and weaknesses, and the advantages of the experiment in comparison with the method of observation.
3. Calculate and briefly describe the main classes of the laboratory animals used in the experiment.

## THE QUESTIONS TO THE LESSON

1. The definition of "pathophysiology."
2. The subject, purpose, and objectives of pathophysiology.
3. The main features and objectives of the pathophysiological experiment.
4. The ratio of clinical observation method with pathophysiological experiment.
5. Is it possible to experiment on human beings?
6. The main stages of the pathophysiological experiment.
7. What are the names of the founders of the well-known method of scientific experiment, and specify their role in the development of experimental pathology and medicine.

## THEORETICAL MATERIAL FOR PREPARATION TO LESSON

### The subject and the tasks of pathophysiology

**Pathologic physiology** (from Greek *pathos* – suffering, disease*; physis* – birth, origin, nature*; logos* – study*)* studies vital activities (functions) of a diseased organism. In other words, it's a physiology of a diseased organism. So, the subjects of pathophysiology are general regularities of functioning, typical for different diseases. It is a well-known fact that there are about a thousand of human diseases. While clinical sciences study issues of diagnostics, treatment and prevention of individual diseases, or nosologic units (from Greek *nosos*-also means "disease"), pathophysiology researches that common features, characterizing different diseases, greater or smaller groups of diseases or even disease in general, i.e. as distinguished from the notion "health". We should notice that in this sense the name used long time ago "general pathology" is reasonable. These general regularities are settled, on the one hand, on different levels of organism organization – cells, tissues, organs, organism systems in the whole, and on the other hand – concerning all disease aspects – its origin, genesis, development, course and result.

Thus, pathological physiology – is a science studying functional changes in a diseased organism and settling general regularities of origin, genesis, development, course and result of a disease.

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

**The place of pathophysiology in a system of medical knowledge**

Pathophysiology ranks as an interim science between medico-biological and clinical sciences, being theirs interlink. From the first ones pathophysiology is different because it is medical, from the second ones – that it is a theoretical medical science. The bases of pathophysiology are biological sciences – biology, normal physiology, biochemistry. In turn, pathophysiology is a theoretical basis of clinics.

The necessary prerequisite for understanding of pathological processes is knowledge of normal physiology and biochemistry, which study the regularities of organism functioning under normal conditions. Besides, pathophysiology widely uses physiological and biochemical methods of research.

Pathophysiology is closely connected to morphological disciplines – anatomy, histology, pathomorphology, as the analysis of function in isolation from structure is impossible. Particularly, we should emphasize the connection of pathophysiology with pathomorphology, which studies the same general regularities of pathophysiological processes, but investigates, at the same time, structural changes. However, morphological analysis alone is insufficient for understanding of the disease essence. Though the functional changes are closely connected with structural, the strict conformity is not always observed between them. Particularly, it is explained that every organ, system, organism possesses compensatory ability, and its function in a changed structure may not be disturbed yet. That's why clinic does not always coincide with morphological changes. Many issues of disease pathogenesis can be solved only in experiment, i.e. by pathophysiology.

Pathophysiology is closely connected with clinic. On the one hand, pathophysiology is a theoretical basis for clinic, equipping it with fundamental information about the essence and the mechanism of disease, principles and experimental methods of treatment. Clinical sciences itself can collect the important data about the disease essence and the mechanism. However, delicate mechanisms and total knowledge about the disease essence can be received only from the experimenter's hands. On the other hand, pathophysiology derives general disease regularities on the basis of investigation of a concrete pathological processes and diseases.

**The tasks of pathophysiology**

- Studying of the most general pathological issues, connected with interpretation of philosophic aspects of medicine. Exactly pathophysiology investigates and provides insight about that problems of general pathology, which have fundamental methodological importance for getting origin and the essence of a disease in general and its certain forms; the formation of medical world outlook or thinking, as general study about a disease, general etiology, general pathogenesis, the role of factors of internal and external environment in pathology; in other words – exposes the laws of a disease.
- Studying of general regularities of the birth, origin, development, course and result of a disease.
- Working out the principles of therapy on the basis of studying general regularities at various diseases and pathological processes.
- Experimental creation of methods of therapy, which after approved first in clinic, and if the approval is successful (the effectiveness is appropriate) – adopted in clinical practice.

**The components of pathophysiology**

Pathophysiology consists from three parts: general pathology, pathophysiology of organs and systems (special pathophysiology) and clinical pathophysiology. In turn, general pathology is divided into general nosology and typical pathological processes. The content of "General nosology" corresponds to the first task of pathophysiology. Under typical we understand such pathological processes, as processes characterized by preservation of the main general regularities of its development regardless of forms of expression and underlie the majority of diseases. They are inflammation, fever, tumor growth, allergy, hypoxia etc. The second part of pathophysiology – "Pathological physiology of organs and systems" ("Specific pathophysiology") – also studies general regularities of various diseases and pathological processes, but on the level of definite organs and systems, in other words the general regularities of organs and systems functioning at different pathology. The general regularities of dysfunction of blood, blood circulation, respiration, digestion, urination, endocrine and nervous systems are studied and lectured here.

Clinical pathophysiology is the component of pathophysiology as well.

**The methods of pathophysiology**

The main method of investigation in pathophysiology is an experiment. As it is known, the experiment – is one of the general methods of gnosiology. However, among all the medical sciences, an experiment is a prerogative exactly of the pathophysiology. The essence of pathophysiological experiment is a reproduction (modeling) of the pathological process on an animal, studying his etiology and pathogenesis and interpretation of the finding for clinic. The importance of the experiment lies in that it allows performing impacts inadmissible on a man, tracing the evolution of pathological process in total volume, investigating its pathogenesis more profoundly, testing of new means.

**The work rules with laboratory animals**

The experiment on animal is performed only at well-grounded necessity of its carrying out; with optimal biological species usage, and a number of animals as well; with anesthetic usage.

At the modeling of pathological processes on living objects the significant value has the principle of selection of laboratory animals, and in every case we should consider its generic and specific features.

**The types of the experiment**

We distinguish acute and chronic experiments. The chronic experiment corresponds more to the natural course of diseases. The acute experiment (vivisection) is irreplaceable at the modeling of acute processes, such as shock, loss of blood, asphyxia, intoxication etc.

**Modern methods and techniques of performing the experiment**

❖ Method of disabling (removal or damaging) any organ with further analysis appeared symptoms in comparison with clinical presentation of a disease and with affection of corresponding human organ.

❖ Method of inclusion – bringing into the animal's organism different substances, excess of which conditions the development of one or another human disease.

❖ Method of duplication – changing of function of one or another organ by various impacts.

❖ Method of isolated organs – establishment of the nature and the degree of lesion of definite organ (heart, lungs) and its contribution into development of blood circulation, respiration etc. deficiency.

❖ Method of parabiosis – joining of the two animals (parabionthosis) through the vascular and lymphatic system for studying mutual humoral impacts (hormones and other metabolites).

❖ Method of tissue culture – separation and cultivation of cells elements of different organs and tissues – is widely used for studying the role of separate tissue elements in regulation of hematosis and immunopoiesis, the mechanism of cell maliglization, the establishment of mechanisms with cytodamaging effect of various pharmacological preparations.

❖ Method of comparative pathology – studying the peculiarities of development and course of different pathological processes in comparative aspect.

**General principles of experimental research planning, accounting, statistic processing and analysis of the results**

*Pathophysiological experience consists of four stages.*

- Preparation of an issue, which the experimenter wants to answer. Any experiment should be preceded by hypothesis, experiment goal-setting and task-setting, detection of the object of experiment (species, age, sex of an animal), composition of the experiment scheme, detection of the experiment capacity.
- Selection of a particular methodology, which the most corresponds to the assigned task, and supplying of a proper control. The control can be an "empty" test, which is carried out with the main one simultaneously. For example, we inject histamine to one animal and isotonic solution of sodium chloride to another one.
- Experiment planning. The test will give the answer on a formulated question only if it is planned correctly.
- Data processing. All numerical material goes through the statistics processing to find out the averages, derivations from them, the difference between the averages and its reliability.

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## PRACTICAL LESSON № 2
## Topic: PATHOGENIC EFFECT OF PHYSICAL FACTORS ON THE ORGANISM

### THE PATHOGENIC EFFECT ON THE ORGANISM OF IONIZING RADIATION AND THERMAL FACTORS

**Relevance of the topic.** Ionizing radiation is characterized by its ability to penetrate into the radiated environment and cause the ionization of atoms and molecules. The biological effect of the ionizing radiation can be local (burns, cataracts) or genera (radiation sickness).

The primary (direct) effect of the ionizing radiation on a living tissue is manifested by ionization and excitation of atoms and molecules and the formation of free radicals, which have a high chemical activity. The combined radicals cause chain reactions as a result of which there is the damage of the structure of DNA, enzymes, and formation of lipid and quinone radiotoxins which inhibit the synthesis of nucleic acids, the activity of enzymes, increase the permeability of biomembranes (indirect action of ionizing radiation). As a consequence, there are disturbances of metabolic processes, functional and structural damages of the cells, organs and body systems. First of all in the tissues and organs with a high proliferative activity (lymphoid, haematopoietic, gonads et al).

Overheating (hyperthermia), evolving under the influence of high temperature on the production, in certain climate zones, is a common pathological condition, leading to the development of some severe pathological changes in the system of thermoregulation and general metabolism of the body, and as a result, can lead to some serious disorders of the cardiovascular functioning circulatory and nervous systems. The local effects of high temperature, resulting in burns and burn diseases, are also of vital importance. The studying in an animal model of high temperature environment can reveal the mechanisms of overheating.

Hypothermia, developing under the influence of a low temperature under certain human activities and in certain climatic zones, is a common pathological condition, leading to the severe pathological changes of thermoregulation and general metabolism of the organism, which can lead to death. The local effect of a low temperature can lead to frostbite.The study in the experiment of the action of a low ambient temperature on an animal can reveal the mechanisms of hypothermia.

**Overall Objective**

- to be able to characterize the pathogenic effect of ionizing radiation on the body, characterize the local and general manifestations of radiation damage, the main mechanisms of its development for prevention and treatment of the radiation pathogenesis disease in the future (depart. of radiotherapy).
- to be able to describe the essence of the violations that occur in the human body when being exposed with a high and low temperature, use knowledge of the mechanisms of these disorders in the practice in the diagnosis and treatment of overheating and hypothermia.

**To do this we should be able to (specific objectives):**

1. To interpret the notions of "ionizing radiation", "free radicals", "lipid per oxidation", "radiolysis of water", "radiation sickness."
2. To explain the mechanism of local and systemic reactions which occur during the radiation.
3. To detect the main manifestations of the radiation damage, to explain the mechanism of the local and general effects of the ionizing radiation on the body.
4. Define the notion of hyperthermia.
5. Show a causal role in the dynamics and conditions of its occurrence and course.
6. Describe the stages of overheating, the basic phenomena of overheating and their mechanisms.
7. Define the notion of heat and sunstroke.
8. Describe the notion of a burn. Describe the stage of burn disease and the mechanisms of its development.
9. Define the notion of hypothermia.
10. Show the role of the causes and conditions of its origin and dynamics of the course.
11. Describe the stages of hypothermia, the main manifestations of hypothermia and their mechanisms.
12. Describe the notion of frostbite. Describe the degree of frostbite

**The necessary basic knowledge and skills to achieve the goals of studying.**

**To be able to:**

1. Describe the ionizing radiation, its types and properties (Department of Biophysics).
2. Interpret the processes of free radical oxidation according to the standard (Department of Biochemistry).
3. Evaluate the results of the study of the lipid peroxidation (Department of Biochemistry).

4. Explain the mechanisms of heat exchange with the external environment of the organism (Department of normal physiology).

5. Explain the meaning of useful adaptive compensatory responses, developing with increasing ambient temperature (Department of normal physiology).

6. Explain the meaning of useful adaptive compensatory reactions developing in the ambient temperature decreases (Department of normal physiology).

**THE QUESTIONS TO THE LESSON**

1. What types of ionizing radiation may have a pathogenic effect on the body?
2. What is the pathogenesis of the systemic and local effects of the ionizing radiation on the body?
3. What is the essence of the direct damaging effects of the ionizing radiation on cells?
4. What is the essence of the indirect progressive effects of the ionizing radiation on cells?
5. What does the radio sensitivity of tissues to the ionizing radiation depend on?
6. What is radiation sickness? Name the form and stage of an acute radiation sickness.
7. What are the most typical symptoms of the period of the developed clinical picture of an acute radiation sickness? What is their pathogenesis?
8. What are the most important long-term effects on the body of the ionizing radiation?
9. What factors render assistance and which ones - prevent the development of radiation damage?
10. The notion of hyperthermia.
11. Cause and conditions of the overheating.
12. Stages of the overheating.
13. Heat and sunstroke.
14. The burn. Burn disease.
15. The notion of hypothermia
16. Causes and conditions of the cooling.
17. Stages of the cooling. Compensatory responses to the action of a low temperature environment and its mechanisms.
18. Major cooling phenomena and their mechanisms.
19. Natural and artificial hypothermia.
20. Frostbite.

## EXPERIMENTAL PART OF LESSON

**Experiment:** studying of the hyperthermia.

**The object of the experiment:** white mice.

**Apparatus:** 250 ml cans, bath, ring-stands, thermometers, electroboiler.

**The conduction of the experiment:** get acquainted with previous state of the animal, take care of the behavior, the reactions on sound and color of seen skins, calculate the amount of respiratory movement per minute.

Place the animal in to the can. Put the can with the mouse into the bath with water (the temperature 40 degree). Then increase the water temperature by 1–2 degree till 45 and observe the changes of animal's behavior.

Draw the scheme of the experiment.

Results you got fix according to this table.

| Time | Temp. of the surrounding | State of animal | | | | Notes |
|---|---|---|---|---|---|---|
| | | Behavior | Sound reaction | Skin colour | Respiratory rate | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

**Result** _____

_____

_____

_____

_____

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## THEORETICAL MATERIAL FOR PREPARATION TO LESSON

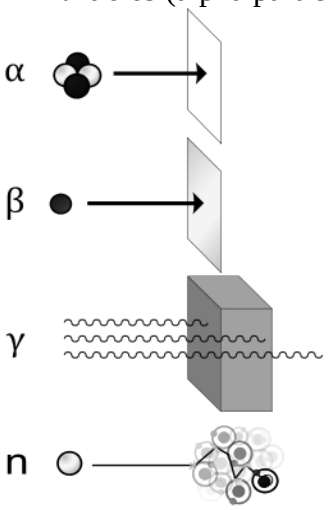
### RADIATION EXPOSURE AND CONTAMINATION

Ionizing radiation injures tissues variably, depending on factors such as radiation dose, rate of exposure, type of radiation, and part of the body exposed. Symptoms may be local (eg, burns) or systemic (eg, acute radiation sickness). Diagnosis is by history of exposure, symptoms and signs, and sometimes use of radiation detection equipment to localize and identify radionuclide contamination. Management focuses on associated traumatic injuries, decontamination, supportive measures, and minimizing exposure of health care workers. Patients with severe acute radiation sickness receive reverse isolation and bone marrow support. Patients internally contaminated with certain specific radionuclides may receive uptake inhibitors or chelating agents. Prognosis is initially estimated by the time between exposure and symptom onset, the severity of those symptoms, and by the lymphocyte count during the initial 24 to 72 h.

***Types of radiation:***

Radiation includes

- ***High-energy electromagnetic waves*** (x-rays, gamma rays)
- ***Particles*** (alpha particles, beta particles, neutrons)

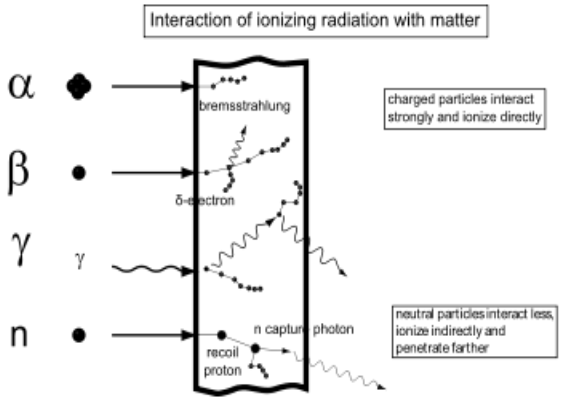



**Alpha particles** are energetic helium nuclei emitted by some radionuclides with high atomic numbers (eg, plutonium, radium, uranium); they cannot penetrate skin beyond a shallow depth (< 0.1 mm).

**Beta particles** are high-energy electrons that are emitted from the nuclei of unstable atoms (eg, cesium-137, iodine-131). These particles can penetrate more deeply into skin (1 to 2 cm) and cause both epithelial and subepithelial damage.

**Neutrons** are electrically neutral particles emitted by a few radionuclides (eg, californium-252) and produced in nuclear fission reactions (eg, in nuclear reactors); their depth of tissue penetration varies from a few millimeters to several tens of centimeters, depending on their energy. They collide with the nuclei of stable atoms, resulting in emission of energetic protons, alpha and beta particles, and gamma radiation.

Alpha (α) radiation consists of a fast-moving helium-4 (4He) nucleus and is stopped by a sheet of paper. Beta (β) radiation, consisting of electrons, is halted by an aluminium plate. Gamma (γ) radiation, consisting of energetic photons, is eventually absorbed as it penetrates a dense material. Neutron (n) radiation consists of free neutrons that are blocked using light elements, like hydrogen, which slow and/or capture them. Not shown: galactic cosmic rays that consist of energetic charged nuclei like protons, helium nuclei, and high-charged nuclei called HZE ions.




**Gamma radiation and x-rays** are electromagnetic radiation (ie, photons) of very short wave length that can penetrate deeply into tissue (many centimeters). While some photons deposit all their energy in the body, other photons of the same energy may only deposit a fraction of their energy and others may pass completely through the body without interacting.

Because of these characteristics, alpha and beta particles cause the most damage when the radioactive atoms that emit them are *within* the body (internal contamination) or, in the case of beta-emitters, directly *on* the body; only tissue in close proximity to the radionuclide is affected. Gamma rays and x-rays can cause damage distant from their source and are typically responsible for acute radiation syndromes (ARS).

***Measurement of radiation:*** Conventional units of measurement include the roentgen, rad, and rem. The roentgen (R) is a unit of exposure measuring the ionizing ability of x-rays or gamma radiation in air. The radiation absorbed dose (rad) is the amount of that radiation energy absorbed per unit of mass. Because biologic damage per rad varies with radiation type (eg, it is higher for neutrons than for x-rays

or gamma radiation), the dose in rad is corrected by a quality factor; the resulting equivalent dose unit is the roentgen equivalent in man (rem). Outside the US and in the scientific literature, SI (International System) units are used, in which the rad is replaced by the gray (Gy) and the rem by the sievert (Sv); 1 Gy = 100 rad and 1 Sv = 100 rem. The rad and rem (and hence Gy and Sv) are essentially equal (ie, the quality factor equals 1) when describing x-rays or gamma or beta radiation. The amount (quantity) of radioactivity is expressed in terms of the number of nuclear disintegrations (transformations) per second. The becquerel (Bq) is the SI unit of radioactivity; one Bq is 1 disintegration per second (dps). In the US system, one curie is 37 billion Bq.

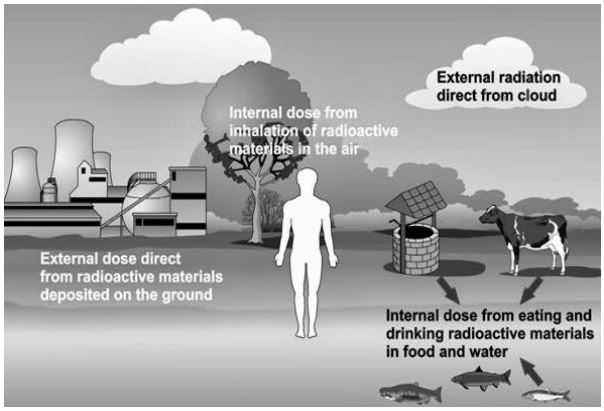
***Types of exposure:***

Radiation exposure may involve

- **Contamination**
- **Irradiation**

**Radioactive contamination** is the unintended contact with and retention of radioactive material, usually as a dust or liquid. Contamination may be

- **External**
- **Internal**




***External contamination*** is that on skin or clothing, from which some can fall or be rubbed off, contaminating other people and objects (*radiation in working environment, working with X-ray equipment, at nuclear reactor and charge particle accelerator, with radioactive isotope, production and treatment of radioactive ore. In clinical practice patients undergo the course of irradiation for medical aims. Irradiation can be the consequence of the use of nuclear weapons and escape of technological products of nuclear enterprises into environment).*

**Irradiation** is exposure to radiation but not radioactive material (ie, no contamination is involved). Radiation exposure can occur without the source of radiation (eg, radioactive material, x-ray machine) being in contact with the person. When the source of the radiation is removed or turned off, exposure ends. Irradiation can involve the whole body, which, if the dose is high enough, can result in systemic symptoms and radiation syndromes (see Acute radiation syndromes (ARS)), or a small part of the body (eg, from radiation therapy), which can result in local effects. People do not emit radiation (ie, become radioactive) following irradiation.

***Sources of exposure:*** People are constantly exposed to low levels of naturally occurring radiation called back-ground radiation. Background radiation comes from cosmic radiation and from radioactive elements in the air, water, and ground. Cosmic radiation is concentrated at the poles by the earth's magnetic field and is attenuated by the atmosphere. Terrestrial sources of external radiation exposure occurs primary due to the presence of radioactive elements with a half-lives comparable to the age of the earth (~4.5 billion years). In particular, uranium (238U) and thorium (232Th) along with several dozen of their radioactive progeny and a radioactive isotope of potassium (40K) are present in many rocks and minerals. Medical diagnostic procedures rarely impart doses sufficient to cause radiation injury, although there is a small theoretical increase in the risk of cancer. Exceptions may include certain prolonged fluoroscopically guided interventional procedures (eg, endovascular reconstruction, vascular embolization, cardiac and tumor radiofrequency ablation); these procedures have caused injuries to skin and underlying tissues. Radiation therapy can also cause injury to normal tissues near the target tissue.

A very small portion of average public exposure results from radiation accidents and fallout from nuclear weapons testing. Accidents may involve industrial irradiators, industrial radiography sources, and nuclear reactors. These accidents commonly result from failure to follow safety procedures (eg, interlocks being bypassed). Radiation injuries have also been caused by lost or stolen medical or industrial sources containing large quantities of the radionuclide.

**Pathophysiology**

Ionizing radiation can damage DNA, RNA, and proteins directly, but more often the damage to these molecules is indirect, caused by highly reactive free radicals generated by radiation's interaction with intracellular water molecules. Large doses of radiation can cause cell death, and lower doses may interfere with cellular proliferation. Damage to other cellular components can result in progressive tissue hypoplasia, atrophy, and eventually fibrosis.

***Factors affecting response:***

**Biologic response to radiation varies with**

- *Tissue radiosensitivity*
- *Dose*
- *Duration of exposure*
- *The age of the patient*

Cells and tissues differ in their radiosensitivity. In general, cells that are undifferentiated and those that have high mitotic rates (eg, stem cells, cancer cells) are particularly vulnerable to radiation. Because radiation preferentially depletes rapidly dividing stem cells over the more resistant mature cells, there is typically a latent period between radiation exposure and overt radiation injury. Injury does not manifest until a significant fraction of the mature cells die of natural senescence and, due to loss of stem cells, are not replaced.The tissues with high mitosis frequency have the greatest radiation sensitivity (Bergonie-Tribando law):

**Cellular sensitivities in approximate descending order from most to least sensitive are**

- ***Lymphoid cells, germ cells, proliferating bone marrow cells, intestinal epithelial cells, epidermal stem cells, hepatic cells, epithelium of lung alveoli and biliary passages, endothelial cells (pleura and peritoneum), connective tissue cells, bone cells, spinal cord cells***

Cells and tissues differ in their radiosensitivity. In general, cells that are undifferentiated and those that have high mitotic rates (eg, stem cells, cancer cells) are particularly vulnerable to radiation. Because radiation preferentially depletes rapidly dividing stem cells over the more resistant mature cells, there is typically a latent period between radiation exposure and overt radiation injury. Injury does not manifest until a significant fraction of the mature cells die of natural senescence and, due to loss of stem cells, are not replaced.The tissues with high mitosis frequency have the greatest radiation sensitivity (Bergonie-Tribando law):

**Damaging effect of radiation includes three stages**:

*a)* ***primary effect of ionizing irradiation*** is manifested in ionization, excitation of atoms and molecules and the formation of the free radicals $HO^{\cdot}$, $HO_2^{\cdot}$ and hydrogen peroxide ($H_2O_{2)}$.

*b)* ***radiation influence on cells*** - ionization and excitation of atoms and molecules of irradiated tissue make up the starting mechanism of irradiation biological activity

*c)* ***radiation effect on the whole organism***

***There are direct and indirect radiation effects.***

**The direct radiation effect** is manifested in ionization and atom and molecule excitation straight by the quantum of irradiation energy. Direct radiation impact on high molecular combinations (proteins, lipids, enzymes, nucleic acids, nucleoproteins, lipoproteins) leads to the rupture of the less solid intramolecular connections, genetic and chromosomal mutation.

**The indirect effect of ionizing radiation** is connected with radiation chemical changes of the DNA structure, enzymes, proteins and lipids. It is provided by the formation of the great amount of free radicals in a cell. The main source for them is a water molecule. The process of hydrogen and hydroxyl free radical formation is called **water radiolysis.**

***Water radiolysis:***

$H_2O + \bar{e} \rightarrow OH^- + H^{\cdot}$

$H_2O - \bar{e} \rightarrow OH^{\cdot} + H^+$

Formed free radicals interact with each other, as a result of which so-called secondary free radicals and hydroperoxides are formed:

$OH^{\cdot} + OH^{\cdot} \rightarrow H_2O_2$

$H_2O_2 + OH^{\cdot} \rightarrow H_2O + HO_2^{\cdot}$

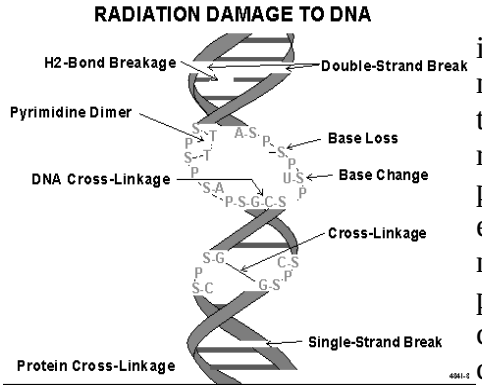
$H_2O_2 + HO_2^{\cdot} \rightarrow H_2O + O_2 + OH^{\cdot}$

$H_2O_2 + H^{\cdot} \rightarrow H_2O + OH^{\cdot}$

**Its accumulation leads to fast activation of the processes of free radical oxidation of nitrogen bases DNA and RNA, proteins-enzymes, lipids, amino acids.**

**Radiotoxins** – are the products of free radical oxidation, formed in tissues under the influence of irradiation. At oxidation of unsaturated fatty acids and phenols lipid and kinone primary radiotoxins are formed, depressing synthesis of nucleic acids, repressing the activity of various enzymes, increasing the penetration of biological membranes and changing diffusion processes in cell.

**Manifestations of radiation damage at molecular, cellular, tissue, organ and system levels.**




The energy of ionizing radiation exceeds the energy of intramolecular and intra-atomic connections. Absorbing by macromolecule, it can migrate through molecule, implementing in the most vulnerable areas. The result is the ionization, excitation, rupture of the less durable compounds, radical abruption, free. The primary target can be high-molecular compounds (proteins, lipids, enzymes, nucleic acids, molecules of compound protein – nucleoprotein complexes, lipoproteins). Free radicals and peroxides are able to change the chemical structure of DNA. complexes, lipoproteins). Free radicals and peroxides are able to change the chemical structure of DNA.

Radiotoxins depress the synthesis of nucleic acids, affect a DNA molecule as chemical mutagen, change the enzyme activity and react with lipid protein intracellular membrane.

Ionizing radiation damages intracellular membranes – nucleus membranes, mitochondrion, lysosome, endoplasmic ribonuclease, deoxyribonuclease, cathepsin, possessing damaging effect on nucleic acids, cytoplasmic and nucleus proteins. Cell nucleus possesses especially high radiation sensitivity in comparison with cytoplasm, the disturbances of nucleus structures have more signifi-cant impact on cell viability. That's why the tissues, in which the processes of cell division are ex-pressed in the most extensive way, possess the most high radiation sensibility.

***Cancer and teratogenicity:***

Genetic damage to somatic cells may result in malignant transformation, and damage to germ cells raises the theoretical possibility of transmissible genetic defects.

CT of the abdomen done in a 1-yr-old child is estimated to increase the child's estimated lifetime absolute risk of developing cancer by about 0.1%. Radionuclides that are incorporated into specific tissues are potentially carcinogenic at those sites. The fetus is exceptionally susceptible to high-dose radiation injury.

**Symptoms and Signs**

Clinical manifestations depend on whether radiation exposure involves the whole body (acute radiation syndrome) or is limited to a small portion of the body (focal radiation injury).

***Acute radiation syndromes (ARS) or radiation sickness:***

After the whole body, or a large portion of the body, receives a high dose of penetrating radiation, several distinct syndromes may occur:

- **Cerebrovascular syndrome**
- **Gastrointestinal (GI) syndrome**
- **Hematopoietic syndrome**

***<u>These syndromes have 3 different phases:</u>***

- **Prodromal phase** (minutes to 2 days after exposure): Lethargy and GI symptoms (nausea, anorexia, vomiting, diarrhea) are possible.
- **Latent asymptomatic phase** (hours to 21 days after exposure)
- **Overt systemic illness phase** (hours to > 60 days after exposure): Illness is classified by the main organ system affected

Which syndrome develops, how severe it is, and how quickly it progresses depend on radiation dose. The symptoms and time course are fairly consistent for a given dose of radiation and thus can help estimate radiation exposure.

The **cerebrovascular syndrome**, the dominant manifestation of extremely high whole-body doses of radiation (> 30 Gy), is always fatal. The prodrome develops within minutes to 1 h after exposure. There is little or no latent phase. Patients develop tremors, seizures, ataxia, and cerebral edema and die within hours to 1 or 2 days.

**Seizures and Tremors**

Intense and prolonged exposure to radiation can impair the central nervous system. This can lead to a general lack of muscle coordination and seizures.

The **GI syndrome** is the dominant manifestation after whole-body doses of about 6 to 30 Gy. Prodromal symptoms, often marked, develop within about 1 h and resolve within 2 days. During the latent period of 4 to 5 days, GI mucosal cells die. Cell death is followed by intractable nausea, vomiting, and diarrhea, which lead to severe dehydration and electrolyte imbalances, diminished plasma volume, and vascular collapse. Necrosis of intestine may also occur, predisposing to intestinal perforation, bacteremia, and sepsis. Death is common. Patients receiving > 10 Gy may have cerebrovascular symptoms (suggesting a lethal dose). Survivors also have the hematopoietic syndrome.

**Bloody Diarrhea and Vomit**

Similar symptoms as above, different cause. Radiation depletes the cells of the intestinal wall and stomach. This irritates the stomach and intestines, leading to bloody vomit and stool.

**Nausea and Vomiting**

The earliest symptoms of Acute Radiation Syndrome (ARS) are nausea and disorientation. If you start vomiting within an hour of exposure this implies a massive dose of radiation, making it far likelier you will die without medical treatment.

The **hematopoietic syndrome** is the dominant manifestation after whole-body doses of about 1 to 6 Gy and consists of a generalized pancytopenia. A mild prodrome may begin after 1 to 6 h, lasting 24 to 48 h. Bone marrow stem cells are significantly depleted, but mature blood cells in circulation are largely unaffected. Circulating lymphocytes are an exception, and lymphopenia may be evident within hours to days after exposure. As the cells in circulation die by senescence, they are not replaced in sufficient numbers, resulting in pancytopenia. Thus, patients remain asymptomatic during a latent period of up to 4.5 wk after a 1-Gy dose as the impediment of hematopoiesis progresses. Risk of various infections is increased as a result of the neutropenia (most prominent at 2 to 4 wk) and decreased antibody production. Petechiae and mucosal bleeding result from thrombocytopenia, which develops within 3 to 4 wk and may persist for months. Anemia develops slowly, because preexisting RBCs have a longer life span than WBCs and platelets.

**Bleeding Out Of Orifices**

Also due to the body's inability to clot, you may bleed spontaneously from the nose, mouth and rectum.

**Fever and Infections**

What will ultimately kill someone suffering from radiation sickness. Radiation destroys bone marrow and white blood cells, leading to increased risk of bacterial, viral and fungal infections.

**Cutaneous radiation injury** (CRI) is injury to the skin and underlying tissues due to acute radiation doses as low as 3 Gy. CRI can occur with ARS or with focal radiation exposure and ranges from mild transient erythema to necrosis. Delayed effects (> 6 mo after exposure) include hyperpigmentation and hypopigmentation, progressive fibrosis, and diffuse telangiectasia. Thin atrophic skin can be easily damaged by mild mechanical trauma.

**Radiation Burns.**Clinically known as cutaneous radiation syndrome, or CRS, the first sign is itching. Exposed skin may then turn red, blister, develop open sores and slough off.

***Focal injury:***

Radiation to almost any organ can have both acute and chronic adverse effects. Focal effects result from radiation therapy. Other common sources of exposure include inadvertent contact with unsecured food irradiators, radiation therapy equipment, x-ray diffraction equipment, and other industrial or medical radiation sources capable of producing high dose rates. Patients with severe CRI have severe pain and often require surgical intervention.

**Diagnosis**

- ***Symptoms, severity, and symptom latency***
- ***Serial absolute lymphocyte counts and serum amylase levels***

Diagnosis is by history of exposure, symptoms and signs, and laboratory testing. The onset, time course, and severity of symptoms can help determine radiation dose. However, some prodromal symptoms (eg, nausea, vomiting, diarrhea, tremors) are nonspecific, and causes other than radiation should be considered. Many patients without sufficient exposure to cause acute radiation syndromes may present with similar, nonspecific symptoms, particularly after a reactor accident.

***Other laboratory test are done if feasible:***

- *C-reactive protein (CRP) level: CRP increases with radiation dose; levels show promise to discriminate between minimally and heavily exposed patients.*
- *Blood citrulline level: Decreasing citrulline levels indicate GI damage.*
- *Blood fms-related tyrosine kinase-3 (FLT-3) ligand levels: FLT-3 is a marker for hematopoietic damage.*
- *IL-6: Marker is increased at higher radiation doses.*
- *Quantitative granulocyte colony-stimulating factor (G-CSF) test: Levels are increased at higher radiation doses.*
- *Cytogenetic studies with over dispersion index: These studies are used to evaluate for partial body exposure.*

**Prognosis.** Without medical care, the LD50/60 (dose expected to be fatal to 50 % of patients within 60 days) for whole-body radiation is about 3 Gy; 6 Gy exposure is nearly always fatal. When exposure is< 6 Gy, survival is possible and is inversely related to total dose. Death may occur within hours to a few days in patients with the cerebrovascular syndrome and usually within 2 days to several weeks in patients with the GI syndrome. In patients with the hematopoietic syndrome, death may occur within 4 to 8 wk because of a supervening in-fection or massive hemorrhage.

## CHRONIC RADIATION SICKNESS

It originates after repeated irradiations of little radiation doses.

Three degrees of severity of chronic radiation sickness are distinguished. The indicator is a number of leukocytes in blood. For the disease of the first degree of severity is typical moderate nonpersistent leukopenia – the quantity of leukocytes in blood – 4–3,5 $\times 10^9$/l, the second – persistent leukopenia – 2 $\times 10^9$/l, the third – to 1 $\times 10^9$/l. We can also observe thrombocytopenia and anemia. The disease of the second and the third degree of severity is charac-terized by the irreversible changes in organs and tissues, its dystrophy. The features of organic changes in nervous system, the exhaustion of hypophisis and adrenals, decrease of vascular tone, rise of vascular permeability, ulcero-necrotic damages of mucous membranes are observed. Infectious complications and inflammatory processes also have necrotic character.

**Hematologic syndrome.** It is manifested by pancytopenia, i.e. the decrease of the blood corpuscles content. The first ones the lymphocytes vanish from blood. Hypolymphemia can already be detected in the period of "imaginary well-being". Then the content of granulocytes (neutropenia) decreases, and then the content of thrombocytes and erythrocytes decreases.

The development of pancytopenia is stipulated by the damage of bone marrow and essentially the death of mature blood corpuscles. As far as the life duration of various blood cells is not the same, initially the content of short-lived blood corpuscles – lymphocytes, neutrophils, and well after – erythrocytes decreases.

**Hemorrhagic syndrome.** Raised bleeding having acute radiation sickness is predetermined by the following factors: a) thrombocytopenia; b) radiation damage of vessel endothelium; c) raise of the permeability of vessel wall under the action of biogenic amines (histamine, serotonin), liberating by tissue basophil at radiation conditions; d) disturbance of blood coagulability in the result of discharge of a great amount of heparin by tissue basophils.

**Bruising and Inability to Heal Wounds**

Radiation depletes clot-forming platelets in the blood, leading to severe bruising and wounds that won't heal. In certain cases, this manifests as purpura, discolored patches caused by bleeding beneath the skin (pictured above).

**Infectious complications.** Its development is connected with the disturbance of a function of external organism barriers (the damage of integumentary skin epithelium, the epithelium of mucous membrane of oral cavity, pharynx, and intestine) and leucopenia, the result of which is a disturbance of specific immune organism reactions and phagocytosis (immunologic deficiency).

**Autoimmune reactions.** The reason of its origination is the appearance of autoantigens in the irradiated tissues. Radiation auroantigens are proper tissue proteins, changed under the action of ionizing radiation.

**Asthenic syndrome.** It consists of the compound complex of clinical features, originating in the result of functional disturbances of central nervous system.

**Intestine syndrome.** It is manifested in the disturbance of the intestine functions (diarrhea, abdominal cramps). It is developing as a result of the damage of epithelium mucous membrane of the intestine.

**Essential mechanisms of antiradiation protection. Pathophysiological foundations of radiation protection.** At molecular level originated pathological changes compensates by essential antioxidant systems. These are the interceptors of free radicals (for example, superoxide dismutase), peroxides inactivators (catalase), donator of sulfhydric groups (gluthathione). Enzymes of damaged DNA reparation, inhibitors and inactivators of biologically active substances are functioning in cell.

**Radioprotectors** are the substances, introduction of which prevent or diminish the degree of the radiation injury development. The most studied from this point of view are oxidants and preparations, which are the donators of sulfhydric groups. Using the latter the effect of proper SH-groups, consisting in active centers of many enzymes protection is reached.

## THEORETICAL MATERIAL FOR PREPARATION TO LESSON
## PATHOGENIC EFFECT OF THERMAL FACTORS

**Morbific effect of high temperature**

Raised temperature of the environment can render general and local effect. Accordingly such pathological processes as overheating and burn can emerge.

**Overheating.** At the significant rising of the environment temperature the mechanism of thermoregulation can be not enough, and it leads to heat accumulation in the organism and the rise of the body temperature – overheating. When the air temperature is normal overheating is possible as well, if the emission of heat is sharply limited and heat production is reinforced. At the leveling of the body temperature (in general 33°) and the environment temperature the heat return from the body surface at the cost of convection and heat radiation ends. At higher environment temperature the heat return is possible only due to the sweat evaporation from the skin.

The end of secretion or evaporation of sweat (high air humidity, moistureproof clothes) can lead to overheating at 33–34 °C. The water stress in the organism and its insufficient replenishment with sweat facilitates overheating. Any factor, complicating heat return and sweat evaporation – high temperature and humidity of air, moistureproof clothes, evident development of hypoderm facilitates overheating. The rise of the body temperature up to 39–39,5 °C is accompanied by reversible disturbances of functional character. Critical temperature is 42°, after which the metabolism in brain tissue sharply disturbs.

**In the development of overheating we can distinguish three stages**: compensation, excitation and oppression. Sometimes the last two stages are united into decompensation stage.

**Compensatory reactions** at overheating include: *acceleration of respiration and pulse, dilatation of peripheric vessels, increase of sweating, i.e. amplification of physical thermoregulation; as a result emission of heat increases and heat production decreases*.

Then, at the beginning of a temperature rise, when the organism is unable to adapt to the environment in order to preserve the temperature of the body, we can observe the second period – the period of excitation. It is expressed in the phenomena from the side of central nervous system – comes anxiety, sharp acceleration of respiratory movements, acceleration of heartbeat and rise of blood pressure. Because of the water loss hemoconsentration takes place, electrolyte metabolism disturbs, erythrocyte hemolysis rises, which is accompanied by the tissue damages and organism intoxication by the hemoglobin decay product. In connection with the destruction of VII, VII, X and other plasmatic factors coagulation fails.

If the hyperthermia is developing, the **stage of excitation changes into inhibition**, the lowering of all vegetative functions, vanishing of reflex and comatose – unconscious, reminding a sleep – state, which if quite often accompanied by the clonic convulsion, inhibition of respiration, heart function, lowering of blood pressure, deep hypoxia. Death occurs at the expiratory apnea and stopping of heart activity in systole. At long and repeated hyperthermia fatty and albuminous degeneration is observed in organs.

Long-term exposure of the environment high temperature can provoke **heat stroke** – sharp organism overheating with rapid raise of temperature. As a result of environment temperature effect more than 50 °C or 40 °C, air humidity 80 % body temperature rises to 42 °C.

**For the I stage** of heat stroke the excitation of cerebral cortex, bulbar respiratory centre, cardiac muscle and its sympathetic innervations, vasomotor centre, the disturbance of heat regulation, increase of heat production and decrease of heat return, blood clotting, which is evident in thermal dyspnea,

tachycardia, arteriole contraction, sharp raise of body temperature (up to 41–43 °C), with the increase of blood viscosity, hyperproteinemia, polycythemia is typical.

**The second stage** of the heat stroke is characterized by the inhibition of the cerebral cortex, loss of consciousness, depression of vasomotor centre, collapse, stopping of respiratory centre. The death caused by the heat stroke emerges because of paralysis of respiratory centre.

The difference between the heat stroke and sunstroke lays in the following. The sunstroke emerges from the direct activity of broiling sun (ultraviolet) rays on the uncovered head (on nervous system). The activity of the ultraviolet radiation on the nervous system mediates through the irradiated blood protein in capillary and cholesterol. There emerges the excitation of the vegetative centers of hypothalamus and basal ganglia, raise and the following fall of the blood pressure, sleepiness, collapse and death from the paralysis of respiratory centre.

**The local and systemic inflammatory response** to thermal injury is extremely complex, resulting in both local burn tissue damage and deleterious systemic effects on all other organ systems distant from the burn area itself (table).

Although the inflammation is initiated almost immediately after the burn injury, the systemic response progresses with time, usually peaking 5 to 7 days after the burn injury. Much of the local and certainly the majority of the distant changes are caused by inflammatory mediators. Thermal injury initiates systemic inflammatory reactions producing burn toxins and oxygen radicals and finally leads to peroxidation. The injured tissue initiates an inflammation-induced hyperdynamic, hypermetabolic state that can lead to severe progressive distant organ failure.

**Cardiovascular Response.** The cardiovascular response to thermal injury has 2 separate phases: the first is the acute or resuscitative phase, which immediately follows the burn trauma. It is characterized by decreased blood flow to tissues and organs and is thought to be caused by hypovolemia following injury. Hypovolemia may be a direct effect of heat, while the liberation of vasoactive materials from the injured area, which increases the capillary permeability and promotes fluid and protein loss into the extravascular compartment, contributes even more to hypovolemia. The acute phase lasts about 48 h and is followed by a hypermetabolic phase characterized by increased blood flow to the tissues and organs and increased internal core temperature. During the hypermetabolic phase rapid edema formation occurs and this has been attributed to hypoproteinemia, which favors the outward movement of water from the capillary to the interstitium. Secondly, an increase in the water permeability of the interstitial space is evident, which further increases edema formation. Cardiac instability in burned patients is associated with hypovolemia, increased afterload and direct myocardial depression.

**Pulmonary Response.** Respiratory failure is one of the major causes of death after burn injury. There is increasing evidence that lung inflammation and lipid peroxidation occur in the first several hours after a local burn injury and these processes are initiated by oxidants, in particular hydroxyl radicals. In accordance with these, we have reported that the levels of the end products of lipid peroxidation are significantly increased in lung tissues 24 h after burn injury, suggesting that pulmonary injury is dependent upon oxygen radicals. Lung inflammation and lipid peroxidation are not simply an initial transient response, but persist for at least 5 days after the burn. In addition, lung antioxidant defenses may also be decreased postburn. Pulmonary vascular hypertension and altered capillary permeability are exaggerated after an inhalation injury. Arachidonic acid, which is released by disturbed cell membranes, is converted by cyclooxygenase to cyclic endoperoxides, thromboxane A 2, and prostacyclin (PGI 2). Both agents mediate pulmonary hypertension, ventilation and perfusion abnormalities leading to progressive hypoxemia and gas exchange disturbances.

**Renal Response.** During the acute phase of burn injury, renal blood flow and glomerular filtration rate (GFR), as measured by creatinine clearance, decrease. In the hypermetabolic phase, creatinine clearance is increased, indicating that both blood flow and GFR are raised; however, tubular function is impaired. Diminished blood volume and cardiac output cause a post burn decrease in renal blood flow and glomerular filtration rate. If untreated, the resulting oliguria may progress to acute renal failure. Two different forms of acute renal failure have been described in burned patients. The first occurs during the first few days after the injury and is related to hypovolemia with low cardiac output and systemic vasoconstriction during the resuscitation period or to myoglobinuria, which damages the tubular cells. Elevated levels of stress hormones like catecholamines, angiotensin, aldosterone and vasopressin have been reported to be implicated in the pathogenesis of this form of ARF. The other form of ARF develops later and has a more complex pathogenesis. This form has been reported to be

related to sepsis and multiorgan failure and is most often fatal. It has been said to occur more often in patients with injury and is considered the most frequent cause of renal insufficiency in burn patients.

**Gastrointestinal Response**. Adynamic ileus, gastric dilatation, increased gastric secretion and ulcer incidence, gastrointestinal hemorrhage and local and general distribution of the blood flow with a decrease of mesenteric blood flow are among the effects of thermal injury on the gastrointestinal system. Intestinal ischemia resulting from decreased splanchnic blood flow may activate the neutrophils and tissue-bound enzymes such as xanthine oxidase and these factors destroy the gut mucosal barrier and result in bacterial translocation. These data indicate an early postburn gut barrier leak after the burn, which may be the source of circulating endotoxin. Endotoxin, a lipopolysaccharide derived from the outer membrane of Gram-negative bacteria, translocates across the gastrointestinal tract barrier within 1 h of thermal injury. Although the burn wound is initially sterile, plasma endotoxin concentration reaches a peak at 12 h and 4 days postburn. Endotoxins are potent activators of the macrophages and neutrophils. This leads to the release of massive amounts of oxidants, arachidonic acid metabolites and proteases, which cause further local and systemic inflammation damage.

**Immune Response** Severe thermal injury induces an immunosuppressed state that predisposes patients to subsequent sepsis and multiple organ failure, which are the major causes of morbidity and mortality in burn patients. Thermal injury increases the macrophage activity, thereby increasing the productive capacity for the pro-inflammatory mediators. There have been several reports indicating that circulating levels of IL-1 β, IL-6 and TNF-α are increased in patients with burn injury. The epidermis of the skin becomes damaged, allowing microbial invasion; the co-agulated skin and exudate of the patient create an ideal environment for microbial growth. Thermal injury produces a burn-sizerelated depression of both the cellular and humoral aspects of the immune response, and the phagocytic activity of both fixed and blood-borne macrophages and neutrophils is decreased. Thermal injury initiates systemic inflammatory reactions producing burn toxin and oxygen radicals and finally leads to peroxidation. The relationship between the amount of products of oxidative metabolism and natural scavengers of free radicals determines the outcome of local and distant tissue damage and further organ failure in burn injury.

**Burn Classification Note:** The list below shows 4 burn degrees. While most of the public does not recognize the 4th degree, it is the correct term. The table below, with 3 degrees, is also correct. Both are acceptable. Determining burn depth is important. Things to consider are temperature, mechanism, duration of contact, blood flow to skin, and anatomic location. Epidermal depth varies with body surface, which can offer varying degrees of thermal protection. Older adults and young children also have thinner skin

**First degree:** Includes only the outer layer of skin, the epidermis Skin is usually red and very painful Equivalent to superficial sunburn without blisters Dry in appearance Healing occurs in 3–5 days, injured epithelium peels away from the healthy skin Hospitalization is for pain control and maybe fluid imbalance

**Second degree: Can be classified as partial or full thickness.** Partial thickness Blisters can be present Involve the entire epidermis and upper layers of the dermis Wound will be pink, red in color, painful and wet appearing Wound will blanch when pressure is applied Should heal in several weeks (10–21 days) without grafting, scarring is usually minimal Full thickness Can be red or white in appearance, but will appear dry. Involves the destruction of the entire epidermis and most of the dermis Sensation can be present, but diminished Blanching is sluggish or absent Full thickness will most likely need excision & skin grafting to heal

**Third degree:** All layers of the skin is destroyed. Extend into the subcutaneous tissues. Areas can appear, black or white and will be dry. Can appear leathery in texture. Will not blanch when pressure is applied. No pain.

**Fouth degree: Full thickness that extends into muscle and bone.** The destruction of the layers of the skin and associated structures in burn injury

**Morbific effect of a low temperature.** Accidental hypothermia is defined as an unintentional fall in core temperature to < 35°C, and is classified into mild, moderate, and severe in different ways, mild usually being 33–35 °C, 32–35 °C, or 32.2–35 °C, and severe usually being defined as < 28 °C, < 27 °C, or < 26,7 °C.

**Etiology.** Normal thermoregulation involves a dynamic balance between heat production and control of heat loss, with the aim of providing a constant core temperature. Two types of cutaneous receptors are involved: cold and warm. Exposure to cold increases activity in the afferent fibres from the cold receptors, which stimulate the preoptic nucleus of the anterior hypothalamus; direct reflex vasoconstriction reduces blood flow to the cooling skin, and colder blood also reaches temperature-sensitive neurons in the hypothalamus. The hypothalamus then initiates responses, the autonomic nervous system, endocrine system, adaptive behavioural responses, extrapyramidal skeletal muscle stimulation, and shivering. These responses aim either to increase heat production or to reduce heat loss. Older people are particularly susceptible to accidental hypothermia because may have a reduced ability to generate heat because of reduced lean body mass, impaired mobility, inadequate diet, and reduced shivering in response to cold.

As a result of the activity of low temperature there are number of local and general reactions in the human organism, which can provoke cold, body temperature reduction, local changes in tissues (frostbites) and can result in organism freezing.

The origination and the intensity of changes in the organism at its freezing depends on the environment temperature and the character of its impact (air, water), the speed of the air motion (wind) and its humidity, individual properties of organism heat protection and other factors. We dis-tinguish general and local organism cooling.

**Cold.** The cooling of organism or its particular parts is often one of the most important conditions for the cold origination. The cold starting mechanism is reflex vasomotor reactions. Vasodilatation takes place in cooled body parts as well as in distant from this area organs. The cooling of lower extremities or a stomach firstly provokes vasospasm in the site of frostbite, then sudden vasodilatation of mucous membrane of airways. As a result its persistence to pathogenic microbes reduces. Sudden blood cooling can lead to albuminuria, and at a number of cases to nephritis origination.

**General cooling can lead to the thermal balance disturbance in the organism and the fall of a body temperature, overcooling (hypothermia).**

Hypothermia emerges:

*1) at intensified heat return and normal heat production;*

*2) at the fall of heat production and normal heat return;*

*3) at the combination of these phenomena.*

The cool activity provokes a number of adaptive responses: vasoconstriction of peripheric vessels, respiration deceleration, rise of muscle tone, shiver, metabolism reinforcement, decrease of sweat secretion. All these reactions assist in decrease of heat return and increase of heat production that provides the preservation of normal body temperature in the beginning of hypothermia. At further cold influence the compensation of heat loss is disturbed, body temperature falls, but oxygen consumption remains increased for a long time, and then the exchange intensity weakens. Simultaneously with the fall of temperatur peripheral blood vessels widen. Blood pressure falls, respiration becomes sparse. Hypoglycemia emerges. Death comes because of the paralysis of respiratory centre.

**Accordingly there are 2 stages in the development of hypothermia**: compensation and decompencation. Human hypothermia, except cases of freezing, can be observed at severe injuries, after significant losses of blood, at severe metabolism disturbances (diabetic coma, myxedema). Hypothermia can originate during some diseases, accompanied by nervous system affection.

Organism resistance in hypothermia development depends on preceding organism state (reactivity, fatness, age) and function of the thermoregulatory apparatus. Especially easy infants catch cooling. According to the severity of the human organism state the degrees of hypothermia are distinguished: moderate ( body temperature about 30 °C), medium (body temperature about 25 °C) and deep (body temperature be-low 25 °C). Hypothermia has an impact on the course of organism reactions as well as on the course of pathological processes.

Evoked by the low temperature activity inhibition of the functions of central nervous system. It is connected with the reduction of sensibility of nervous cells to scarcity of oxygen. Metabolism decrease in tissues assists in the reduction of organism oxygen need. It is known that hypothermia raises organism resistance to intoxication, infection and some other unfavorable environmental impacts.

***Local low temperature effect can provoke frostbite*** of different severity, pathogenesis of which is connected with the changes of tissue colloidal state, disturbances of intracapillary blood flow and blood flow properties. Frostbite depends not only on the degree of the temperature fall, but also on the duration of its effect and accompanying atmospheric actions, for example, humidity, wind. The great

importance in the frostbite development has the organism state – exhaustion, exchange fall, fatigue. Blood circulation disturbance, evoked by tight clothes or shoes, and the absence of motions assists in the frostbite development. Frostbite at the availability of appropriate conditions (for example, high humidity) can emerge even at the temperature 7–8°.

The changes of different severity are detected (from the inflammation up to necrosis). The character of these changes depends on the degree of tissue damage.

**There are three frostbite degrees**.

The ***first*** degree is characterized by the vasospasm at the beginning, fading of the damaged area, then the development of arterial and venous hyperemia: tissues become blue and lose sensibility, surface skin inflammation is developing.

The ***second*** degree accompanied by the evident inflammatory reaction, bubbling with serous and serous bloody content.

The ***third*** degree is characterized by the coming tissue dying off with the scab formation. As a result of scab rejection ulcerous surface is formed. Inflammatory changes at frostbite are the reactions on the damage or the death of the given tissue area.

Hypothermia slows all physiologic functions, including cardiovascular and respiratory systems, nerve conduction, mental acuity, neuromuscular reaction time, and metabolic rate. Thermoregulation ceases below about 30 °C; the body must then depend on an external heat source for re-warming. Renal cell dysfunction and decreased levels of vasopressin (ADH) lead to production of a large volume of dilute urine (cold diuresis). Diuresis plus fluid leakage into the interstitial tissues causes hypovolemia. Vasoconstriction, which occurs with hypothermia, may mask hypovolemia, which then manifests as sudden shock or cardiac arrest during rewarming (rewarming collapse) when peripheral vasculature dilates. Immersion in cold water can trigger the diving reflex, which involves reflex vasoconstriction in visceral muscles; blood is shunted to essential organs (eg, heart, brain). Also, hypothermia due to total immersion in near-freezing water may protect the brain from hypoxia by decreasing metabolic demands. Symptoms and Signs Intense shivering occurs initially, but it ceases below about 31° C, allowing body temperature to drop more precipitously. CNS dysfunction progresses as body temperature decreases; people do not sense the cold. Lethargy and clumsiness are followed by confusion, irritability, sometimes hallucinations, and eventually coma. Respirations and heartbeat slow and ultimately cease. Initially, sinus bradycardia is followed by slow atrial fibrillation; the terminal rhythm is ventricular fibrillation or asystole.

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## PRACTICAL LESSON № 3

## Topic: THE PATHOLOGY OF REACTIVITY. THE BIOILOGICAL BARRIERS. THE ABNORMALITIES DURING PHAGOCYTOSIS. THE ROLE OF A MONONUCLEAR PHAGOCYTE SYSTEM

**Relevance of the topic.** The notion of reactivity has been firmly established in medical practice and contributes to the assessment of the patient's state. Origin, development, course, and outcome of the disease are primarily determined by the state of reactivity as the ability to respond with changes in the life of an organism to various environmental influences. Any pathological process, in varying degrees, changes the reactivity of the organism and at the same time, the change of reactivity, which exceeded the physiological limits, can be the basis of the disease.

A barrier function of the body has been developing in the course of evolution, the adaptation of the organism to the environment. Penetration of pathogens into the body encounters an obstacle, primarily by anatomical and physiological formations of nonspecific protections, which protect the body or its parts from the pathogenic effects of the environment and ensure the preservation of homeostasis. Violation of these devices facilitates the penetration of agents into the body. Penetrating through the skin or mucous membranes, microbes encounter internal protective devices. These include lymph nodes, the reticuloendothelial elements, a liver, kidneys, hematoencephalic barriers, and biochemical and physicochemical properties of the tissues. The study of these defense mechanisms is very important. Performing protective and regulatory functions, biological barriers maintain an optimal composition of the culture medium for the organ and promote the maintenance of cellular homeostasis. Permeability of the barriers changes because of pathological processes is actively developing.

The theory of phagocytes was formulated by Mechnikov I.I. in 1883. Nowadays the teaching in phagocytes – is a set of ideas about the free and fixed cells of bone marrow origin, which have a powerful catatonic potential, an exceptional high reactivity, and a mobilization readiness, appear in the first line of immunological effector mechanisms of immunological homeostasis. Phagocytes – are one of the most important ways of nonspecific protection of cellular immunity.

Phagocytes are an example of the process, the interest for which cannot disappear. All the new factors are coming to light that stimulates its activity or inhibits the activity of its system of mononuclear phagocytes. Clarifying the subtle mechanisms of interaction of macrophages with lymphocytes, cells of the interstitium, with antigenic structures. In particular, this may be topical and urgent at the moment due to the problem of tumor growth and AIDS. Cells of the mononuclear phagocyte system (monocyte-macrophage system, MPS) perform a dual function in the body. On the one hand, they are directly involved in the defense of the body against some foreign substances mainly with the help of the phagocytes and antibody-dependent killing. These functions of monocytes and tissue macrophages are implemented within the innate nonspecific immunity. On the other hand, these cells are able to interact with lymphoid ones, "including" and regulate the mechanisms of the specific adaptive immunity. These functions of the monocyte-macrophage cells perform due to the ability to present (present) the foreign antigenic material to detect T-lymphocytes and produce cytokines. Peripheral blood monocytes and tissue macrophages are derived from pluripotent stem cells. Getting into the bloodstream, monocytes during 2–3 days settle down in tissues where they are converted into the tissue macrophages.

**Overall Objective** – to examine the impact of environmental factors on the reactivity of the body. To be able to describe the internal and external barriers when being exposed to environmental factors. To explore the nature of the processes of a phagocyte reaction, its mechanisms, and its place in the body's immune system, to assess its biological significance.

**To do this we should be able to (specific objectives):**

1 Define the notion of reactivity.
2. Describe the types and mechanisms of reactivity.
3. Show the value of endogenous factors in the formation of pathological reactivity.
4. Describe the influence of endogenous factors on the development of pathological reactivity.
5. Define the notion of the barriers.
6. Describe the mechanisms which ensure the barrier role of the skin and mucous membranes.
7. Identify mechanisms that ensure the barrier role of the blood, bone marrow, spleen, lymph nodes, liver, and kidneys.
8. Characterize histohematogenous barriers, barrier role of the cell membranes, and cell organelles.

9. Show the value of breaches the barrier function of the organism in pathology.
10. Expand the essence of the notion of phagocytes.
11. Describe the stages of phagocytes and their mechanisms.
12. Evaluate the biological significance of phagocytes and their essence.
13. Expand the essence of the notion of the MPS (Mononuclear phagocyte system).
14. Describe the structure and function of MPS (Mononuclear phagocyte system).
15. Explain the role of mononuclear phagocytes in the specific immunological reactions

**The necessary basic knowledge and skills to achieve the goals of studying.**

**To be able to:**

1. Explain the general patterns of the functioning of the body, its separate organs, and systems (Department of the normal physiology).
2. Explain the general mechanisms of the actions of environmental factors on the body
3. Explain the anatomical features of the barrier devices (Department of Human Anatomy).
4. Explain the physiological characteristics of the barrier devices (Dep. of normal physiology).
5. Describe the basic properties of leukocytes (Dep. of normal physiology)
6. Characterize phagocytes as a biological phenomenon (Dep. of Microbiology, Virology, and Immunology).
7. To characterize the basic properties of tissue macrophages (Department of normal physiology).

## THE QUESTIONS TO THE LESSON

1. The notion of reactivity, types, and mechanisms.
2. The meaning of endogenous factors in the formation of pathological reactivity.
3. The impact of exogenous factors on the development of pathological reactivity. Mechanisms of changes in sensitivity to hypoxia during the hypothermic. The value for the clinic.
4. The notion of the barrier devices of an organism. External and internal barriers.
5. Mechanisms that ensure the barrier role of the skin and mucous membranes.
6. Mechanisms that ensure the barrier role of blood, bone marrow, spleen, lymph nodes, liver, and kidneys.
7. The histogematogenous barriers, barrier role of cell membranes and cell organelles.
8. The breach of the barrier functions in the body pathology.
9. The notion of phagocytes.
10. The phagocyte theory by Mechnikov I.I.
11. The classification of phagocytes and its principles.
12. Stages of phagocytes, their mechanisms. Regulation of phagocytes.
13. Pinocytes and ultramicrophagocytes.
14. The disorders of phagocytes and their role in the pathology.
15. The notion of the mononuclear phagocyte system.
16. The principles of combining cellular elements in the mononuclear phagocyte system, its structure, and functions.
17. The role of mononuclear phagocytes in specific immunological reactions.

## EXPERIMENTAL PART OF LESSON

**Experiment 1:** The examination of barrier functions of organism.

**The object of the experiment:** rabbit.

**Apparatus:** pneumograph, liquid ammonia.

**The conduction of the experiment:** fix the rabbit, put pneumograph on the chest thorax, and connect rubber tube with the Morey capsule and write down the initial respiratory rate. Put the cotton watered by liquid ammonia. Write down the breathing changing. Repeat the action of liquid ammonia on the breathing. Pay attention on the time of breathing stopping after each irritation. Write down pneumograph.

**Results:**

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**Experiment 2:** studying barrier property of mucous stomach.

**The object of the experiment:** frogs.

**Apparatus:** sounds, 10% solution of sulfur magnesium injectors, pincers.

**The conduction of the experiment:** take 2 frogs of same weight, study the initial state. Inject 2–3 ml 10 % solution of sulfur magnesium to the lymphatic sack of one frog and to the stomach (with help injector and sound) to other. See the state of d ring an half an hour. Make the first observation after 7–10 min after sulfur magnesium injection. Pay attention on changing of reflexes (horn, painful ) which are characteristic for sulfur magnesium poison.

**Results:**

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**Experiment 3:** studying barrier property of the skin.

**The object of the experiment:** frogs.

**Apparatus:** stand-rings , pincers , solution hydrochloric acid 0,5 %.

**The conduction of the experiment:** decerebrate frog , hung the frog's low jaw on the stand. Wait for 5–7 min, immerse the back paw of the frog into 0,5 % solution of hydrochloric acid and see the reaction. Mark the time of reaction. Wash the par, immersing it into a glass of water, that remove the skin carefully and again immerse it into 0,5 % solution of hydrochloric acid.

Pay attention to the absence of the response reaction.

**Results:**

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**Experiment 4**: studying of haematoencephalic barrier.

**The object of the experiment**: white mice.

**Apparatus**: injectors, scissors, solution trypan dark blue 10 %, ether.

The conduction of the experiment: insert 0,5–1,0 ml 10 % solution of trypan dark blue under the skin of mouth. After 10 min kill it with ether. Open the chest, abdominal cavity, skull. Compare the intensiveness of color endogenic organs and cephalic brain.

**Results:**

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## THEORETICAL MATERIAL FOR PREPARATION TO LESSON
## THE PATHOLOGY OF REACTIVITY. THE BIOILOGICAL BARRIERS. THE ABNORMALITIES DURING PHAGOCYTOSIS. THE ROLE OF A MONONUCLEAR PHAGOCYTE SYSTEM

### PATHOLOGY OF REACTIVITY

**Reactivity as a condition of disease development**

All living objects have the ability to change their condition or activity, to react to the impacts of the external environment. This ability is usually called irritability. However, not everybody reacts to the same irritant in the same way. Some animal species change vital activity to external impact, not like other species; some groups of people (or animals) react to one and the same impact not like the other groups. Every individual separately has its own peculiarities of reaction. Thereby, organism reactivity (from Latin reaction – opposition) – is its ability to respond by changes of vital activity to the impacts of the factors of the external and internal environment. Reactivity is typical for all living things. The reactivity to a large extent depends on the adaptability of the human or animal organism to the external environment, and the maintenance of homeostasis. The emergence of a disease under the influence of the disease-producing factor and the course of a disease depends exactly on the organism's reactivity.

**Manifestations of reactivity at the molecular, cellular, tissue, organ and system levels and at the level of the whole organism**

Talking about reactivity at the molecular, subcellular, tissue, and organ level, there are organismal and even population reactivity forms. At the molecular level of reactivity complementary interactions, based on the single-valued structural aptitude of recognizing molecules have the key value.

The receptor subunit of adenylate cyclase recognizes peptide bioregulator in a specific way and cooperates with it according to a principle of “key-lock”, which leads to the activation of the catalytic subunit of this ferment. Complementarity is evident in the interaction of enzymes and their substrates,

antigens and antibodies, and cis-regulatory elements of chromatin, and ligands, which change gene expression, which, in turn, shows structurally single-valued correspondence between them. Hormones and their receptors are encoded, accordingly to sense and antisense RNA, which are written off the symmetric complementary DNA. Molecular, subcellular, and cellular mechanisms of reactivity bear the seal of individuality to the same extent, as its superior integral manifestations. A bonds oxygen in different ways. Mitochondrion of skeletal muscles prefers as the energetic substrates active single carbonic fragment, received from glucose, and mitochondrion of cardiac histiocyte – the fragments, received from fatty acids. Tissue and blood thromboplastin are different in content and the mechanism of formation. Macrophages of different tissues, for example, hepatocytes and osteoclasts, despite common origination, look different.

The following hierarchical levels of the substrate are tissue and organ levels. By the differentiation, cells leave only part of genetically inherited programs in actively used program apparatus, the rest are archived. That's why they respond to irritation by reactions, which are typical for this particular tissue. The example of the manifestation of tissue mechanisms reactivity can serve local response of vascularized tissue to the damage – the inflammation.

Along with the development of organogenesis, we can connect the beginning of the formation of system responses, because every organ consists of various tissues. The important component of tissue and organ substrate of reactivity is the structural-functional organ's (tissue's) element. Despite the differences in names, structural-functional units of organs and tissues have common features of the constitution. The significance of this original approach we see in the fact that histions really serve as the primary arena of protective adaptive reactions, and such pathological processes, like inflammation, hyperemia, ischemia, stasis, and thrombosis – unfurl exactly in histions. On the basis of activity of any system, integrating the mechanisms of reactivity (nervous, endocrine, or immune) lays complementary interaction of regulator with receptor discriminator system. The activity of the three integrative systems is closely interconnected. It is established that the immune system, thanks to cytokine and specific autoantibodies, can purposefully regulate the function of nervous and endocrine systems, and vice versa – the cells themselves of the immune system is regulated by hormones and neurotransmitters. Proceeding from these and similar data, the concept is formulated, according to which immune, nervous and endocrine systems maintain informational balance in the organism, and if it is necessary compensate and modulate signals of influence on each other. The example of the reactivity of the organ system and the organism as a whole serves the reorganization of thermoregulation and the main life-supporting systems as a response to pyrogen's action. In the development of many pathological processes (allergy, inflammation) we can trace the changes in reactivity at different levels.

**Types of reactivity** The formation of reactivity has happened in measure of combined complication of the following cardinal characteristics of the living beings: reaction – is a response of the organism or of its part to internal or external action; sensitivity – is the ability to perceive and define the character, force, allocation and periodicity of the agent, which influences on the organism; irritability – is the feature of the organism to perceive the impacts of the factors of the external and internal environment and react on them, as a rule, by the generalized and low differentiated response, for example, the change of metabolism, form, sizes; resistance – is the opposition, counteraction, the steadiness of the organism or of its part to the influence of particular factors of the external and internal environment.

Reactivity is defined by many factors and is manifested in different forms of changes in individual vital activity. In connection with that several categories of reactivity are distinguished. The criteria for distinguishing reactivity diversities are the main biologic properties of the organism, the degree of specificity of the organism's response, the evidence of the organism's reaction to the action, and the nature of the agent, which evokes the organism's response, the biological value of organism's response**.**

**There is specific, group and individual reactivity.**

Specific reactivity is determined by specific peculiarities (for example, atherosclerosis is often observed among people, but is not detected in such form among rabbits; rabbits, in contrast to people, don't have syphilis after infection of them by the agent of disease). In the course of evolution, specific peculiarities of an organism's reactivity are formed as a result of changeability (in connection with mutations), hereditary fixation of cardinal properties of species, and natural selection of the individuals of this species.

**Group reactivity** – is the reactivity of the particular groups of individuals in the range of one species, which are united by certain signs, which defines the peculiarities of reaction of all the representatives of the given group on the influence of factors from the external environment. We distinguish age-related, sexual, and constitutional reactivity from group reactivity.

**Age-related reactivity** manifests in the fact, for example, that children are more amenable to infectious diseases than adults due to the immaturity of their immune system.

**Special reactivity** is typical for children and the old. This was used as a basis for the separation of special divisions in medicine-pediatrics and geriatrics.

**Sexual reactivity** is characterized, in particular, by different resistance to loss of blood among men and women (men have higher resistance), and to physical load (men have higher resistance). Men have such diseases as gout, pyloric stenosis, gastric ulcer, duodenal ulcer, cancer of the head of the pancreas, and coronarosclerosis significantly more often than women; women have rheumatic gout, cholelithiasis, myxedema, hyperthyroidism more often than men.

**Constitutional** reactivity includes relatively stable morphofunctional, including mental, peculiarities of the organism, which are defined by inheritance and long influence of the factors of the external environment. Thus, asthenic in contrast to normosthenic are less resistant to strong and long physical and mental loads.

**Individual** reactivity is defined by the inherited information, individual changeability. As opposed to specific and group, individual reactivity of the organism can be physiological and pathological. Physiological and pathological reactivity reflects biological value of organism's response.

**Physiological reactivity** – is a response, which is adequate to the character and intensity of the impact, and also has adaptive nature. As an example, we can name one of the diversities of immunogenic reactivity – immunity.

**Pathological reactivity** – is a reaction, which is non-adequate according to the intensity and the character of the organism's vital activity. It is accompanied by a decrease in its adaptive abilities. An example is allergic reactions.

The degree of specificity and differentiation of the organism's response allows for distinguishing specific and non-specific reactivity. Specific reactivity – is, for example, the development of an immune response to antigen impact. Non-specific reactivity – is, for example, the activation of phagocytic reaction of leukocytes by contact with foreign cells, inorganic particles, bacteria, viruses, and parasites.

Depending on the intensity reactivity can manifest in the following forms: normal – normergy, heightened – hyperergy, reduced – hypergia (anergy) and perverted – dysergia.

When one has hyperergy (from Greek hyper-more, ergon – act) the processes of excitation prevail. That's why the inflammation has a more violent course, the symptoms of the disease manifest more intensive with evident changes of the organs and systems activity. When one has hypergia (anergy) the processes of inhibition prevail. Hypergic inflammation has a flaccid, latent course, and the symptoms of the disease are effaced, and unobtrusive. In turn, hypergia (anegry) can be positive and negative. Having **positive** hypergia (anergy) external manifestations of reaction are decreased (or absent), but it is connected with the development of active reactions of protection. Having negative hypergia external manifestations of reaction are also reduced, but it is connected with the fact, that the mechanisms, which regulate an organism's reactivity, are deferred, depressed, exhausted, and damaged, for example, slow course of traumatic process with flaccid pale granulations, weak epithelization is observed after a long and serious infection. An example of dysergia can be atypical (perverted) reaction to any medicine, an action of cold (vasodilatation and increase of perspiration).Depending on the agent's nature, which evokes organism's response, there is immunologic and non-immunologic reactivity.

**Non-immunologic** reactivity – is the changes of the organism's vital activity, evoked by the impact of various agents of mental, physical, chemical or biological character, which do not possess antigenic properties. Thereby, the reactivity – is dynamic, constantly changing property of the organism. From the position of a doctor it is important, that the property can be changed purposefully with the aim of increasing organism resistance to the action of various pathogenic factors.

**Dependence of reactivity on the sex, age, inheritance, state of immune, nervous and endocrine systems**

**Reactivity and sex.** If reactivity is an inherited sign, then the sexual determination of reactivity can be considered as a derivation from its inherited conditionality. Sexual dependence on reactivity manifests in many phenomena. For example, females of warm-blood animals are more resistant to loss of blood, and mechanical injury, and males – are to a number of toxins. Among people, the majority of

diseases (autoimmune pathology, asiderotic anemia, cholecystitis, and pancreatitis) affect women more often, than men. Other, no less multiple ailments (gout, duodenal ulcer, atherosclerosis, and polycythemia vera) are observed more often among the representatives of the stronger sex.

Under the influence of men and women, sexual hormones change the production of lipoproteins of high density, which is reflected in the relative risk of atherosclerosis development. Sometimes we face polygenic diseases, which have one of the genes in the sexual chromosome (podagra). The part of differences in the spectrum of morbidity is connected with hereditary diseases, coupled with sex and limited by sex. Particular differences are explained by the influence of cyclic changes in the woman's organism (thus, the menstrual cycle is reflected on an iron exchange, higher frequency of anemia among women is connected with that). Undoubtedly, the peculiarities of metabolism, which are typical for men's and women's organisms, are important for the explanation of sexual differences in reactivity. For example, a woman's body contains a significantly lesser percentage of water, than a man's body. The activity of alcohol dehydrogenase is higher among men. It is interesting that gynecomasty and gipoandrogenizm among men – are practically signs of the development of alcoholism and connected with reduced resistance to alcoholic drinks. It is known, that the basis of sexual dimorphism of reactivity is connected with the regularities of chromosomal sexing.

**Reactivity and age.** The peculiarities of reacting to the actions of the external environment and accordingly the diseases are typical for any age. Neonatal diseases, children's diseases, diseases of the pubertal period, diseases of mature age, and diseases of senile age are distinguished.

***There are three stages of changes of age-related individual reactivity:***

1) reduced reactivity in infancy,

2) the increase of reactivity in the pubertal period;

3) the decrease of reactivity in senile age.

Reduced reactivity in infancy is conditioned by the insufficient development of the nervous system and higher nervous activity, immaturity of barrier systems of the newborn organism, and the child's organism in the first year of life.

The development and the improvement of the nervous system are accompanied by the development and the improvement of organism barrier systems, the ability to produce antibodies, and the emergence of other protective components. Newborns are significantly less receptive to many childhood infections than children 6–12 months old because the newborn has antibodies in the blood, received from the mother through the placenta. At the age of 6–12 months, these antibodies vanish, and the abilities to rigorous production of antibodies in their own organism are absent yet. In senile age the reception to infections again increases due to a decrease of reactivity of the nervous system, weakening of barrier system functions, a decrease of the ability to antibodies production, and weakening of cell phagocytic activity.

**The role of inheritance.** Human inheritance is inseparable from the organism, as whole, providing stability of vital functions, without that the preservation and maintenance of life is impossible at any balance level.

**Inheritance** – is one of the main preconditions of evolution. At the same time, inherited information, which realizes in any individual organism, provides the formation of all signs and properties in the interaction with conditions of the external environment. In connection with that normal and pathological signs of the organism – is the result of the interaction of hereditary (internal) and environmental (external) factors. That's why general understanding of pathological processes is possible only with a glance of interaction of inheritance and environment.

**Immune mechanisms** are the central link of the organism's reactivity, which supports its homeostasis. Contact of a human with various infectious and toxic agents leads to the adaptation of immune mechanisms, which "protect" its organism by means of lysis, neutralization, and elimination of foreign substances, meanwhile preserving the constancy of the internal environment. However, the result of immune reactions can be not only "protection" of the organism, but also evident damage. In this case, one or another type of immunopathology is developing – a pathological process of disease, the basis of which is the damage to immune response. With a glance at the mechanisms, laying in the basis, we can conditionally single out two big groups of diseases, which have immune nature:

1) the diseases which are conditioned by the disturbances of immune response (immunologic insufficiency) or the damage of immunologic reactivity in relation to foreign agents;

2) the diseases which are conditioned by the breaking of immunologic reactivity (tolerance) in relation to their own antigen structures**.**

**The reactivity of a human and animal depends** on the force, mobility, and balance of the main processes (excitation and inhibition) in the nervous system. The weakening of higher nervous activity due to its overstrain dramatically lowers the reactivity (resistance) of the organism to chemical poisons, bacterial toxins, and the action of microbes and antigens.

In reactivity mechanisms, special importance has the endocrine system – hypothalamus, hypophysis, adrenal bodies, thyroid body, and pancreatic gland. The greatest impact on the manifestation of organism reactivity has the hormones of the front lobe of the hypophysis (tropic hormones), which stimulate the secretion of adrenal cortex hormones, the hormones of thyroid, sexual and other glands of internal secretion. The importance of adrenal bodies in reactivity mechanisms is defined generally by the hormones of cortical substances (corticosteroids).

The thyroid gland has a significant impact on reactivity manifestation, because of its functional interconnection with hypophysis and the adrenal gland.

**Influence of environmental factors on the organism reactivity**

It is essential that the reactivity of the organism as a whole is closely linked with the problems of ecology, and the action of various factors: mechanical, physical, chemical, and biochemical. Active adaptation to the lack of oxygen in the form of reinforcement of lungs ventilation and blood circulation, the increase of the quantity of RBC, and hemoglobin, and also active adaptation to the rise of temperature in the form of heat production and heat exchange.

Overheating and cooling of the organism evokes reflect reconstruction of its reactivity in relation to any irritant. Poisoning by alcohol, carbon monoxide, poisoning, lead, mercury, and hydrocyanic acid reduces the processes of internal inhibition in the cerebral cortex and the resistance of the organism to the impact of the agents of disease. Chronic alcoholism noticeably weakens their general reactivity. Radiant energy in the form of ultraviolet rays in some amounts increases organism resistance to infections, in others – weakens. The long action of X-rays and gamma rays has an especially hazardous impact on organism reactivity. There are even data about the influence of a number of other factors (for example, atmospheric pressure, injury) on reactivity. Nutrition influences greatly organism reactivity. The diversity of people (inherited, constitutional, and age-related) in combination with the constantly changing impacts of the external environment on every person creates countless variants of his reactivity, which finally depends on the emergence and the course of pathology.

## THE NOTION OF RESISTANCE

**Resistance (from Latin resisteo – resistance) – is the stability of the organism against various morbific impacts.**

**Organism resistance to morbific impacts is expressed in different forms.**

**Natural (primal, inherited)** resistance (tolerance) is expressed in the form of absolute unresponsiveness (for example, of a human to the plague of horned cattle, to own tissue antigens, of animals to venereal diseases of human) and relative unresponsiveness (of a human to camel plaque and its disease after strong fatigue). Natural resistance is formed in the embryonic period and is maintained during all individual's life. Its basis is the morphofunctional peculiarities of the organism due to which it is resistant to the action of viral factors. Hereditary immunity to infection is conditioned by the molecular peculiarities of the organism.

**Acquired (secondary, individual)** resistance can emerge as a result of sustained infectious diseases, after the injection of vaccines and serums, antigen overload as a response to the injection into the organism of a big amount of protein antigen (immunologic paralysis) or at multiple injections of small quantities of antigens – small doses tolerance. Resistance to non-infectious impacts is gained by training, for example to physical loads, the action of accelerations and overloads, hypoxia, and low and high temperature.

**Active resistance** emerges as the result of active adaptation (active inclusion of protective mechanisms) to damaging factors. To such, we refer multiple mechanisms of non-specific (for example, phagocytosis, resistance to hypoxia, connected with reinforcement of lungs ventilation and increase of red cells quantity) and specific (the formation of antibodies during the infection) protection of the organism from the morbific influences of the environment.

**Passive resistance –** is not connected with the active functioning of protective mechanisms (skin, mucous membranes, blood-brain barrier, and others). The example can be the obstacle to microbes and other poisoning substances penetration into the organism from the side of the skin and mucous membranes, which affect so-called barrier function, which in tote depends on their construction and properties, inherited by the organism.

**Resistance can be specific** – to the action of any one definite pathogenic agent (for example, resistance to definite infections) and **non-specific** – in relation to different impacts.

Reactivity corresponds to the general designation of resistance mechanisms, and resistance – is the expression of reactivity as an active, protective, adaptive act, which is the qualitative factor of reactivity. I.e. these notions are examined jointly because reactivity – is the expression of active mechanisms of organism resistance emergence to various pathogenic actions. However, there are states of the organism when reactivity and resistance are changed in different directions (when animals have hypothermia, some types of starvation or winter sleep the resistance of their organisms reduces but the resistance to infections rises).Mechanisms of non-specific resistance

To the mechanisms of non-specific resistance, which provide organism stability to the actions of infectious agents we refer: 1) cell reactivity, 2) physical and physical-chemical endogenous factors, 3) biological barriers, 4) antagonistic interrelations between normal and pathogenic microflora, 5) functioning of physiological system of connective tissue, 6) humoral factors of non-specific resistance, 7) phagocytosis, 8) inflammation.

Cell reactivity – is their inability to interact with an infectious agent.

It can be stipulated by: a) absence of receptors to viruses on the skin surface; b) absence of receptors to bacterial toxins in cells; c) connection of toxin by cell receptors, which are insensitive to its action (receptors shielding). To physical and physic-chemical endogenous factors of non-specific resistance of the organism, we refer to body and tissue temperature, the value of environment pH, tissue oxygen tension, and others. The temperature level of a bird provides insensibility to the causative agent of anthrax. At the rise in body temperature, the reproduction of many viruses is disturbed and they die. Many causative agents of infectious diseases, in particular, comma bacillus die in the acidic content of the stomach. In usual conditions, pO2 in tissue prevents the development of anaerobic infections. Non-specific systems act uninterruptedly, neutralizing pathogenic factors and not allowing organism damage at all levels. Non-specific systems of protection are heterogeneous. These are mechanical obstacles in the way of implementation of pathogenic factors, the production of fungicidal, bacteriostatic, and antivirus substances, and the activity of cytotoxic cell clones, fever, barriers, and others.

## ROLE OF CONNECTIVE TISSUE PHYSIOLOGICAL SYSTEM IN ORGANISM RESISTANCE

A. A. Bogomolets was the first who pointed out the important role of connective tissue in ensuring organism resistance. He introduced into circulation the term “connective tissue physiological system”. Cellular elements of connective tissue (macrophages, fibroblasts, reticular cells), in the interaction with other organs and physiological systems, take part in the formation of organism reactivity. They possess phagocytic activity, barrier, and antitoxic abilities, and provide the intensity of wound healing, performing the following functions: 1) protective (the formation of biological barriers, phagocytosis, and reactions of humoral and cellular immunity); 2) trophic (provision of nutrition of parenchyma elements); 3) supporting, plastic.

The blockade of macrophage system functions weakens the manifestations of allergic reactivity, while its stimulation leads to reinforcement of antibody production. Inhibition of the higher nervous system (shock, narcosis) is accompanied by reinforcement of stripping function of connective tissue elements in relation to stains, microbes, inhibition of the wound healing processes, and inflammation. The excitation of higher nervous activity stimulates mentioned functions of connective tissue cells.Bogomolets’s serum is called antireticular cytotoxic serum (ACS), first received and offered in medical practice by A.A. Bogomolets. Serum consists of antibodies against the components of connective tissue. At the injection of it in small amounts the processes of wound and ulcer healing accelerate, and the resolution of slow-moving processes occurs. The mechanism of ACS action is connected to the development of cytotoxic immune reactions.

## BIOLOGICAL BARRIERS, THEIR CLASSIFICATION, THE SIGNIFICANCE IN ORGANISM RESISTANCE

Barrier devices are physiological mechanisms of non-specific protection of the organism from the action of morbific agents, in particular, infectious onsets and their toxins.

There are external and internal barriers. External barriers are skin with its appendages and mucous membranes included in its glands. Skin is covered by multilayer keratinizing epithelium, which protects organisms from penetration by the mechanic, chemical, and infectious agents. The degree of

permeability of cutaneous covering, development, and thickness of the corneal layer is very important in the protection of organism from penetration of effecting skin causative agents of infection. Desquamation of the superficial corneal layer forwards skin purification and prevents bacteria storage. Causative agents of infection penetrate through damaged skin, and also through apertures of excretory ducts of sweat and sebaceous glands. Besides, the secretions of sweat and sebaceous glands which excrete on the skin surface wash off microbes and prevent penetration of infectious agents into the organism. Skin functions not only as a mechanical barrier.

Significant value in barrier function has perceptibly sensing apparatus of skin and mucous membranes – the initial link of the reflex arc. Mechanic, thermal of chemical agents, at the impact on the skin, evoke motor reflex, in the result of that body can be removed from the hazardous agent.

Mucous membranes of eyes, nasopharynx, respiratory, digestive, and urogenital tracts conjunctiva, covered by epithelium, bear barrier function, due to which the penetration of morbific agents into the organism is prevented. It is expressed, from one side, in the impermeability of mucous covering for some infectious agents, and from the other side – in the ability to remove mechanically foreign substances due to the activity of mucous glands and cilia of respiratory epithelium. Motor reflexes of protective nature, such as sneezing and coughing, which forward ejection of foreign particles with mucus and sputum, are of great importance. Detaching mucous membranes possesses bactericidal properties. In this aspect, great importance has a special substance – lysozyme, which dissolves a number of microbes.

And with that, we can find microbes in mucous membranes (except mucous membrane of the stomach), as on the skin, which is constant flora of these surfaces. In the normal state of the organism, this flora of absolutely harmless and has a protective function in relation to microbes, which are found in the mucous membrane. Gland secretions, which excrete on the surface of mucous membranes, also act the part in the realization of protective functions.

Irritating substances are often disarmed and washed off from tissues by means of exudates. Exudates can wash off bacteria and toxins, evoking in the given area inflammatory reaction. The inflammatory process can condition not only disarming and release of the hazardous agents by exudates, but also its isolation by the formation of granulation bank and connective tissue capsule.

Penetrating through the skin and mucous membranes into the internal environment of the organism, the hazardous agent collides with a number of other obstacles to its spreading and development in the organism. These are internal barrier devices.

The liver is a strong obstacle against penetration into the organism of foreign substances of different origins. Liver barrier function is connected with the role of this organ in the processes of interstitial metabolism. In the liver occurs the processing of some hazardous for the organism substances – the products of metabolism, neutralization of acids and alkalis, and also deactivation of a number of intermediate products of metabolism by means of formation of binate glucuronic and ether- sulfuric acids, deducible after through renal filter. In the liver occurs the delay of heavy metals, poisons, and also bacteria, which are quite often released by the liver into the bowels with bile. The delay of colloidal substances and microbes is stipulated by the presence of macrophage elements in the liver.

Kidneys have the function of barrier, protecting the organism from the action of chemical substances, mainly the products of metabolism. Kidneys disarm some metabolic products. Animals' (dogs') kidneys form hippuric acid from benzoic acid and glycocoll (these functions are performed by the human liver, not kidneys), and take part in the processes of deaminization. Kidneys, depending on their secretory properties, can condition the removal of toxic substances from the organism, which are alien to it. The placenta during the pregnancy performs some barrier functions in relation to a number of infectious inceptions, chemical substances, and metabolic products, protected by this the fetus from the action of hazardous agents.

Spleen, lymphatic nodes, and other organs provide barrier function due to the availability of cells in the mononuclear phagocyte system.

The founder of the theory of barrier function L. S. Stern 1921 suggested that there are differentiated protective regulatory devices – histogematogenous barriers between blood and tissue fluid. Each organ has its own environment because the blood doesn't touch organ cells. The functional characteristic of barriers depends on the physiological and morphological peculiarities of the corresponding organs and tissues. The peculiarity of each barrier is selective permeability. To specialized barriers, we refer blood-brain, blood-labyrinth, and blood-ocular barriers. The main structural elements of barriers are blood capillaries. Capillary endothelium in different organs possesses typical for the corresponding organ

peculiarities and is the morphological basis of barrier selective permeability. Under the endothelium is the basal membrane, consisting of fiber of collagen and glycosaminoglycan.

**Autoantibodies, evoking the damage of testicle cells and spermatogenesis, are formed.** In the thyroid gland, the barrier has a tissue level of organization and is ensured with the help of parenchymatous cells, which by means of intracellular contacts form tissue membrane, delimiting zones in organs, to which protein doesn't penetrate. In skeletal muscle, barrier function is performed by sarcolemma.

On the basis of barrier function lie the mechanisms of dialysis, ultrafiltration, osmosis, and metabolic cellular activity, which are constituents of the barrier structure. Transport intensity through the barrier depends on the organ's requirement, hemodynamics, nervous and humoral impacts, and the presence or absence of morphological and functional disturbances. Barrier functions change with age, sex, nervous and humoral impacts, and various impacts of the internal and external environment. The functional state of barriers can change at alternation of sleep and wakefulness, starvation, fatigue, injury, irradiation by infrared, ultraviolet, and X-rays, influences of ultrashort, high-frequency waves, and ultrasound. Barrier permeability changes at pathological processes. The increase of permeability makes organs more sensitive to poisons, and intoxication reinforces tumor growth.

**Blood-brain barrier** – is a whole set of formations, which regulate substance arrival from the blood into the cerebrospinal fluid and nervous tissue. These formations are brain tunic, ependyma of the cerebral cavity, choroidal plexus, and endothelium of brain vessels.

**Blood-lymphatic barrier** – affects mechanical and physical-chemical protection of organ and tissue cells from the penetration and action of pathogenic factors. The barrier is formed by endotheliocytes, the basal membrane of capillary, arteries and veins, interstitial space, which is filled with intracellular fluid, cells of initial lymphatic vessels, and cells of lymphoid organs, the mass of which of a human comes up to 2 kilos.

**Histohematic barriers** have organs, the cells of which need the delivery of extracellular environment only of particular nutritious materials. To this group, we refer also to organs, which have autoantigens in the content of cytopenia, the penetration of which into blood provokes the development of destroying autoimmune process. Selective permeability of histo - hematogenous barrier for nutritious substances, circulating in the blood, provides tropism of parenchymatous cells. The blockade of tissue antigens by the cells of the organism system prevents its participation in the mechanisms of autoimmune processes.

**In the blood-testis barrier**, the barrier function is performed by vascular walls, which have solid endothelium, own tunic of the testicular tubule, Sertoli's cells, interstice, and testicle protein tunic. These structures provide high selectivity of substances penetration into testicular tubule and isolate spermatogenous epithelium from immune apparatus of the proper organism. At the damage of the blood-testis barrier (injury, the action of raised temperature, infections – tuberculosis, viral parotitis) the autoantigens, which induce the synthesis of the appropriate autoantibodies, evoking the damage of testicle cells and spermatogenesis, are formed.

**Blood-follicular barrier** is formed from the cells of the internal theca of the maturing follicle and follicular epithelium. Trophic requirements of ripening ovum are ensured by the granuloma cells because the direct contact between follicular fluid and ovum doesn't exist. Follicles, which undergo atresia, don't have a blood-follicular barrier.

**Pulmonary barrier** delay circulating in blood small particles – micro clots of fibrin, shadows of red blood cells, tumor cells, microbes, fat drops up to 7 micrometers. Occluding pulmonary vessels, small particles evoke local homeostatic bronchoconstriction and vasoconstriction. In the area of obstruction leucocytal infiltration emerges and activated microphages and macrophages destroy pathogenic factors, after that local bronchoconstriction and vasoconstriction disappear.

**Barriers of isolating type** protect parenchymatous cells from the contact serum and xenogenic proteins. Delimitation can occur at the expense of:

a) definite microstructure of vessel wall, through which due to endothelium continuity proteins practically don't penetrate: vessels of the blood-brain barrier, aorta, and big arteries, vessels of muscular type (arterioles);

b) functioning of adjuvant organ cells, which even at the availability of vessels permeability for proteins isolate parenchymatous cells on the ways of extravascular protein transport (blood-brain,

blood-neuron, blood-testis, blood-ocular barriers). The barriers of isolating types are easily disturbed by autoimmune processes, for example, encephalitis, disseminated sclerosis, and polyneuritis. At this, the permeability of vessels of microcirculatory race and also the vessels of muscular type increases dramatically, in a result of that serum and xenogenic proteins in significant amounts can penetrate into interstitial space and react with parenchymatous, adjuvant, and other types of cells, inducing the development of pathological processes at the molecular, cellular and system levels of the organization.

**Barriers of partially isolating types** are characterized by penetration of serum and xenogenic proteins from the vessels into interstice (vascular plexus of the cerebral sinus in relation to plexus epithelium, terminal lobules of the salivary gland, bile capillary of the liver, reticular and zona glomerulosa of adrenals).

**Barriers of non-isolating types** are permeable for serum and xenogenic proteins in compliance with a coefficient of permeability, concentration, and generic specificity (cardiac lipocytes, fibers of skeletal muscles, adrenal medullary substance, adipocytes).

The damage or the disturbance of barrier functions precedes the development of any pathologic process.

## PHAGOCYTOSIS AND ITS MECHANISMS. THE DISTURBANCES OF PHAGOCYTOSIS: CAUSES, MECHANISMS AND CONSEQUENCES

Phagocytosis – is one of the most brilliant discoveries of the I. I. Mechnikov it is a biological phenomenon in the vital activity of unicellular and multicellular organisms, consisting of absorption by cells of other cells and solid particles.

Phagocytosis – is a particular case of receptor endocytosis. The last can manifest in other forms: transcytosis, adsorptive, and liquid-phase pinocytosis. Phagocytosis is a way of nutrition and protection among unicellular and the lowest multicellular organisms. Higher animals have phagocytosis not only in the way of protection from exogenous factors but also as one of the mechanisms of elimination of proper old cells and apoptotic bodies in the process of planned cell death during morphogenesis. Phagocytosis provides the development of preimmune and immune responses, and removes immune complexes from blood flow, preventing complex immune diseases.

The participants of phagocytosis are phagocytes. I. I. Mechnikov singled out macrophages and macrophages, afterwards, it was established that the first – are monocytes and their descendents, and granulocytes. To present time it is established that monoblasts and promonocytes of bone marrow, monocytes of bone marrow and blood, and various tissue macrophages – are a cells dynasty. Recommended to change the term “reticuloendothelial system” for the term “system of mononuclear phagocytes”. Thus phagocytes are presented by the system of mononuclear phagocytes and polymorphonuclear phagocytes, in general, neutrophils. The ability to phagocytosis is inherent also to eosinophils and basophils but is not one of the main ones.

Phagocytosis can also take part in platelets, though this function is strongly stimulated by alpha-fetoprotein. According to some data, some prolymphocytes are able to phagocytes, but mature lymphoid cells are not phagocytes. Occasionally other cells, which don’t refer to the blood system, phagocytes; notably, nervous and epithelial are not professional phagocytes.

**Neutrophil** – is a short-living cell. In blood, it is, on an average, for 12–24 hours, in tissues – not more than 2–4 days. Neutrophils don’t take part in antigen presentation and specific immune response, otherwise, they as terminal effectors. Nevertheless, it is shown that they, like macrophages, which take part in inflammation and immune response like effectors, and regulators, are also functionally heterogeneous. Neutrophils differ by a less wide repertoire of phagocyte objects than macrophages. The latter are able to phagocyte almost all objects, which are available to neutrophils (for example, cocci and fungi), and also many others, which are not phagocyted by granulocytes. Phagocytosis of tumor cells, cells infected by viruses and persistent intracellular pathogens, is put into effect solely by macrophages.

In phagocytosis of staphylococci, and streptococci, including pneumococci, diplococci, and many other causative agents the role of neutrophils is decisive. Partly, that is why scarlet fever, gonorrhea, and meningococcus are accompanied by neutrophilic, and whooping cough, parotitis, and mononucleosis – by monocytic lymphocytic leukocytosis and corresponding composition of exudates.

**Macrophages. I.I. Mechnikov introduced the term “macrophages”, described free and fixed macrophages in different organs.**: 1) a number of bone marrow cells – committed stem cells (colony-forming units of granulocytes and monocytes and colony-forming units of monocytes), monoblasts,

promonocytes, monocytes; 2) blood monocytes; 3) mature macrophages of different organs: a) skin histiocytes; b) liver stellate cells (Kupffer cells); c) lung alveolar macrophages; d) free and fixed macrophages of lymphatic modes; e) fixed macrophages of bone marrow; f) pleural macrophages; g) peritoneal macrophages; h) brain microglia; i) macrophages of fibrous connective tissue of organ stroma; j) osteoclasts.

***On the basis of functional and morphological peculiarities, and also the differences in superficial markers mononuclear phagocytes are divided into 2 big groups:***

1) typical, or "classic", macrophages

2) the system of dendritic cells (they don't possess all the criteria, see above).

The most important mechanism of the interaction of macrophages with each other, blood cells, connective tissue and partly, with cells of other tissues is their secretion of biologically active substances [about 100 substances].

**These substances can be divided at several groups:** 1) hydrolytic ferments (lysozyme, collagenase, elastase, plasminogen activator, enzyme, destroying proteoglycans, neutral proteases, acid hydrolase); 2) modulators of cells behavior: interleukin-1, the factor of tumor necrosis, chemotactic factor for polymorphonuclearleukocytes, colony-stimulating factors, the inhibitor of monocytes and granulocytes proliferation, the factors, which influence on lymphocytes formation and ripening, the inductor of fibroblasts growth, the inhibitor of fibroblasts growth, the inductor of collagen synthesis, chemoattractant for fibroblasts, angiogenesis stimulator; 3) the products of arachidonic acid oxidation – prostaglandins, thromboxanes, leukotrienes; 4) active forms of oxygen; 5) complement components; 6) interferon; 7) other substances: coagulation factors, the proteins of extracellular matrix and cellular adhesion (fibronectin, thrombospondin, chondroitin sulfate – proteoglycans and others); proteins which connect metals (transferrin, acid izoferritin, transcobalamin); proteins which connect lipids, enzyme inhibitors and others.

The system of mononuclear phagocytes is presented by professional phagocytes and antigen-presenting cells of different locations. It is, firstly, monoblasts and promonocytes, monocytes and macrophages of bone marrow, proliferation and differentiation of which is under the influence of a number of successively acting cytokines (interleukin (IL) – 6, IL-1, IL-3, GM-CSF), monocytes of peripheral blood, situated in it, on average, for 1–2 days and leaving blood race through high-endothelial venules and sinusoids.

**In tissues,** *monocytes change into the lung, pleural, pericardial, and articular alveolar macrophages and peritoneal macrophages of the serous sac, splenic macrophages, Kupffer's cells in the liver, lymph nodes macrophages, brain microglia, bone osteoclasts, histiocytes of connective tissue, mesangial macrophages of glomerule and epithelioid cells. Phagocyte macrophages are especially active at metabolic outbreak and exocytosis of inflammation mediators.*

**The process of phagocytosis is divided into 4 stages:**

***1. The approach to the object of phagocytosis.***

***2. The adherence of phagocytes to the surface of the object (the recognition of opsonic determinants of the object phagocyte receptors).***

***3. The immersion of the object into the phagocyte's cytoplasm.***

4. ***The digestion (or wider – killing-effect, the degradation of the object).***

**The approach** can be accidental, but its main mechanism is chemotaxis. Chemotaxis is a directed concentration gradient motion of living cells of any recognizable substance. The substances, which attract cells, are called chemoattractants. In medias res, chemoattractive sensibility is typical for all the leucocytes, including non-phagocyte cells.

Chemoattractants, if they are on the surface of their evolving object, are, at the same time, opsonins, because direct binding of phagocytal receptor of chemoattractant with its ligand provides opsonisation (immunoglobulin and complement factors work as chemoattractants and opsonins). Along with chemotaxis we distinguish chemokinesis – the phenomenon of non-directed increase of locomotor cell activity under the influence of inflammation mediators. Histamine, acts on H-receptor of neutrophils and eosinophils, activates their mobility, but non-obligatory in the direction of growing gradient of its concentration. Phagocyte cells have superficial receptors for chemoattractants. The chemoattractants can be exogenous and endogenous, specific for the particular type of leukocytes and also universal.

**The main groups of chemoattractants are the following:**

1) ***Microorganisms and their products;***
2) ***The components of the complement system;***
3) ***The products of damage and metabolism;***
4) ***Some other inflammation mediators;***
5) ***Immune complexes and immunoglobulins.***

The **adherence of leukocytes** to the objects of phagocytosis is connected with the recognition of target superficial dominants by phagocyte receptors.

The **opsonization** increases adherence activity many times, and the effect of immunoglobulins and complement is additive. C-reactive protein is, practically, co-opsonin too, because it connects the C-protein of pneumococci and other microbes and mediates attachment of complement and phagocytes factors to them.

The immersion outwardly looks like coverage of phagocytosis by the pseudopods or phagocytosis recuperation on them. At the immersion occurs successive binding of opsonic determinants of the object with opsonic receptors of phagocyte, thus, the object moves forward into the cell's cytoplasm.

The **absorption** of the object, covered with immunoglobulins, occurs without extra effort. At opsonization of a complement by C3b-fragment simultaneous activation of fibronectin and laminin receptors of phagocyte by extracellular ligands is needed, as if the cell "leaned" on intracellular substance. The activation of cytokine receptors of phagocytes also can promote the immersion of the object, opsonized by complement C3b-fragment. As the result of immersion, the object is in phagocyte cytoplasm, fully surrounded by phagosome, formed by invagination and closure of cell membrane area.

The process of phagosome formation, apparently, has a lot in common with the formation of receprosomes at receptor endocytosis, when bordered fosses of the plasma membrane, which consist of protein of cytoskeleton clathrin, are closed into a descended vesicle. With the participation of microfilaments of the cytoskeleton and special proteins – fusion genes, phagosome connects with lysosomes and specific granules of phagocytes, forming phagolysosome, which occurs in the final stage of phagocytosis. All these processes depend on calcium, protein kinase C, and lipid intercellular mediators, such as chemotaxis.

**The degradation** of the phagocytosis object serves as a final stage of phagocytosis. Oxygen-depending cytotoxic mechanisms of phagocytes (halogenisation and peroxidation of the captured object's components with the participation of hypochlorite, hydrogen peroxide, singlet oxygen, hydroxyl radicals, superoxide anion, oxyiodide and nitric oxide) have here the main part.

The adjuvant part performs anoxic mechanisms: cationic antibiotic proteins, lactoferrin, and lysozyme. pH in phagolysosome changes in successive steps because of the phasic action of these agents. In the beginning, the reaction is close to neutral. The liberation of superoxide-anion evokes alkalescence of the phagolysosome contents, which conditions the action of cationic protein, lactoferrin, and defensins. The inflation of hydrogen ions in the phagolysosome changes its pH into an acid. At this acid, hydrolase activates, and lactoferrin continues acting. There is multi enzymatic system of NADF-depending oxidase in phagocytes, the components of which are situated in the cytoplasm and on the phagolysosome membrane. Neutrophils, endotheliocytes, and the majority of cells of different tissue have managed to form the mechanism thanks to the ability of NADF-depending enzyme of nitroxidesynthase and its cofactor tetrahydrobiopterin to oxidize alpha-arginine into nitric oxide and then into nitrogen dioxide. Active nitrogen-containing radicals and anoxic antibiotic proteins can kill fungi and mycobacteria, despite lowered sensitivity of these pathogens to oxygen radicals. Hereditary defects of phagocytosis, as a rule, autosomal-recessive, except described above variant of the chronic granulomatosis and defect of glucose-6-phosphate dehydrogenase, linked with X-chromosome. Myeloperoxidase defect of neutrophils is found the most often. The deficiency of leucocytal adhesive molecules is evoked by the defects, which are localized in long arm of the chromosome 21. In neutrophils, lymphocytes and macrophages the adhesion, aggregation, chemotaxis and the activation of the leucocytes by lymphokines is disturbed, and also the opsonization by the factor of C3b complement decreases.

**The disturbances of phagocytosis**

Table

| The disturbed function | Hereditary defects | Acquired defects |
|---|---|---|
| **Adhesion Aggregation** | Insufficiency of leucocytal adhesion of the 1 type (defect of selectins receptor) | Newborn, pancreatic diabetes, the consequences of hemodialysis |
| **Plasticity** | – | Newborn, pancreatic diabetes, hyperregeneratory left shifts, leukoses |
| **Locomotion** | Chediak-Higashi syndrome (defect of microfilaments, defect of actin-binding protein), Job's syndrome, deficiency of specific neutrophils granules | Newborn, pancreatic diabetes, oncological diseases, AIDS, combined immunodeficiency, collagenoses, starvation, influenza, herpes, Down's and Wiskott-Aldrich syndromes, parodontosis, deficiency of alpha-mannosidase,sepsis, |
| **Objects degradation** | Chediak-Higashi syndrome, chronic granulomatosis (defects NADF-oxydase), deficiency of neutrophils granules) | Newborn, pancreatic diabetes, sepsis, burns, AIDS, splenectomy, starvation hemocytopenies, leukosis |
| **Metabolic outburst** | Chronic granulomatosis, pyruvate kinase deficiency, glucose-6-phosphate dehydrogenases | Pellagra |
| **Myeloperoxidase activity** | Deficiency of MPO (defect of myeloperoxidase) | Acute myeloid leucosis |

**Humoral factors of non-specific organism resistance to infectious agents**

To humoral factors of non-specific organism resistance to the actions of infectious agents, we refer lysozyme, interferons, C-reactive protein, and others.

**Lysozyme.** This substance is found in tears, sputum, and saliva, and dissolves a number of microbes. Lysozyme possesses the ability to dissolve some types of saprophytes, such as also gonococci, meningococci, comma bacillus, and other microbes. However, the availability of lysozyme doesn't exhaust, apparently, the bactericidal action of mucous membranes. Lysozyme hydrolyzes muramylglucosamine of gram-positive bacteria but can damage other peptidoglycans. It is constantly secreted by monocytes, and histiocytes and is periodically produced by excited neutrophils leucocytes in the period of exocytosis of specific and azurophilic granules. The concentration of lysozyme in the blood plasma of a healthy human is quite high: general content reaches 150 mg. The concentration of lysozyme in the gland secretions of mucous tunics is defined by the activity of the secretory process and the speed of catabolism in tissues. For the manifestation of the bactericidal effect of lysozyme in the beginning we need the fixation of complement and normal antibodies of blood serum on the surface of the cytoplasmic membrane of foreign cells, which leads to its alteration.

**Interferons –** re low-molecular proteins, which are formed in cells infected by viruses and protect other cells from the affection. Interferons protect cells not only from a type of virus, by which the organism is infected but from other viruses too. Interferons refer to a group of proteins, which protect cells against viral infections. They correspond to glycoproteins and are divided into alpha-, beta- and gamma types. Alpha-, beta- and gamma-types consist of interferon of 1 type because they all possess similar antigen properties and get connected with each other by one and the same receptors of the cellular cytoplasmic membrane. Gamma-type is represented by interferons of the 2 types, which bind only with their own receptors of the cytoplasmic membrane of almost all cells of the organism.

**The inductors of interferon synthesis** are viruses, chlamydiae, rickettsia, mycoplasma, protozoa, mitogens, and antylymphocytic antibodies.

Antiviral action of interferon is connected with the blockade of the replication of DNA and RNA viruses as the result of the induction of special protein-repressor synthesis and depression of viral reproduction because of the loss of the ability of viral RNA and ribosomes to form polyribosomes. Along with that interferons reduce the activity of natural killers, and macrophages and reinforce antibody production.

Anticancer action of interferon is directed at the reinforcement of anticancer immunity at the expense of the increase of the quantity and growth of the cytotoxicity of immunocompetent cells – natural killers, T-lymphocytes-killers, macrophages, and macrophages. Phagocytic activity of macrophages by interferons increases at the expense of the reinforcement of receptor expression to Fc-fragment of antibodies, and also by means of stimulation of synthesis by lysosomes. Interferons inhibit also the growth of malignant cells and reinforce elimination by systems of cytotoxic and phagocyte cells.

**C-reactive protein (CRP)** C-reactive protein (CRP) consists of 5 identical non-glycolic polypeptide chains, joined by disulfide bridges. The concentration of CRP in the blood plasma of a human – is 680–800 ng/l. CRP is synthesized by hepatocytes. At the damage to tissues and organs, the concentration of CRP in blood plasma after 6–8 hours can be tens and hundreds of times higher. In blood plasma, CRP gets connected with polycations, proteins of destroyed leucocytes, phosphocholine-containing xenobiotics – bacterial polysaccharides. CRP includes also the mechanisms of blood coagulation control, where its cofactor is thrombomodulin. In this case, CRP is activated under the influence of such a low concentration of thrombin, which doesn't evoke thrombocytes activation and factors of coagulation – X and other. In the active form, CRP significantly lengthens the time of blood coagulation, inhibits thrombocyte aggregation, and depresses the activity of V and VII coagulation factors.

**Complement** – is a system of blood serum proteins, the successive activation of which evokes the damage (perforation) of cellular membranes, and, as a consequence, the elimination (lysis) of bacteria.. Complement takes part in the mechanisms of non-specific protection from infectious pathogenic factors, is an independent communication system for cells of organs and tissues, and is a stimulator of monocytes, macrophages, granulocytes, and B-lymphocytes activity. All components of complement are primarily synthesized in the form of united chains – the molecules of precursors. The synthesis of complement components is regulated by hormones, especially by sexual steroids, and different mediators. The complement system consists of 11 proteins, which compound 9 fractions, labeled C1, C2…C9. Complement proteins are regulated by the same quantity of inhibitors and inactivators.

***There are several mechanisms of complement activation.***

- Classic way (antibody-mediated). The activation of the complement is connected with the formation of antigen-antibody complexes on the surface of bacterial cells. The classic way of the activation of complement components occurs mainly in infectious and autoimmune diseases. Activators C1 are usually immune complexes, lipids in the content of lipopolysaccharide. The stage of C1 activation in a human includes three stages.
- The first stage consists of the proteolysis of the N-terminal area of the alpha-chain with the formation of C3a anaphylatoxin. This component can interact with smooth-muscle cells, neutrophils leucocytes and mast cells.
- The second stage is represented in the fixation of C3b on the surface of the membrane, bacteria immune complexes, viruses, and many other types of cells.
- The third stage – is the formation of a center, which is recognizable by receptors for C3b on the surface of the cytoplasmic membrane of monocytes, B-lymphocytes, and other target cells. It gives the possibility of fixation of insoluble and soluble pathogenic factors on cells. Such mechanism is very important in the immobilization of antigens on the cells of lymphoid follicles, in cooperation of B-lymphocytes and macrophages in immune response, in the clearance of immune complexes and viruses' neutralization. Complement-mediated lysis of target cells happens by the formation of membrane attack complex, which consists of terminal components C5b–C9 as the result of activation of components C5 and C5a by convertases of classic and alternative ways.
- **Alternative way (properdin).** The activation of complement directly evokes poly- and lipopolysaccharides of bacterial wall. This mechanism requires the participation of serum proteins, which have received the names of properdin. The alternative way of activation of complement components provides the first line of protection from infectious agents in non-immunized organism during the whole period of formation of specific immune response.
- **Non-specific activation.** Can be implemented by active proteases (trypsin, plasmin, kallikrein, lysosomal enzymes, and others) at any stage of this process.

- Inactivation of complement components the definite part has the interaction of their subcomponents with specific receptors on the surface of the cytoplasmic membrane of target cells – B-lymphocytes, red blood cells, monocytes, thrombocytes, and fibroblasts.
- is a system of blood serum proteins, the successive activation of which evokes the damage (perforation) of cellular membranes, and, as a consequence, the elimination (lysis) of bacteria. Complement takes part in the mechanisms of non-specific protection from infectious pathogenic factors, is an independent communication system for cells of organs and tissues, and is a stimulator of monocytes, macrophages, granulocytes, and B-lymphocytes activity. All components of complement are primarily synthesized in the form of united chains – the molecules of precursors. The synthesis of complement components is regulated by hormones, especially by sexual steroids, and different mediators. The complement system consists of 11 proteins, which compound 9 fractions, labeled C1, C2…C9. The main function of the activated complement – is the lysis of bacterial cells, conditioned by the perforation of their membrane.

**There are two groups of disturbances in complement system are possible**

**The deficiency of complement components.** The disturbances of the synthesis of complement components emerge at genetic (primary) and acquired (secondary) damages of complement-formative cells.

Congenital defects of synthesis of complement components have autosomal-recessive character. People can have the deficiency of all complement components except C9, the components of an alternative way of complement activation. Congenital defect of C1q synthesis is typical for the cases of severe combined immune insufficiency. Genetic insufficiency of C1r is often observed in the illnesses of glomerulonephritis. The weakening or shutoff of C3 formation sharply decreases human organism resistance to bacterial infections. The lack of C5, C6, and C7 components is characterized by the development of systemic lupus erythematosus.

Acquired disturbances, as a rule, are connected with general disorders of protein biosynthesis and intensified inactivation of complement components. They emerge with sharp obstructive jaundice, thyroiditis, dermatomyositis, and sharp myocardial infarction.

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## PRACTICAL LESSON № 4
## Topic: THE VIOLATIONS OF IMMUNOLOGICAL REACTIVITY

**Relevance of the topic.** The immunological reactivity provides the body's response to an antigenic stimulus, it provides the control over the individual antigenic composition of an organism, the inactivation, removal of foreign antigens from the body, so to say – the immunity. One of the immunity disorders is the immunosuppressive and immunodeficiency states, which substantially influence the development and course of the disease.

Overall Objective – to be able to characterize the patterns of the immunosuppressive or immunodeficiency states.

**To do this we should be able to (specific objectives):**

1. Identify the immunosuppressive and immunodeficiency states.
2. Characterize the types of immunodeficiency states
3. Determine the reason, mechanism of development, and the manifestation of the acquired immunodeficiency syndrome

**The necessary basic knowledge and skills to achieve the goals of studying.**

**To be able to:**

1. Characterize the structure of the immunocompetent system
2. Explain the functions of individual cells of the immunocompetent system.

### THE QUESTIONS TO THE LESSON

1 The notion of immunity and immunological reactivity.
2. The physiological and pathological immune reactivity.
3. The specific and non-specific, cellular and humeral mechanisms of the immune reactivity (immune response).
4. The notion of immunodeficiency and immunosuppressive states.
5. The classification of immunodeficiency states. Characteristics of individual species.
6. Immunodeficiencies associated with violation T-lymphocytes.
7. Immunodeficiencies associated with the violation of B-lymphocytes.
8. The combined immunodeficiency states.
9. Etiology, the pathogenesis of the acquired immunodeficiency syndrome (AIDS).
10. The immune tolerance.
11. The pathophysiological basis of transplantation of organs and tissues.

### THEORETICAL MATERIAL FOR PREPARATION TO LESSON
### THE VIOLATIONS OF IMMUNOLOGICAL REACTIVITY

**Mechanisms of immune response of humoral and cellular types, mechanism of immunologic tolerance, its types and its reproduction in experiment**

**Immune response –** is a process of interaction of immune system cells, which is induced by antigen and leads to the formation of effector cells, and the mechanisms, which destroy this antigen. The immune response is usually a specific process, which progresses only in peripheral organs of the immune system. It is accompanied by non-specific reactions, such as phagocytosis, and activation of complement and NK cells.

At the initial stages of the immune response at least three types of cells: macrophages, T- and B-lymphocytes take part. On whole, all cells, which are involved in this process, can be divided, as it was stated above, into antigen-presenting, regulatory, effector, and memory cells. There are two ways of the immune response: 1) T-cellular response; 2) B-cellular, or humoral, response.

The first one is regulated by T-helpers of type 1 and leads to the formation of 1) effector CD4+-T- cells of inflammation and 2) cytotoxic CD8+-T-lymphocytes, also corresponding to them T-memory cells. The second way is regulated by T-helpers of type 2 and ends by the formation of plasma cells (antibody producers of M, G, A, and E classes) and memory B-lymphocytes. The switching to the synthesis of some antibody isotopes is partially controlled by T-helpers of type 1. Except for the latent inductive period, immune response at the average continues for about 3 weeks with maximal tension at 1 week**.**

**We can separate out several main stages of immune response:**

*1. Antigen endocytosis, its processing and load in molecules HLA 1 and HLA 2 for the presentation to lymphocytes.*

*2. The recognition of complex antigen peptide-HLA 1 and –HLA 2 and other stimuli.*

3. *Signal transduction and activation of cellular clone.*
4. *Clone expansion, or proliferation.*
5. *Ripening of effector cells or memory cells.*
6. *Effector's reactivity.*

Antigen-presenting cell (macrophage, dendritic cell, or B-lymphocyte) connects with native antigen and endocytic it. Macrophages phagocyte mainly pathogens, for which intercellular parasitization is typical: dendritic cells pinocytic viruses; B-cells internalize different toxins. The following event is processing – it is enzymatic catalysis of antigen macromolecule inside the antigen-presenting cell. As the result of processing occurs the release of dominating antigen determinant, which loads at the grooves of the own molecules HLA1 and HLA2 class, is taken into cell surface for presentation to lymphocytes. Depending on antigen origin we distinguish two ways of processing. Exogenous antigens are presented in the complex with molecules HLA2 to existing CD4+-T-cells. Firstly these antigens are endocytic and fragmented with the help of proteolytic enzymes in endosomes. At the same time molecules HLA2, connected with operons, are synthesized and gathered in the endoplasmic reticulum.

Endogenous, or intracellularly located, antigens of microbial nature load on molecules HLA 1(the way, mediated by HLA 1) for the presenting of existing CD8+-T-cells. In the beginning, unlike exogenous antigens, such cytoplasmic antigens are transported into the cytosol, where they split into the large proteolytic complex – proteasome. After that antigen peptide is transported into the endoplasmic reticulum. Simultaneously there takes place the assembly of the HLA1 molecule, the groove of which is "under protection" of operons, and the insert of the whole HLA1 molecule further becomes stable by additional molecules. After a load of antigen peptide at the groove of HLA 1, this complex is transported on the cell's surface.

Perhaps, it leads to a delay of the whole immune response to a pathogen. Clinic manifestations of this stage are a rise in temperature, muscle weakness, and anorexia.

The meeting of T- and B-lymphocytes of the corresponding clone with antigen-presenting cells is necessary for the start of a specific immune response at the concrete antigen. Some antigens of bacteria are recognized with the help of BCR B-cells and don't need help from T-helpers. The majority of native pathogens are recognized at "full scale" by CD4+-T-helpers of type 1 and CD8+-T-cells, and also CD4+-T-helpers of type 2. It is interesting that for priming CD8+-T-cells the participation of CD4+ -T- helpers 1 is necessary.During recognition lymphocytes perceive three types of signals – one specific and two – non- specific: 1) antigen peptide HLA 1 or HLA 2; 2) cytokines; 3) costimulating molecules.

Cytokines have one of the most important roles in the non-specific regulation of immune response. T- and B-lymphocytes receive cytokine signals from antigen-presenting cells, NK cells, and mast cells. The inverse signal from lymphocytes, for example secreting IFNγ, favors the reexpression of HLA1and HLA2 at antigen-presenting cells. Cytokines, which act at different stages of an immune response, can be divided into two groups depending on their direction: 1) IL-2, IL-12, IL-18, IFNγ, TNF alpha/ beta (for the way of T-helpers of type 1); 2) IL-4 (for the way of T-helpers of type 2). However, at the following stages of an immune response, other cytokines are involved in the process. Costimulating molecules also have an important role in the non-specific regulation of immune response. The activation of cells is the result of immune transduction, which is implemented by a series of complex intercellular reactions.

Clonal expansion of lymphocytes corresponds to their proliferation in the peripheral organs of immune systems. Proliferating B-lymphocytes from secondary follicles in lymphatic nodes, at this cell's reproduction is regulated by a number of cytokines – IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-14, IFN-g, TNF. In the process of cell maturing B-cells undergo morphological changes and migrate into bone marrow and MALT for the synthesis of antibodies of different classes. Synthesis of IgM is observed by the end of the first day of the clinical infectious episode, the synthesis of high-specific IgG – at 5th – 7th day.

On the termination of immune response along with effector cells T- and B-memory cells are formed. Unlike short periods of life, which are typical for effector lymphocytes, memory cells remain viable for a long period of time. There are CD4+- and CD8+-T-memory cells, B-memory cells, and long-living plasmatic cells. As opposed to available T-lymphocytes T-memory cells are characterized by phenotype CD45 RA+, CD44+, rapid HLA-independent cycle, and the ability to secrete big amounts of cytokines. Long-living plasmatic cells provide an additional mechanism of maintenance of immunoglobulins synthesis without additional antigen stimulation for 1,5 years.

**Secondary immunity** progresses in the accelerated regimen at the expense of memory cells. Manifestation of IgM in blood serum often points to fresh infection or the reaction of a persistent pathogen, and the synthesis of IG corresponds to the presence of immune memory of once tolerated infection. At such accelerated synthesis of IgG clinical manifestations of infectious disease are usually absent.

**Immunologic tolerance –** is a state of specific immunologic reactivity to the given antigen, which is conditioned by the previous contact with this antigen and is characterized by the "tolerance" of the immune system against it. At this, the ability of the organism to give an immune response to all other antigens is preserved.

***For the receiving immunologic tolerance state, it is used the injections of:***

*• antigen into fetus organism at the critical period of formation of natural immunologic tolerance to own antigens;*

*• great amounts of soluble antigen (Felton's immune paralysis);*

*• hapten, connected with a non-immune carrier;*

*• antigen against the background of an artificially created state of immunodeficiency;*

*• anti idiopathic antibodies, i.e. antibodies against specific determinants of immunoglobulins;*

*• antigen-specific T-suppressors, which are taken from the tolerant organisms. Immunologic tolerance is divided into physiologic, pathologic, and artificial.*

**Physiologic tolerance** – implies "tolerance" of the system of immunobiological surveillance to own antigens. There are the following mechanisms for the development of physiological tolerance. Elimination at the antenatal period of that lymphocyte clones, which undergo antigen overload – massive influence of own antigens. The isolation of antigens of a number of organs from contact with immunocytes by structural physiological barriers. To such organs, we refer brain, eyes, testicles, and thyroid gland, which are separated from the internal environment of the organism by hemato-tissue barriers. This type of tolerance is called isolation. The depression of proliferation and differentiation of autoaggressive T-lymphocytes in central organ of immune system – thymus. This phenomenon is called central selection and elimination of autocytotoxic lymphocytes.

The death (apoptosis) of lymphocytes' clones, activated by autoantigens. In such a situation T-lymphocytes, reacting to antigens of their own organism, express Fas-receptors, at which Fas-ligands of normal cells act, and it activates the apoptosis program.

**Pathologic tolerance** – implies "tolerance" of a system of immunobiological surveillance to foreign antigens, the most often – bacteria, viruses, parasites, cells of malignant growths, or transplants.

**<u>There are the following mechanisms of pathologic tolerance:</u>**

- The emergence of the immunodeficiency state.
- Excessive rise of T-suppressors activity. The latter is characterized by the maturing inhibition of effector cells of the immune system: T-killers, natural killers, and plasmatic cells.
- The inhibition or blockade of cytotoxic reactions of cellular immunity at the corresponding antigen (the most often tumor cells, transplant of virus-containing cells).
- The reload of immunocytes by the excess of forming in the organism or injected foreign antigens into it from without. It can be observed in the synthesis of anomalous proteins in the liver, amyloidosis, denaturation of protein molecules at massive burns, and injection of big amounts of protein-containing solutions (whole blood, plasma).
- The death of cytotoxic T-lymphocytes with the development of T-cellular immunodeficiency. It is observed in the expression of Fas-ligands by other cells. Fas-ligands, interacting with Fas-receptors of cytotoxic T-lymphocytes, activate the program of their apoptosis.

**Induced (artificial, medical) tolerance** is replicated with the help of impacts, which depress the activity of the immune system. Usually, for this purpose ionizing radiation, high doses of cytostatic agents, and immunosuppressive agents are used. Special (impermeable for immunocytes) chambers, which are implanted under the skin, into mucous membranes, muscles, and body cavity, are used for the creation of the state of artificial tolerance. Homogenate or fragments of foreign tissues are put into a chamber. Such diversity of tolerance is called isolation. The state of induced tolerance is used for the efficiency increase in transplantation of organs and tissues, allergy treatment; the diseases of immune auto aggression, endocrine insufficiency, and some other states.

**Immunologic insufficiency, the definition of the notion, classification (WHO)**

Immunologic insufficiency – is congenital or acquired deficiency of the immune system, which manifests in the inability of the organism to fully carry out the reactions of humoral and (or) cellular immunity.

Immunodeficiencies – are independent diseases (nosologic forms) and subtend syndromes, which are characterized by insufficiency of the immune system.

Immunodeficiencies are divided according to the origin at primary (congenital) and subtend (acquired), according to clinic evidence – at clinical and minor, according to the localization of the defect – at the deficiency of antibodies, T-lymphocytes, combined deficiencies of T- and B-cells, defect of NK-cells, phagocytosis, deficiencies of adhesive molecules, complement.

**The reasons, mechanisms of development, types of primary immunodeficiencies**

Under primary immunologic insufficiency, we understand genetically conditioned development defects of one or another immune system link. A number of diseases are linked with sex, for example, only boys can have Bruton's agammaglobulinemia or Wiskott- Aldrich syndrome. Other diseases are inherited by autosomal-recessive type, for example, Nezelof-type thymic dysplasia, Louis-Bar syndrome, severe combined immunologic insufficiency, selective deficiency Ig A and others. Some diseases are developing sporadically.

Primary immunodeficiencies are divided into combined (with simultaneous defect of T- and B-systems), selective T-deficiencies, and selective B-deficiencies.

The greatest number of uncovered immunodeficiency diseases are combined. And they, naturally, are the most severe. The most examined are Swiss-type immune deficiency, Louis-Bar syndrome, and Wiskott-Aldrich syndrome.

**Combined immunodeficiencies**

1. **Swiss-type of immune deficiency** – is severe combined immunologic insufficiency (SCII). It is transferred by autosomal-recessive type; linked with sex and sporadic forms are possible. It manifests by hypolymphemia and hypogammaglobulinemia, which are found in the first weeks of life. The thymus gland has rudimentary forms, the cortex and its medullary substance are not differentiated. In peripheral lymphoid organs (spleen, lymph nodes) the quantity of lymphocytes and plasma cells is sharply reduced. The reactions of transplant rejection and other delayed skin reactions are absent. The traces of IgG are defined; the traces of IgM and IgA are absent. Quite often it combines with deficiency of the adenosine deaminase enzyme, adenosine, which becomes toxic for lymphocytes, and stores.Clinically it manifests in severe recurrent inflammatory processes of respiratory and digestive tracts, thrush, weight lagging, and others. Without treatment children who have SCII die in the first 6–12 months of life. The only effective way of treatment – is the transplantation of bone marrow.
2. **Louis-Bar syndrome** – is combined immunodeficiency with telangiectasia and ataxia.

It is inherited by autosomal-recessive type. The thymus gland is in germ, and the quantity of T-lymphocytes is reduced. The damage of the B-system manifests in the deficiency or total lack of IgA, the quantity of IgG is reduced or stays in the norm, quite often there is IgE deficiency; the level of IgM remains in the norm. It manifests by neurologic disturbances (ataxia, hypotaxia); vascular (skin and conjunctiva telangiectasia); psychological (mental retardation); endocrine (adrenal dysfunction, gonad dysfunction, and other); recurrent from early childhood sinus pulmonary infections.

Embryonic proteins of type alpha- and beta-fetoproteins, IgMs – monomer IgM can be found in the blood serum of the majority of diseased people. The frequency of tumors grows to 10 % among these diseased people. More often tumors are localized in the lymphoid system: lymphosarcoma, lymphoreticulosarcoma and others.

3. **Wiskott-Aldrich syndrome** – is combined immunodeficiency with thrombocytopenia and eczema. It is linked with sex and manifests among boys older than 10 years. At first, after the birth, the affection of the T-system doesn't manifest, but after some time the number of lymphocytes in T-zones of peripheral organs of immunity(lymph nodes) progressively reduces, and the reactions of cellular immunity (the response to antigens and at allogenic cells) are inhibited. Despite the normal number of B-lymphocytes the production of natural antibodies and the production of antibodies at immunization of polysaccharide antigens are sharply inhibited. The concentration of IgM at normal content of IgA (it is usually increased) and IgG in reduced blood serum. It manifests by creeping diseases (eczema), thrombocytopenia, and recurrent inflammatory processes; in 10 % of cases, malignant neoplasms are developing.
4. **Good's syndrome** – is combined immunodeficiency with thymoma. It occurs more seldom.

5. **Gitling's syndrome** – is thymus hypoplasia with reduced level of immunoglobulins.
6. **Immunologic insufficiency having dwarfism with short limbs.**

The most variegated combinations of defects of T- and B-lymphocytes, which it is hard to relate to one or another known group of diseases with immunologic insufficiency, are singled out as variable immunodeficient diseases with non-classifying forms. Leading clinical signs of people having such diseases are recurrent inflammatory processes.

The diversity of pathological changes, which are connected with the affection of other systems (inflammatory recurrent processes, the affections of the digestive system, malnutrition, creeping diseases – pyodermia, eczema, herpes, mycotic lesion, candidiasis; affections of the liver, pancreatic gland, endocrine glands; tumors) is typical for the diseased people with congenital immunologic insufficiency.

**Selective T-deficiencies**

Genetic block of reproduction and differentiation is possible at any period of T-lymphocyte genesis: prethymic, thymic and postthymic. At the 1 stage of thymic period block manifests by combined immunodeficiency, about what was said above, beginning from the 2 stage of prethymic period – the disturbances in the system of T-lymphocytes only; depending on the level – the fall of all functions of T-lymphocytes, the disturbances of T-lymphocytes differentiation, the disturbances of formation of corresponding T-lymphocytes subpopulations.

**Two forms of immunologic insufficiency of T-type,** conditioned by thymus aplasia or hypoplasia – DiGeorge syndrome and Nézelof-type thymic dysplasia are described fully enough.

1. **DiGeorge syndrome.** It is developed as the result of the formation of 3rd and 4th peripharyngeal branchial pockets during the embryonic period. As the result along with the absence of thymus gland and T-lymphocytes grain defects, aplasia of the thyroid gland and parathyroid glands, defects of the circulatory system emerge. The deficiency of lymphocytes in T-depending zones is noticed in peripheral organs of immune systems. Inhibited reactions of DSR, in particular, the rejection of the transplant, at preserving humoral immunity. It manifests by tetany, which response to treatment by hormones of parathyroid glands (but not calcium); high sensitivity to skin infections, infections of respiratory and digestive tracts.

2. **Nézelof-type thymic dysplasia.** It is an autosomal-recessive form of thymic aplasia (without aplasia of parathyroid glands), and is accompanied by underdevelopment of T-depending component of peripheral lymphoid organs with deep deficiency of reactions of cellular immunity. The reactions of humoral immunity can be preserved. This disease is evident by recurrent infectious processes and substantially viral and fungous etiology from the neonatal period. The treatment – is the transplantation of the thymus right after the birth.

**Selective B-deficiencies**

As it was stated above that, if the genetic block is at the level of formation of a general precursor of T- and B-lymphocytes (I stage), then combined deficiency of both lymphocytes lines emerge. Starting from II stage, block manifests by the disturbances of B-lymphocytes differentiation, and it leads to insufficiencies of various B-lymphocytes subpopulations. Starting from V stages, the final differentiation of B-lymphocytes and memory cells is disturbed, and it leads to the stoppage of synthesis of definite immunoglobulins classes.

I. Physiological hypogammaglobulinemia. Is observed among children of 4–12 weeks old. It is explained by the decrease of the level of Ig, received from the mother, and transfer to the synthesis of own Ig.

II. Bruton hypogammaglobulinemia. It is linked with sex and manifests among boys. B-lymphocytes and plasma cells are absent in blood and lymph nodes. The quantity of Ig G is10 times less, Ig A and Ig M – 100 times. Accordingly, the reactions of humoral immunity are sharply inhibited, while cellular – can be preserved. The thymus is also preserved. The genetic block is, probably, at the level of the B-lymphocyte cell precursor. It manifests by recurrent, mainly pyogenic infections, which develop from the middle of the 1st year of life, when received from the mother Ig stops rendering protective action.

**Ig A immunodeficiency** – is developing at the genetic block at the final stage of B-lymphocyte differentiation in plasma cells, which synthesize Ig A. It is transmitted as autosomal, recessive, and sometimes dominant indicators. The synthesis of other Ig classes is usually preserved. The diseases can have an asymptomatic course; in the majority of cases, we observe infections of respiratory and digestive tracts and autoimmune processes. Besides the block of B-lymphocytes differentiation Ig A

deficiency is developing at the genetically conditioned defect of the synthesis of secrete component S, which is necessary to transform Ig A into secreting form, into the epithelium of glandular organs. As a result the content of Ig A in secrete reduces.

I. Ig G and Ig A immunodeficiency. The synthesis of Ig M is preserved. Genetic block can be on the level of final stages of B-lymphocyte differentiation in plasmatic cells, and also at switching of Ig N synthesis at Ig A and Ig G synthesis in one and the same plasmatic cell.

II. Immunodeficiency, which is conditioned by a genetic block of synthesis of Ig light chain, in the result of which the synthesis of fully-chain Ig is disturbed.

III. Immunodeficiencies, which are connected with immunocyte dysfunction. This is the deficiency of Ig G (and quite often Ig A), which is accompanied by an increase in Ig M synthesis. It is inherited as linked with sex or autosomal-recessive indicator. Having syndromes of a-, hypo-, or disimmunoglobulinaemia the treatment is implemented by means of replacement injections of blood plasma Ig fractions of healthy people or people, which are immunized from an antigen, and also fresh blood plasma.

**The role of physical, chemical, and biological factors in the development of secondary immunodeficient (immunosuppressive) states.** Unlike the primary, secondary immunologic insufficiency is not connected directly to a genetic block of any immunogenetic stage and is developing under the influence of multiple damaging factors, which act primarily on the invariable immune system. Acquired immunodeficiencies are extremely various, and accompanied by the affection of T- as well as B-system of the immunity, and quite often of both systems.

**The reasons of secondary immunodeficiency:**

transient immunodeficiency among children during the first time after birth and among seniors – is a physiologic phenomenon;

- ✓ severe inflammatory processes;
- ✓ infections – measles, rubella, leprosy, and others;
- ✓ tumors;
- ✓ lymphogranulomatosis;
- ✓ losing of proteins of blood serum (bleedings, through bowels – at lymphangioma, through kidneys);
- ✓ the disturbances of the immune system:

**The role of factors in the development immunodeficiency**

surgical – the removal of thymus, spleen, lymph nodes, or the removal of lymphocytes – chronic drainage of the thoracic lymphatic duct;

- physical – general irradiation by X-rays, gamma-rays, and others;
- chemical – the action of immunosuppressive agents (analogs of purine and pyrimidine bases, which are alkylated compounds, inhibitors of protein synthesis, corticosteroids, and others);
- immunologic – the action of antilymphocyte serum, antithymic, and antiglobulin serums;
- viral (AIDS).

They manifest by heightened sensitivity to infections; engraftments of foreign (allogeneic) transplants for a long period of time; an increase in the frequency of malignant tumors emergence.

In laboratory investigations of hypolymphemia, a decrease in indexes of lymphocyte functional activity, level of serum IgM, G, and A, and inhibition of skin test development to delayed-type hypersensitivity with tuberculin, 2,4-dinitrochlorobenzene and others are found.

**Etiology and pathogenesis of acquired immunodeficiency syndrome (AIDS)**

**AIDS** – is an infectious disease, which emerges as the result of affection from viruses of the immune and other systems, and owing to that the organism becomes highly sensitive to secondary infections and malignant tumors. The reason for AIDS is lymphotropic retrovirus – human immunodeficiency virus (HIV). Owing to protein gp120 virus gets connected with CD4+-marker and, at the participation of own protein fusion gene gp41, penetrates into B-lymphocytes-regulators and macrophages. Reverse transcriptase copies the virus's genome in the form of DNA, and integrase allows the copy of the viral program to integrate into the genome of the master's cell. The activation of charged lymphocytes and macrophages favors the synthesis and assembly of components of new virions. At the beginning of disease pathogenesis, there is a phase of sharp virus attack, which is accompanied by the liberation of lymphokines and the activation of immune system cells and resembles mononucleosis according to the manifestations.

During the first 6 months the antibodies for the virus are formed, with, though, don't provide protection, but serve for diagnostics. During the latent period, the quantity and functional activity of

CD4-positive lymphocytes progressively decrease. The functions of these cells, including cytokines synthesis, and interactions with cytotoxic lymphocytes and B-cells, weaken earlier than their quantitative deficiency emerges. The virus persists in lymphocytes, evoking lymphadenopathy. When the quantity of CD4+-lymphocytes falls down to less than 200 cells per blood microliter, the AIDS clinical stage starts, which manifests, first of all, by so-called AIDS-associated symptom complex (persistent hyperplastic lymphadenopathy, the symptoms of system actions of cytokines and skin fungi). Lacking of T-helpers help, B-lymphocytes decrease their stimulated response to antigens, but manifest increased spontaneous antibody-forming and cytokine-synthesizing activity. The result of this is antibodies production, the excess of IgM low affinity and IL-6, and also TNF α. Owing to cytokines' action catabolism reinforces and the patient loses weight. HIV has cytopathogen for macrophages, persists in it and is delivered all over the organism. HIV penetrates into glia cells and neurons, because some of them express CD4+, and other – galactosyl ceramide , alternative entrance receptor for virus.

**Pathophysiological foundations of organs and tissues transplantation.** The reaction of transplant rejection, its reasons, and mechanisms

The development of medicine in the XX century has led to the creation of fundamentally new technology of treatment – the transplantation of organs and tissues. The transplantation of kidneys, bone marrow, liver, lungs, and heart began to be widely implemented, especially in developed countries and has allowed the prolonged life of millions of people.

**Types of transplantation**

**1. Allotransplantation** – (allogenic transplantation, homotransplantation, homological transplantation) – is the transplantation between two individuals of one and the same kind, typical transplantation of organ or tissue from man to man, and also between two similar animals, for example, dogs or mice.

**2. Isotransplantation (isogenic transplantation)** – is the transplantation between identical twins or between animals, which are in germaneness, and their genetic substance in media is equal.

**3. Autotransplantation –** is the transplantation of tissue at one and the same patient or animal, for example, the transplantation of thigh skin at the place of burn.

**4. Xenotransplantation (heterotransplantation)** – is the transplantation between two animals of different species, for example from a rat to a mouse.

**The main problem in transplantology** way is an immunological incompatibility of allotransplants (from the other representative of the same species) with the host's organism. The only way to bypass this barrier – are is through transplants (from monovalent twins and cloned individuals) and autotransplants (from the same individual). However, it appeared that on whole the mechanisms of transplant rejection correspond to the main directions of the immune response to foreign antigens. Different clones of native recipient T-lymphocytes recognize:

**1) HLA transplant;**

**2) antigen peptides of transplant + HLA transplant;**

**3) antigen peptides of transplant + own HLA.**

Subsequently, all variants of the immune response are developing, and it leads to the formation of cytotoxic T-lymphocytes, T-helpers of immune inflammation, specific immunoglobulins, and corresponding T- and B-memory cells. A significant part in the initiation of the immune response at transplant antigens have lymphocytes, which have avoided positive selection in the thymus and which don't recognize "own" HLA from "not own".

There are two forms of transplant rejection in the experiment: primary and secondary. Sharp primary reaction develops during 10 days mainly at the expense of effector T-cells and macrophages. During the first 4–5 days the flap seems to be accustomed, but on the $6^{th}$–7th day edemas, hemorrhages, and lymphocytic-monocytic infiltration emerge, and on the 10th–11th day the rejection occurs. Sharp secondary rejection is accelerated according to time and occurs during 1–5 days from the moment of transplantation; the skin flap at this has no time to vascularize and looks like a "white transplant".

**Reaction "graft-versus-host"** The reactions "graft-versus-host" (GVH; homological or transplantation disease) – is immune aggression of the donor's grafted cells, which is directed against recipient's antigen structures.

**Its origination demands a number of conditions, in particular:**

1) the state of the recipient's immunologic insufficiency (fetus's and newborn's immunologic immaturity, primary and secondary immunodeficiencies);

2) transplantation of immunocompetent cells;

3) antigen differences between the donor and recipient.

Immunologic interrelations in the system "mother-fetus" The reaction "graft-versus-host" develops in two variants: at the transplantation of homologous transplants to recipients with the broken immune system (homologous, or transplantation disease) and at the disturbances of placental barrier and penetration of mature immunocompetent cells of mother to the system of fetus circulation with the undeveloped immune system (homologous disease, or allogenic disease). As a result of penetration of the mother's viable immunocompetent cells through the placental barrier, their settle in lymph nodes, spleen, and fetus bone marrow occurs. Here allogenic cells depress the immunocompetent ability of fetus cells and form in these structures clones of allogenic T-helpers damage fetus organs and tissues, inhibit its growth, and further the development of infections and new formations. The cells of the mother's immune system release also cytokines, which regulate the growth of trophoblast, and antibodies, which stop the reaction of rejection. Under pathology, the interactions of NK cells with HLA-G are disturbed, and the killer starts its activity. During cytokine absence trophoblast's development disturbs. Another reason for fetus death can be an autoimmune reaction (antibodies to phospholipids).

**The main principles of immunostimulation and immunosuppression**

There are the following methods of increase of immune system activity (immunostimulation):

1) the injection into the organism of adjuvant or biological modifiers of response. Adjuvants – are the substances, which reinforce antigen immunogenicity independently of its specificity;

2) the usage of pharmacological immunostimulants (levamisole, derivatives from vitamin C, cimetidine);

3) the usage of factors of the thymus gland – thymopoietin, tymalin, humoral thymic hormone, thymopeptin, thymosin;

4) the injection of lymphokines and other cytokines (IL-2, interferons, IL-1);

5) substitutional transplantation of red bone marrow, the injection of immunoglobulins.

| The full student's name | The date | The marks | Teacher's signature |
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## PRACTICAL LESSON № 5
## Topic: ALLERGY

**Relevance of the topic.** Humanity is going through a time of rapid increase in the frequency of allergic reactions. Among the reasons for the increase may be noted the use of different vaccines and drugs, particularly antibiotics, and 30 % of all allergic reactions are allergic reactions to penicillin. The next factor that causes the growth of allergic diseases is the development of the chemical industry, plastics, paints, solvents, and other chemicals. Along with the increased incidence of allergic diseases caused by various allergens from the environment, currently, the attention of physicians is turned to allergic diseases caused by endogenous allergens. Modern understanding of the mechanisms of various allergic reactions has developed mostly on the basis of the experimental study of anaphylaxis and allergy. Therefore, experimental data on the pathogenesis of allergic diseases are the foundation of the modern theory of allergies.

**Overall Objective** – is to study the causes and mechanisms of allergic reactions in humans and animals. To be able to simulate the anaphylactic shock in an experiment to explain the mechanisms of the main clinical manifestations of anaphylaxis.

**To do this we should be able to (specific objectives):**

1. Define the concept of allergy
2. To characterize the basic properties of allergens and allergic antibodies.
3. Explain the types and mechanisms of sensitization.
4. Give a general description of immediate and delayed-type of allergic reactions.
5. Explain the basic conditions to reproduce an anaphylactic shock in the experiment.
6. To characterize the stages of anaphylactic shock.
7. Explain principles of desensitization and its types.

**The necessary basic knowledge and skills to achieve the goals of studying.**

**To be able to:**

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

### THE QUESTIONS TO THE LESSON

1 The concept of allergy.
2. Exo-and endoallergens. Sensitization.
3. Classification of allergic reactions, its principles.
4. Immediate type allergic reactions and their mechanisms.
5. Anaphylaxis. The role of IgE and mastocytes.
6. Immune reactions. Arthus phenomenon.
7. Delayed type of allergic reactions, their mechanism. Role of T-lymphocytes.
8. Stage of immediately and delayed-type allergic reactions.
9. Autoallergy.
10. Desensitization.
11. Allergoid reaction.

### EXPERIMENTAL PART OF LESSON

Experiment 1: studying of degranulation of mast cells of the peritoneal cavity of sensibilities rats during their contact with a specific allergen.

Object: white rats

Apparatus and reactive: injectors, Paster's pipettes, tubes, bunnels, objective and cover glasses, 0,3 % spirit solution of a neutral rod, ether, cotton, vaseline, glass sticks, horse serum, microscopes, immersion oil.

The conduction of experiment: under light ether's narcosis get peritoneal wash off sensibilize rat. Into drops of taken of cell's weight put on different pollis of object-glass, painted by neutral red, to one of them add one drop of normal allergen, to another – physiological solution. Both drops are covered with covered glasses of grease with vaseline. Placed at temperature 37 °C for 15 min. Take into consideration the reaction under the microscope with an immersion system. Count not less than 20 mast cells (round or over) with large granules painted into a brick-red color. Draw mast cells unchanged and degranulated.

**normal mast cells**

**degranulation of mast cells**

THEORETICAL MATERIAL FOR PREPARATION TO LESSON

## ALLERGY

**History.** The concept of "allergy" was originally introduced in 1906 by the Viennese pediatrician Clemens von Pirquet, after he noted that some of his patients were hypersensitive to normally innocuous entities such as dust, pollen, or certain foods. Pirquet called this phenomenon "allergy" from the Ancient Greek words ἄλλος *allos* meaning "other" and ἔργον *ergon* meaning "work". All forms of hypersensitivity used to be classified as allergies, and all were thought to be caused by an improper activation of the immune system. Later, it became clear that several different disease mechanisms were implicated, with the common link to a disordered activation of the immune system. In 1963, a new classification scheme was designed by Philip Gell and Robin Coombs that described four types of hypersensitivity reactions, known as Type I to Type IV hypersensitivity. With this new classification, the word "allergy" was restricted to type I hypersensitivities (also called immediate hypersensitivity), which are characterized as rapidly developing reactions.

A major breakthrough in understanding the mechanisms of allergy was the discovery of the antibody class labeled immunoglobulin E (IgE) – Kimishige Ishizaka and co-workers were the first to isolate and describe IgE in the 1960s.

Many allergens such as dust or pollen are airborne particles. In these cases, symptoms arise in areas in contact with air, such as eyes, nose, and lungs. For instance, allergic rhinitis, also known as hay fever, causes irritation of the nose, sneezing, itching, and redness of the eyes. Inhaled allergens can also lead to asthmatic symptoms, caused by narrowing of the airways (bronchoconstriction) and increased production of mucus in the lungs, shortness of breath (dyspnea), coughing and wheezing.

Aside from these ambient allergens, allergic reactions can result from foods, insect stings, and reactions to medications like aspirin and antibiotics such as penicillin. Symptoms of food allergy include abdominal pain, bloating, vomiting, diarrhea, itchy skin, and swelling of the skin during hives. Food allergies rarely cause respiratory (asthmatic) reactions, or rhinitis. Insect stings, antibiotics, and certain medicines produce a systemic allergic response that is also called anaphylaxis; multiple organ systems can be affected, including the digestive system, the respiratory system, and the circulatory system. Depending on the rate of severity, it can cause cutaneous reactions, bronchoconstriction, edema, hypotension, coma, and even death.

**Cause** Risk factors for allergy can be placed in two general categories, namely host and environmental factors. Host factors include heredity, gender, race, and age, with heredity being by far the most significant. However, there have been recent increases in the incidence of allergic disorders that cannot be explained by genetic factors alone. Four major environmental candidates are alterations in exposure to infectious diseases during early childhood, environmental pollution, allergen levels, and dietary changes. The cause of allergy can be any antigen. This, and also the fact that on average about 10% of earth population have allergy, and the manifestations of allergy at one and the same antigen can be different, testifies that heightened pathological immunological organism's reactivity, that is allergic reactivity, has the leading part at allergy emergence.

The important condition of the development of allergic reaction is antigen's properties. They are defined by their molecular mass, chemical heterogeneity, genetic foreignness, dose and the ways of penetration into the organism. Antigen, evoking allergy is called allergen. It can be initial antigen – with multiple antigen determinants, also – the mixture of antigens (herb pollen, particles of epidermis), often – macromolecular, and also hapten, which becomes antigen only after the connection with proteins of organism tissues (medicine metabolites, simple chemical substances).

Haptens evoke allergy in two ways: 1) connecting with organism's macromolecules, induce antibodies production, the specificity of which is directed against hapten, and not against it carrier; 2) forming antigen complexes with organism's molecules, formed at this antibodies react only with complex, but not with its components. According to their nature, antigens are more often proteins, protein-polysaccharide or protein-lipid complexes (serum, tissue, bacterial allergens), complex compounds of non-protein nature (polysaccharides, polysaccharide-lipid complexes – the allergen of

home dust, bacterial allergens), simple chemical substances, including separate elements (bromine, iodine, chromium and nickel).

**Allergen classification.** Allergens are divided into exogenous and endogenous (autogenous).

Exogenous allergens, in turn, are divided into:

I.Infectious: bacterial, viral, fungous (antigens of tuberculosis, toxoplasmosis, brucellosis, measles virus, influenza, herpes, infectious hepatitis, candid, trichophytosis, epidermophytosis, actinomycete and other diseases stimulant).

II. Noninfectious:

1.Vegetable (antigens of pollen, plants juice).

2. Medicinal (antigens of vaccines, serums, antibiotics, sulfanilamides, vitamins, insulin, arsenic preparations, iodine, mercury and other).

3. Alimentary (antigens of products of animal and vegetable origin – cow's milk, eggs, meat, fish, citrus plants, strawberry, chocolate and other).

4. Domestic (antigens of home, library dust, wool and dandruff of domestic animals, down of poultry, poisons of humenopterans, bed mites, fish food, detergents and other).

5. Simple chemical substances (ursol, benzene, formalin and other).

Endoallergens are the reasons of autoallergy (autoimmune diseases). They are divided into natural (primary) and acquired (secondary). To first we refer antigens of marrow tissues, lens, testicles, thyroid glands, the immunological tolerance to which is absent. Acquired endoallergens can be noninfectious and infectious. To noninfectious we refer cold, burn and radial allergens (they form in the organism by denaturalization of protein and other macromolecules and the liberation of new determinant groups), to infectious – simple and complex (tissue-microbe, tissue-toxin) endoallergens, which form under infection's influence.

**Genetic basis** Allergic diseases are strongly familial: identical twins are likely to have the same allergic diseases about 70 % of the time; the same allergy occurs about 40 % of the time in non-identical twins. Allergic parents are more likely to have allergic children, and those children's allergies are likely to be more severe than those in children of non-allergic parents. Some allergies, however, are not consistent along genealogies; parents who are allergic to peanuts may have children who are allergic to ragweed. It seems that the likelihood of developing allergies is inherited and related to an irregularity in the immune system, but the specific allergen is not.

The risk of allergic sensitization and the development of allergies varies with age, with young children most at risk. Several studies have shown that IgE levels are highest in childhood and fall rapidly between the ages of 10 and 30 years. The peak prevalence of hay fever is highest in children and young adults and the incidence of asthma is highest in children under 10. Overall, boys have a higher risk of developing allergies than girls, although for some diseases, namely asthma in young adults, females are more likely to be affected. Sex differences tend to decrease in adulthood. Ethnicity may play a role in some allergies; however, racial factors have been difficult to separate from environmental influences and changes due to migration. It has been suggested that different genetic loci are responsible for asthma, to be specific, in people of European, Hispanic, Asian, and African origins.

**Other environmental factors**

International differences have been associated with the number of individuals within a population have allergy. Allergic diseases are more common in industrialized countries than in countries that are more traditional or agricultural, and there is a higher rate of allergic disease in urban populations versus rural populations, although these differences are becoming less defined.

Exposure to allergens, especially in early life, is an important risk factor for allergy. Alterations in exposure to microorganisms is another plausible explanation, at present, for the increase in atopic allergy. Endotoxin exposure reduces release of inflammatory cytokines such as TNF-α, IFNγ, IL-10, and IL-12 from white blood cells (leukocytes) that circulate in the blood. Certain microbe-sensing proteins, known as Toll-like receptors, found on the surface of cells in the body are also thought to be involved in these processes.

Gutworms and similar parasites are present in untreated drinking water in developing countries, and were present in the water of developed countries until the routine chlorination and purification of drinking water supplies. Recent research has shown that some common parasites, such as intestinal worms (e.g., hookworms), secrete chemicals into the gut wall (and, hence, the bloodstream) that suppress the immune system and prevent the body from attacking the parasite. This gives rise to a new slant on the hygiene hypothesis theory – that coevolution of man and parasites has led to an immune system

that functions correctly only in the presence of the parasites. Without them, the immune system becomes unbalanced and oversensitive. In particular, research suggests that allergies may coincide with the delayed establishment of gut flora in infants. However, the research to support this theory is conflicting, with some studies performed in China and Ethiopia showing an increase in allergy in people infected with intestinal worms. Clinical trials have been initiated to test the effectiveness of certain worms in treating some allergies. It may be that the term 'parasite' could turn out to be inappropriate, and in fact a hitherto unsuspected symbiosis is at work.

**Pathogenesis**

Irrespective of type of allergic reaction it is possible to allocate three stages of its development:

1. **Stage of Immune Reactions** (or the Immunologic Stage). It includes the primary contact of the organism with antigen (the sensitising contact), the period of sensitisation (production and accumulation of the specific antibodies or specific sensitised T-lymphocytes), the interaction of antigen with antibody or antigen with T-lymphocytes (the permitting contact). In this stage two key moment of allergy are predertermined – type and form of the future allergic reaction. The type of reaction - immediate or delayed – is predetermined by the nature of response, i.e. by production of antibodies or T-lymphocytes. The form of the response is predetermined by the class of produced antibodies or subpopulation of sensitised T-lymphocytes. The above mentioned, in its turn, is predetermined by properties of allergen (its nature, properties, quantity), by way of its administration into the organism, and especially by reactivity of the organism.

2. **Stage of Biochemical Reactions** (or the Biochemic or Pathochemic one). In response to interaction of the antigen with the antibody or the antigen with the sensitised T-lymphocytes activation of the target cells and of the biochemic factors of liquid environments (plasma, tissue fluid) is occurred with release or production of the correspond biologically active substances (mediators of allergy). The primary mediators of allergy involve the other cell effectors and the other humoral factors with formations of the secondary mediators. The mechanisms of release and formation of mediators of allergy are standard, they are involved in any physiologic and pathologic processes (vasoactive amines, kinins, components of complement, products of leukocytes, etc.). The difference is that the starting (trigger) mechanism of activation of mediatoric cascade is immunologic one and that the list and amounts of mediators depend on the process. With reference to allergy it depends on the type of immunologic mechanism underflying the allergy, i.e. on the target cells and factors and the primary mediators of allergy.

3. **Stage of Functional and Structural Changes** (or the Pathophysiologic Stage). It consists in clinical manifestations of allergy. [Sensitisation does not cause a disease yet, only the repeated contact of the sensitised organism with the specific antigen can result in undesired effect]. The clinical manifestations of allergy are result of pharmacologic effects of mediators of allergy and, hence, they depend on the list and amounts of released and formed mediators.

**Diagnosis**

Effective management of allergic diseases relies on the ability to make an accurate diagnosis. Allergy testing can help confirm or rule out allergies. Correct diagnosis, counseling and avoidance advice based on valid allergy test results will help reduce the incidence of symptoms, medications and improve quality of life. For assessing the presence of allergen-specific IgE antibodies, two different methods can be used: a skin prick test or an allergy blood test. Both methods are recommended and have similar diagnostic value. Skin prick tests and blood tests are equally cost-effective and health economic evidence show that both the IgE antibody test and the skin prick test were cost effective compared with no test. Also, earlier and more accurate diagnoses save cost due to reduced consultations, referrals to secondary care, misdiagnosis and emergency admissions.

Allergy undergoes dynamic changes over time. Regular allergy testing of relevant allergens provides information on if and how patient management can be changed, in order to improve health and quality of life. Annual testing is often the practice for determining whether allergy to milk, egg, soy, and wheat have been outgrown and the testing interval is extended to 2 to 3 years for allergy to peanut, tree nuts, fish, and crustacean shellfish. Results of follow-up testing can guide decision-making regarding whether and when it is safe to introduce or re-introduce allergenic food into the diet.

Skin testing is also known as "puncture testing" and "prick testing" due to the series of tiny punctures or pricks made into the patient's skin. Small amounts of suspected allergens and/or their extracts (pollen, grass, mite proteins, peanut extract, etc.) are introduced to sites on the skin marked with pen or dye (the ink/dye should be carefully selected, lest it cause an allergic response itself). If the

patient is allergic to the substance, then a visible in-flammatory reaction will usually occur within 30 minutes. This response will range from slight red-dening of the skin to a full-blown hive (called "wheal and flare") in more sensitive patients similar to a mosquito bite.

**Blood testing.** Allergy blood tests measure the concentration of specific IgE antibodies in the blood. Quantitative IgE test results increase the possibility of ranking how different substances may affect symptoms. A general rule of thumb is that the higher the IgE antibody value, the greater the likelihood of symptoms. Allergens found at low levels that today do not result in symptoms can nevertheless help predict future symptom development. The quantitative allergy blood result can help determine what a patient is allergic to, help predict and follow the disease development, estimate the risk of a severe reaction and explain cross-reactivity.

## HYPERSENSITIVITY REACTIONS

Hypersensitivity refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. Hypersensitivity reactions can be divided into five types: type I, type II, type III, type IV and type V, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

### TYPE I HYPERSENSITIVITY

Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis). The reaction may cause a range of symptoms from minor inconvenience to death. The reaction usually takes 15–30 minutes from the time of exposure to the antigen, although sometimes it may have a delayed onset (10–12 hours). Immediate hypersensitivity is mediated by IgE. The primary cellular component in this hypersensitivity is the mast cell or basophil. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils. A biopsy of the reaction site demonstrates mainly mast cells and eosinophils. The mechanism of reaction involves preferential production of IgE, in response to certain antigens (often called allergens). The precise mechanism as to why some individuals are more prone to type-I hypersensitivity is not clear. However, it has been shown that such individuals preferentially produce more of TH2 cells that secrete IL-4, IL-5 and IL-13 which in turn favor IgE class switch. IgE has very high affinity for its receptor (Fcε; CD23) on mast cells and basophils.

A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances (*figure 3*). Cross-linking of IgE Fc-receptor is important in mast cell triggering. Mast cell degranulation is preceded by increased Ca++ influx, which is a crucial process; ionophores which increase cytoplasmic $Ca^{++}$ also promote degranulation, whereas, agents which deplete cytoplasmic $Ca^{++}$ suppress degranulation.

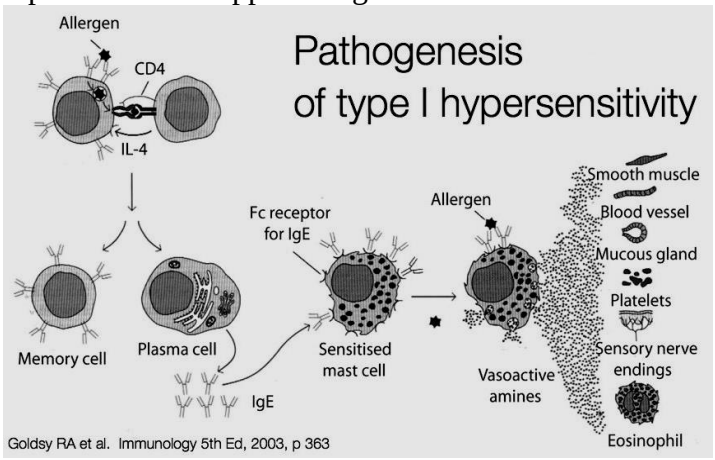
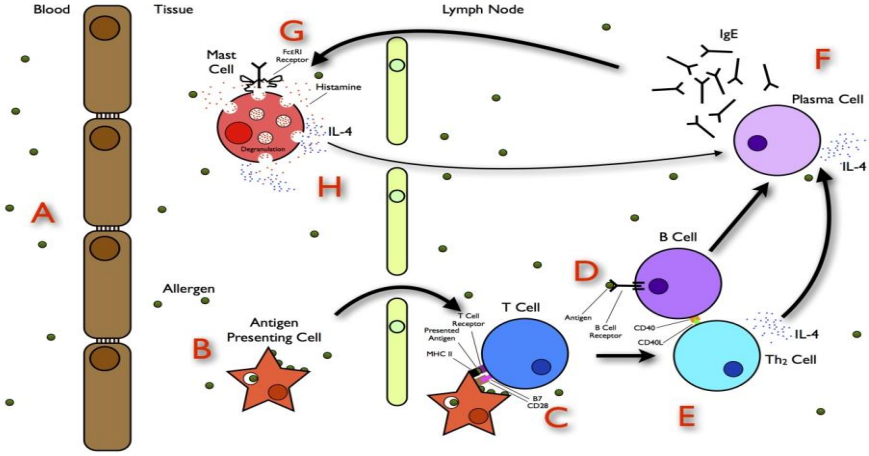



**Figure 3.** Pathogenesis of type I hypersensitivity

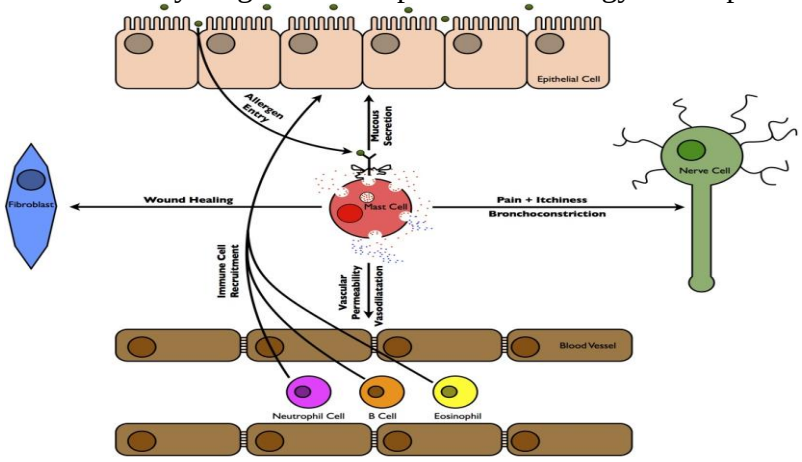
Mast cells may be triggered by other stimuli such as exercise, emotional stress, chemicals (*e.g.*, photographic developing medium, calcium ionophores, codeine, *etc.*), anaphylotoxins (*e.g.*, C4a, C3a, C5a, *etc.*). These reactions, mediated by agents without IgE-allergen interaction, are not hypersensitivity reactions, although they produce the same symptoms. The reaction is amplified by PAF (platelet activation factor) which causes platelet aggregation and release of histamine, heparin and vasoactive amines. Eosinophil chemotactic factor of anaphylaxis (ECF-A) and neutrophil chemotactic factors

attract eosinophils and neutrophils, respectively, which release various hydrolytic enzymes that cause necrosis. Eosinophils may also control the local reaction by releasing arylsulphatase, histaminase, phospholipase-D and prostaglandin-E, although this role of eosinophils is now in question. Cyclic nucleotides appear to play a significant role in the modulation of immediate hypersensitivity reaction, although their exact function is ill understood. Substances which alter cAMP and cGMP levels significantly alter the allergic symptoms. Thus, substances that increase intracellular cAMP seem to relieve allergic symptoms, particularly broncho-pulmonary ones, and are used therapeutically. Conversely, agents which decrease cAMP or stimulate cGMP aggravate these allergic conditions.

**Allergic contact dermatitis** Although allergic contact dermatitis is termed an "allergic" reaction (which usually refers to type I hypersensitivity), its pathophysiology actually involves a reaction that more correctly corresponds to a type IV hypersensitivity reaction. In type IV hypersensitivity, there is activation of certain types of T cells (CD8+) that destroy target cells on contact, as well as activated macrophages that produce hydrolytic enzymes (*figure 4*).




A summary diagram that explains how allergy develops.




Tissues affected in allergic inflammation

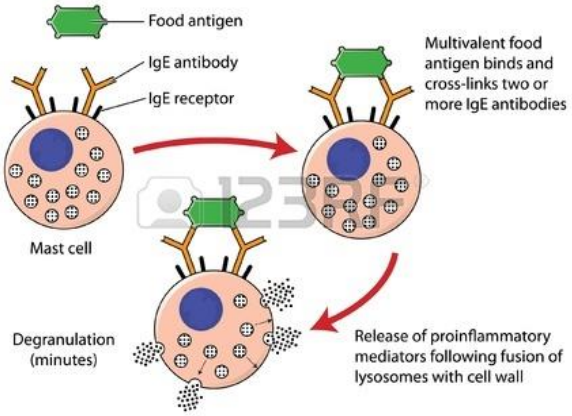



**Figure 4.** Degranulation process in allergy. Second exposure to allergen.

**TYPE II HYPERSENSITIVITY**

Type II hypersensitivity is also known as cytotoxic hypersensitivity and may affect a variety of organs and tissues. The antigens are normally endogenous, although exogenous chemicals (haptens) which can attach to cell membranes can also lead to type II hypersensitivity. Drug-induced hemolytic anemia, granulocytopenia and thrombocytopenia are such examples. The reaction time is minutes to hours. Type II hypersensitivity is primarily mediated by antibodies of the IgM or IgG classes and complement (*Figure 5*).

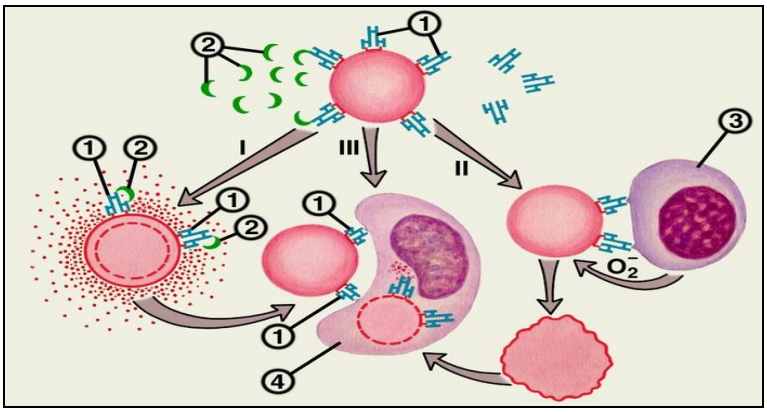



Figure 5. Pathogenesis of type II hypersensitivity. As a result of complement activation causes damage to the target cell membrane, resulting in lysis. II – antibody-dependent cellular cytotoxicity caused by addition of K-cells (3) forming the superoxide anion radical (O2-), damaging the target cell (arrow). III – phagocytosis antibodies opsonized target cells occurs through the interaction of antibodies, fixed on a cage (1), with phagocyte Fc receptor, the target cell uptake phagocyte (4) and digesting it. Additionally, phagocytes absorb target cells damaged by complement-mediated (I) antibody-dependent cellular cytotoxicity (II).

**TYPE III HYPERSENSITIVITY**

Type III hypersensitivity is also known as immune complex hypersensitivity. The reaction may be general or may involve individual organs including skin, kidneys, lungs, blood vessels, joints or other organs. This reaction may be the pathogenic mechanism of diseases caused by many microorganisms. The reaction may take 3–10 hours after exposure to the antigen. It is mediated by soluble immune complexes. They are mostly of the IgG class, although IgM may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous. The antigen is soluble and not attached to the organ involved. Primary components are soluble immune complexes and complement (C3a, 4a and 5a). The damage is caused by platelets and neutrophils (*Figure 6*).

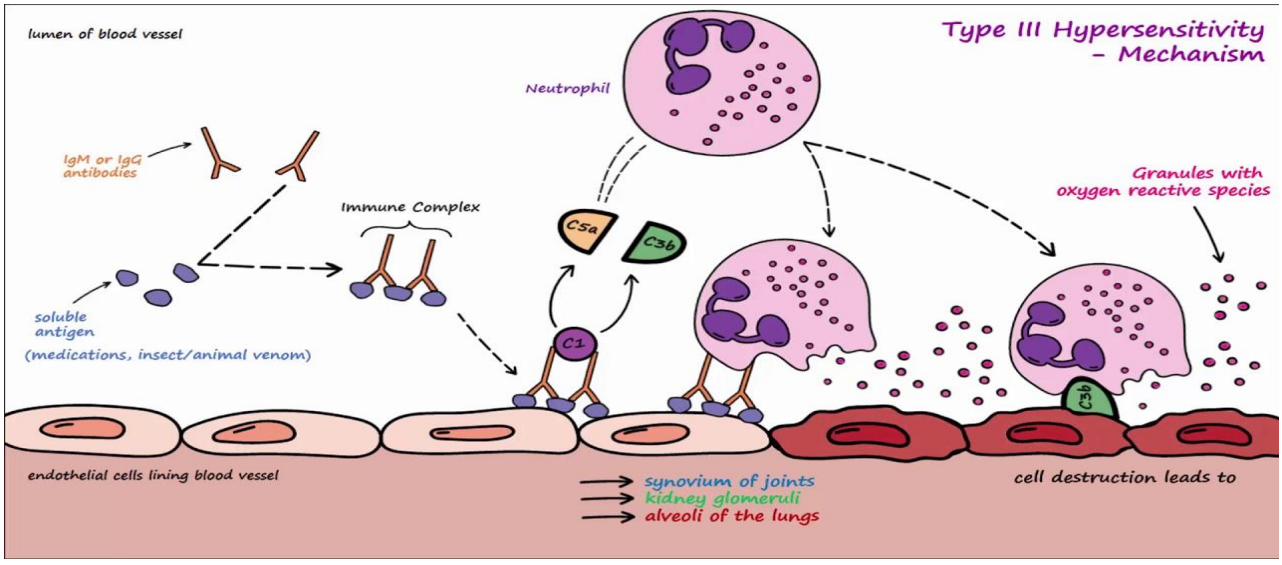



**Figure 6.** Pathogenesis of type III hypersensitivity.

The lesion contains primarily neutrophils and deposits of immune complexes and complement. Macrophages infiltrating in later stages may be involved in the healing process.

The affinity of antibody and size of immune complexes are important in production of disease and determining the tissue involved. Diagnosis involves examination of tissue biopsies for deposits of immunoglobulin and complement by immunofluorescence microscopy. The immunofluorescent staining in type III hypersensitivity is granular. The presence of immune complexes in serum and depletion in the level of complement are also diagnostic. Polyethylene glycol-mediated turbidity (nephelometry) binding of C1q and Raji cell test are utilized to detect immune complexes. Treatment includes anti-inflammatory agents.

**TYPE IV HYPERSENSITIVITY** Type IV hypersensitivity is also known as cell mediated or delayed type hypersensitivity. The classical example of this hypersensitivity is tuberculin (Montoux) reaction (*figure 7*) which peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema.

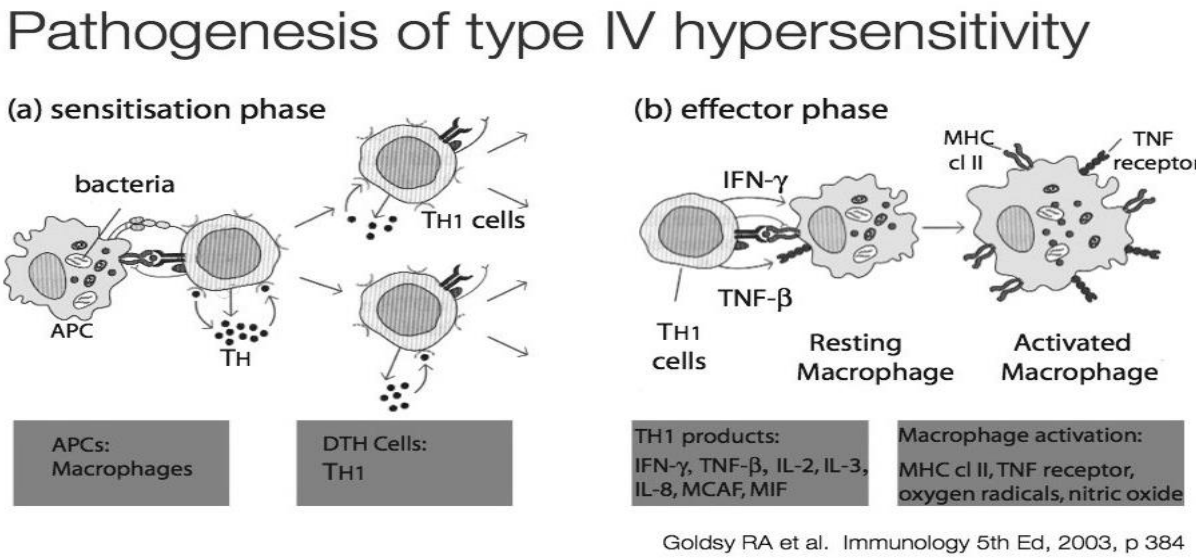



**Figure 7.** Pathogenesis of type IV hypersensitivity

Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, *etc.*) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is contact dermatitis (poison ivy, chemicals, heavy metals, *etc.*) in which the lesions are more papular. Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation.

**TYPE V HYPERSENSITIVITY**

**Stimulating allergic reactions.** In the result of antibodies action on cells, bearing antigen, the stimulation of their functions occurs, the mechanism of this function is connected with specific interaction of produced antibodies with cell receptors, intended for the activation of hormones or mediators liberation. To this type of reactions we refer, for example autoimmune mechanism of Basedow's disease, which leads to the hyperfunction of thyroid gland. Having many allergic diseases we can simultaneously find pathogenic mechanisms of different types of allergy. For example, having atopic bronchial asthma and anaphylactic shock the mechanism of I and III types take part, having autoimmune diseases – the reactions of II and IV types etc. To establish the leading mechanism is very important for pathogenetically grounded therapy.

**Prevention** The consumption of various foods during pregnancy has been linked to eczema; these include celery, citrus fruit, raw pepper, margarine, and vegetable oil. A high intake of antioxidants, zinc, and selenium during pregnancy may help prevent allergies. This is linked to a reduced risk for childhood-onset asthma, wheezing, and eczema. Further research needs to be conducted. Probiotic supplements taken during pregnancy or infancy may help to prevent atopic dermatitis. After birth, an early introduction of solid food and high diversity before week 17 could increase a child's risk for allergies. Studies suggest that introduction of solid food and avoidance of highly allergenic food such as peanuts during the first year does not help in allergy prevention.

| The full student's name | The date | The marks | Teacher's signature |
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## PRACTICAL LESSON № 6

**Topic: The final control of students' knowledge on topics «GENERAL NOSOLOGY – GENERAL STUDIES ABOUT ILLNESS, ETIOLOGY AND PATHOGENESIS. PATHOGENIC ACTION FACTORS OF ENVIRONMENT. A ROLE OF INTERNAL FACTORS IN PATHOLOGY»**

**On the Moodle platform, in the section corresponding to the lesson number, control questions and tasks of the KROK-1 database are presented.**
**https://distance.knmu.edu.ua/mod/folder/view.php?id=92477**

## PRACTICAL LESSON № 7 (7–8-stomat.)

**Topic: STANDARD VIOLATIONS OF PERIPHERAL BLOOD CIRCULATION AND MICROCIRCULATION**

**Relevance of the topic**. For existing of a live organism it is needed the systems of circulation of liquids in the body of the human and an animal transfer the nutrients and exchange products are taken out. Circulation – is an indispensable condition of metabolism and, therefore, life. Violations of peripheral blood circulation and microcirculation are among the most widespread states conducting to a large number of negative consequences in the work of all without an exception of bodies and systems of an organism. For example, arterial hyperemia leads to a rupture of vessels and hemorrhages. At venous stagnation, oxygen starvation and accumulation of carbonic acid appear leading to violations of food and body functions. Ischemia is especially dangerous in the central nervous system because the last one is most sensitive to hypoxia. Among embolisms, thromboembolism is the most common. The embolism of coronary arteries and brain vessels that can be accompanied by a heart attack is especially dangerous.

**General aim** – to study changes in local blood circulation, characteristics for arterial and venous hyperemia, ischemia, and embolism, their types, the reasons, and development and manifestation mechanisms.

**For this it is necessary to be able to (specific objectives):**

1 To characterize arterial hyperemia: definition, classification, main signs, etiology, and pathogenesis.

2. To characterize venous hyperemia: definitions, reasons, development mechanisms, main signs, consequences.

3. To define mechanisms of development of ischemia, and the principles of pathogenetic therapy.

4. To characterize an embolism: definition, types of emboli, embolism mechanisms.

**Required to achieve the learning basic knowledge – skills.**

**To be able to:**

1. To adumbrate peripheral blood circulation, its main departments and their.

2. To characterize nervous and humoral regulation of the microcirculation stream.

3. To explain mechanisms of maintenance of a tone, mechanical integrity, and permeability of microvessels.

4. To explain mechanisms of transport of substances through a vascular wall.

### THE QUESTIONS FOR THE LESSON

1. Concept of peripheral blood circulation and microcirculation.

2. Arterial hyperemia, its reasons, types, and pathogenesis. Manifestations, their mechanisms. Consequences.

3. Venous hyperemia, its reasons, pathogenesis. Manifestations, their mechanisms. Consequences.

4. Ischemia. Reasons, types, pathogenesis. Manifestations, their mechanisms. Consequences.

5. Stasis. Its types, pathogenesis.

6. Thrombosis. Reasons. Process of a thrombus formation, its mechanisms. Types of blood clots. Thrombosis consequences.Embolism. Reasons, types. Experimental models. Consequences.

### EXPERIMENTAL PART OF LESSON

**Experiment 1:** studying of arterial hyperemia.

**The object of experiment:** rabbit.

**The conduction of the experiment:** look at the ear vessels of the rabbit through the light. Expose the ear to mechanical irritation (make hand massage) and observe the changes in the ear's color, the number of visible vessels, their diameter, and ear temperature.

Describe the character of changes observed and explain their mechanisms.

**Result:** _____

_____

**Experiment 2:** investigation microcirculatory phenomena in arterial hyperemia.

**The object of the experiment:** frogs.

**Apparatus:** cork plate, pins, pincers, microscope, 0,1% hydrochloric acid solution.

**The conduction of the experiment:** decerebrate frog and fix it on cork plate back up, in such a way that the front side of the low jaw was at the site of the plate's foramen. Fix the low jaw with 2 pins at the site of the mouth corner. Strain the tongue over plat's foramen. Pins fixing the tongue prick slopingly at the angle to the center, so as not to disturb the microscope.

On small magnification examine the blood circulation in the tongue vessels. Then put the drop of 0,1 % hydrochloric acid solution on the surface of the tongue. Observe the changes in blood circulation, the size of the diameter of vessels, and quantitive functioning vessels.

Draw the observed phenomena and explain their mechanisms.

normal

after action of hydrochloric acid

**Result**:

_____

_____

**Experiment 3:** studying of venous hyperemia.

**The object of experiment:** rabbit.

**Apparatus:** the cork with kennel, rubber band.

**The conduction of the experiment:** observe the vessels of the rabbit's ear. Put on the ear's auricle the cork with the kennel so that the central artery of the ear passes under the kennel. Put the rubber band on the outside part of the ear. After 15–20 min compare two ears of the rabbit (state of vessels, color, thickness, transparency, temperature).

Explain mechanisms of venous hyperemia.

**Result:**

_____

_____

**Experiment 4:** studying of ischemia

**The object of the experiment:** rabbits

**Apparatus:** anatomic pincers

**The conduction of the experiment:** Examining the rabbit's ear vessels with the help of pincers makes painful irritation. Observe the changes in the ear's color, blood circulation, and the number of visible vessels. Explain the mechanism and define the type of ischemia.

**Result:**

_____

_____

**Experiment 5:** Studying of embolia

**The object of the experiment:** frogs

**Apparatus and reactives:** the cork plate for fixation, pins, anatomic pincers, scissors, injectors, and oil emulsion.

**The conduction of the experiment:** decerebrate frog and fix it on the cork plate belly up. Take the tongue out and straighten it above foramen. Open the chest and heart. Put pericardial away. Observe the blood circulation of the tongue under the microscope. Slowly inject 0,1–1 ml of the fat emulsion into the heart's ventricle. Shake up emulsion in advance. Observe the emboli passage in lucid vessels and changing of blood circulation.

Describe the character and mechanisms of observed phenomena.

embolism

## THEORETICAL MATERIAL FOR PREPARATION TO LESSON

### TYPICAL DISORDERS OF PERIPHERAL BLOOD CIRCULATION AND `MICROCIRCULATION

Peripheral (local, organ) is the blood circulation within separate organs, this means in the vessels from small arteries to small veins.

Now we divide peripheral blood circulation into microcircular bloodstream, which also divides into the blood and lymphatic stream. Micro circular bloodstream consists of vessels, which diameter is less than 100 microns, e.g. arterioles, venulae, and arteriovenular anastomosis. There it's carried out the providing of nutrients and oxygen to tissues and cells, and removal of carbonic acid and metabolites, etc. Micro circular lymphatic stream is the first part of lymphatic system, the lymph and its entering to the lymph capillaries. The process of lymph creation is quite complicated. It consists in passing of blood and dissolved substances through the vessels' walls into intercellular space, spreading of substances in the perivascular connective tissue, resorption of capillary infiltration into the blood, resorption of proteins, and of liquid excess into lymphatic tracts.

Volume velocity of bloodstream Q through every organ or tissue equals the arteriovenular difference of pressure of that organ: PA – PB or ΔP, so the resistance R over the period of the peripheral vessel $Q = \Delta P / R$

The more arterio venular difference of pressure (ΔP), the more intense the peripheral blood circulation. But the more peripheral blood resistance R, the less is a difference in pressure. Changes in both ΔP and R lead to disorders of peripheral blood circulation. Correlation between linear volume velocity of blood circulation and total area of microvessel stream comes to formula, reproducing the law of continuity, which reproduce the mass conservation law:

$$Q = V \times S \text{ or } V = Q / S,$$

There Q – volume velocity of blood circulation; V – linear volume velocity; S – area of lateral section of micro circular stream.

Comparison of those quantities in different types of hyperemia and ischemia is the character symptom of a form of disorders of peripheral blood circulation.

Disorders of peripheral blood circulation and microcirculation involve arterial and venular hyperemia, ischemia, and stasis. The causes of local disorders of blood circulation often are thrombi and emboli.

#### Arterial hyperemia

Arterial hyperemia (hyper – over, haima – blood) – is the increase of blood filling of part of organ and tissue and the quantity of blood flowing through it because of increased flow to it of arterial blood by extended adducting arteries and arterioles.

We thought before, that only the smallest precapillary arteries are the regulators of peripheral blood circulation and microcirculation. Now it's proved that those regulators are all branches of or-gan arteries.

**Causes of arterial hyperemia:**

increased action of usual physiologic irritants;

– the action of pathologic irritants (high temperature, low pressure, chemical substances, etc.);

– growth of sensibility of vessels to physiologic irritants (in allergies);

– primary damages of the nervous system. Leading to paresis and paralysis;

<u>According to this arterial hyperemia can be:</u>

1) physiological, appearing as:

a) functional, accompanying increasing of organ function (hyperemia of the pancreas while digestion, etc.);

b) reactive (postischemic), appears in vessels of cavities (pleural, peritoneal), when the inflammatory or stagnant liquid in them is quickly removed;

2) pathological (inflammatory, thermal, etc.) – in decompression illness.

#### Mechanisms of arterial hyperemia

By pathogenesis, it's divided into two types – neurogenic and after the action of local humoral factors.

1. Neurogen arterial hyperemia can be:

a) neurotonic type (reflector, because of irritation of extero- and interoreceptors, and vasodilating nerves).

Arterial hyperemia, caused by cholinergic mechanism, appears in organs and tissues, which are innervated by parasympathetic nerves. In absence of those nerves, the development of hyperemia is caused by sympathetic (choline-, histamine- and β-adrenergic) system,

In the experiment (rabbits and dogs) this hyperemia was represented by K.Bernar. He irritated chorda tympani (branch of n. facialis, consists of parasympathic fibers).

b) neuroparalytic type (in paralysis of α-adrenergic fibers and nerves, providing vasodilating properties). It can appear after damaging vasodilating centers (trauma of spinal cord in neck or chest),

the action of some bacterial toxins on vasodilating vegetative centers (diphtheria, typhoid fever). In an experiment the hyperemia of head skin in rabbits can appear after legation of peripheral sympathetic nerve and removal of upper neck nod (K.Bernar, 1851), the frog's leg – after cutting of sympathetic fibers of the sciatic nerve. This hyperemia also can appear by chemical way, blocking the signals from sympathic nods or the sympathic nervous endings, which blocks the incoming of extracellular $Ca^{2+}$ into the cell and this makes impossible their contraction.

2. Arterial hyperemia can appear by conditioned-reflex mechanism. It is arterial hyperemia after the action of local factors. An important role in vasodilating acts is the increased partial pressure of oxygen and increasing – carbon dioxide, excess of some metabolites (lactate, organic acids, ATP, etc.), and bioactive substances, circulating in the blood or forming in the vessel's wall or surrounding tissue.

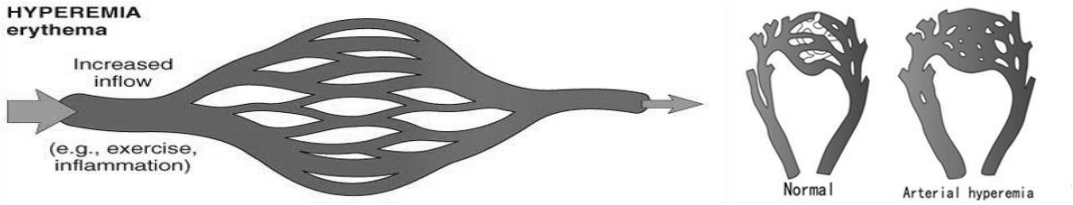
**Signs of arterial hyperemia**: reddening, widening of vessels, pulsation of small arteries, increase of the number of functioning vessels, local heightening of temperature, an increase in volume of the hyperemic area, an increase in blood circulation, and increase of organs function

**Microcirculation in arterial hyperemia**

Owning to increasing arterio-venular difference of pressures the speed of blood circulation in capillaries increases, intracapillary pressure heightens and so does the number of functional capillaries.

The volume of microcirculation in arterial hyperemia increases because of the increase in the number of function capillaries and veins. Capillaries open due to an increase in intracapillary pressure and changes of mechanical properties of connective tissue.

Due to increase in the number of function capillaries the area for transcapillary metabolism grows, and increases of the opening of vessels, this leads to increasing of volume velocity of circulation.




An increase of pressure in capillaries leads to a raise in liquid filtration in tissue slots so that the quantity of tissue fluid. While this, lymph outflow increases.

**Significance of arterial hyperemia**

The positive significance of arterial hyperemia is connected with the growth of oxygen and metabolites provided to the tissues. In pathology, arterial hyperemia can compensate for some disorders. If local blood circulation was weakened (ischemia), the appearance of hyperemia has compensatory properties. An example of arterial hyperemia of compensatory type is the local widening of arteries and increase of blood circulation in area of inflammation.

Otherwise, it can have a negative significance. Due to local increase of pressure in microvessels might be the hemorrhages, because of rupture of vessels wall or in diapedesis way. Those phenomena are dangerous to the central nervous system. Increased inflow of blood to the brain is accompanied by unpleasant feelings such as headache, dizziness, and noise in the head.

**Venous hyperemia**

Venous hyperemia is the increase of blood filling of part of an organ or tissue and decreases in the quantity of flowing blood due to complicated outflow to the venous system.

Causes:

1) compression of veins (ligation, compression by tumor, etc.)or narrowing of their opening by cicatrizing tissue;

2) thrombosis;

3) heightening of pressure in large veins due to heart illnesses;

4) disorders of the flexibility of lung tissue, accompanied by the change of intrathoracic pressure and decreasing of sticking action of chest;

5) long stay of ill persons in the bed;

An important role in the pathogenesis of venous hyperemia acts the difficulties in the passing of blood and disorders of nervous mechanisms of its regultion.

**Signs of venous hyperemia:**

1) reddening of the organ with a blue tinge – cyanosis (gr. cyanosis – dark-blue) due to stagnation of blood and increasing of reduced hemoglobin. Dark-blue color of reduced hemoglobin, looking through the skin becomes blue.

2) decreasing temperature of damaged area (due to decreasing of the intensity of bloodstream area gets less warm, this causes the disorders between the balance of temperature). In the organs, this doesn't happen, because the heat emission in them to the environment is absent.

3) increasing of blood pressure in venae from interception to the peripheral area, due to hardening of bloodstream to heart, and decreasing of volume velocity of blood circulation and accumulation of blood in the venues lower-lying post interception.

4) increasing volume, swelling of the hyperemic area due to increasing the blood inflow, and increased transudation of liquid to tissue.

5) delay of blood flow to the heart due to interception. In the final stage of hyperemia, there can appear the pendulous passing of blood and stasis.

Decreasing of volume velocity of the bloodstream is that the less quantity of oxygen and nutrients comes to the organ and tissues suffer from circulated hypoxia.

**Microcirculation in venous hyperemia**

Blood pressure in veins increases before interception to the bloodstream. This leads to decreasing arterio-venous equal pressure and to the slowdown of the bloodstream in low arteries, capillaries, and veins. If the outflow stops totally, the pressure before the interception reaches the diastole level in arteries. In those cases, the bloodstream in vessels stops during the diastole of the heart and begins while systole. This flowing of blood is called impulse. If the pressure in veins before interception exceed the diastole pressure in addictive arteries, the normal blood flow appears only during systole, but while diastole there appears the retrograde flow. This flow is called pendulous. Increased intravascular pressure stretches the vessels and causes their widening. All functioning veins become wider, and the afunctional veins open. Capillary also becomes wider, usually in vein areas. The blood supply of organs increases. Although the area of the opening of vessels increases, the linear velocity falls and the volume velocity is called decreased. So microcirculation in organs does down.

**Significance of venous hyperemia**

Effects of venous hyperemia can be the disorders of tissue trophy, hardening, atrophy of specific elements of tissue, and reactive growth of connective tissue as the result of hypoxia. General disorders of blood circulation are expressed due to the fast-closing of large veins. So while closing of portal vein the blood stays in the organs of the peritoneum. This leads to a decrease in arterial pressure, cardiac activity, and breathing. Especially dangerous is the ischemia of the brain. It can promote fainting then breathing paralysis and death. But in some cases the venous hyperemia is useful, speeding up the wound cure.

**Ischemia**

Ischemia (gr. Ischeim – keep, haima – blood) – decreasing of blood filling of part of an organ or tissue due to weakening or stop of inflow to it of arterial blood.

Causes:

1) compressive – compression of adducing artery or the part of tissue by growing tumor, ligation, increase of intracranial pressure.

2) obturation – narrowing or total closing of arterial opening (thrombus), its obliteration.

3) angiospastic – reflector spasm of vessels due to irritation of vasodilating apparatus. This appears while emotional action (anger, fear), the action of physical factors (cold, trauma), chemical, biological, etc. Angiospasm appears while irritation of vessel center. The appearance of reflector ischemia is possible while huge blood inflow to any other part of organ-ism.

There are some mechanisms for developing spasms of arteries:

a) extracellular – the cause of constriction of arteries is vasoconstriction substances (histamine, vasopressin, angiotensin II);

b) membrane – changes of processes of repolarisation of membranes of smooth tissue cells, increasing penetrability to Na2+, Ca2+, K+, Cl-;

c) intracellular – disorders of the intracellular flow of Ca2+ ions, their income to the cell from out of it, or changes into the mechanisms of constriction proteins – actin and myosin.

An important role in that ischemia development act is the increasing sensitivity of muscular elements of the wall to noradrenalin and vasoactive peptides, the cause is the accumulation of Na2+.

**Signs of ischemia**: pale part of the organ, decreasing temperature, increasing sensitivity as paresthesia, pain syndrome, etc., a decrease of arterial pressure, a decrease in forming of intracellular liquid, and dystrophic changes. The volume of organs in ischemia decreases too.

**Microcirculation in ischemia**

Increasing resistance in the adductive arteries causes decreasing in intravascular pressure and causes their narrowing. Pressure falls at first in small arterioles and arteries from the periphery to the area of constriction, this causes the decrease of linear and volume velocity of blood circulation into the capillaries. As the result of the narrowing of arteries in the area of ischemia there begin the reallocation of erythrocytes, which the capillaries get the blood poor with forming elements. This causes the change of most parts of function capillaries to plasma ones. The number of function capillaries in the ischemic area decreases. The disorder of microcirculation causes problems with the food supply of tissues.

As a result of decreasing pressure into the capillaries, the filtration of liquid from the vessels to the tissue decreases and there are the conditions for the strengthening of resorption from the tissue into capillaries. So that the quantity of tissue liquid in the tissue decreases and the lymph outflow from the ischemia area weakens till it stops at all.

**Compensation of disorders of inflow of blood in ischemia**

While ischemia frequently happens during the whole or partial recovery of blood supply, this depends on collateral blood inflow.

There are:

1. Organs with good arterial anastomosis (the sum of their opening is close to that one into the closed artery). In those cases, the thrombosis of arteries isn't accompanied by blood supply disorders.
2. Organs where arteries have few anastomoses. So the collateral inflow of blood is possible only in the capillary net. The result of ischemia is infarction.
3. Organs with insufficiency of collaterals. The opening of collateral arteries in them is insufficient, to provide the collateral blood inflow.

Physiologic factor promoting the collateral blood inflow is the active dilatation of arteries of the organ. As the deficit appears the physiologic mechanism begins working. This mechanism provides vasodilatation, all collateral ways of blood flow become wider and the speed of blood circulation increases.

For effective collateral blood circulation, the important role is the state of the vessels' walls: sclerosed and less flexible collateral vessels aren't able to become wide enough.

**Aftereffects of ischemia**

Described changes lead to limited oxygen and nutrient supply of tissue. Also, the metabolites accumulate.

Very dangerous is the ischemia for the CNS. It leads to the disorders of function of proper areas of the brain. So while the damage of motor center the quick developments become of paresis and paralyzes. Ischemia in limbs is accompanied by pains and dysfunction of muscles.

When the bloodstream in the ischemia area doesn't normalize, the infarction develops. In some cases there locates the white infarction. It usually occurs in those organs where the collaterals are poorly developed (heart, kidneys). In other organs (lungs) it's red infarction or hemorrhage infarction. It appears then the blood gets in by collateral ways but the quantity of it is not enough and slowly, so the tissue dies, the walls become destroyed and erythrocytes fill in all tissue, making it red. The factors that promote infarction are the disorders of the bloodstream, atherosclerosis, increasing viscosity, etc.

**Stasis**

Stasis (gr. Stasis – stop) – stop of bloodstream in the capillary, small arteries, and veins in the part of organ or tissue.

There is true or capillary stasis (the result of pathologic changes in capillary or disorders of rheological properties of blood), ischemic stasis (complete stop of inflow of blood into the capillary net), and venous (compression of veins).

**Causes and mechanisms of stasis**

The normal flow of blood is possible if

a) forming elements can deform;
b) they don't stick together;
c) concentration of forming elements is normal.

Factors that define the disorders in rheological properties of blood:

1. Disorder of deformation of erythrocytes. It slowly decreases with their age. That's why there are difficulties with their passage through the vessel wall. Membranes of erythrocytes become harder under a lot of pathogen factors. This happens while heart diseases, cancer, etc.
2. Disorder of structure of stream of blood in the vessels. So if the stream slows down longitudinal orientation of erythrocytes often changes to cross one. This leads to changes in the rheological properties of blood and an increase in resistance.

3. Strengthening of intravascular aggregation of erythrocytes. This happens under factors that change both surface properties of erythrocytes and their environment. While the strengthening of aggregation blood becomes from erythrocytes suspension with high fluidity to net-like suspension. This phenomenon is called "sludge". Features of it are the adhesion of erythrocytes, leukocytes, and thrombocytes and increasing viscosity, the character of their surface, etc.

There are some types of sludge:

1) classical (high size of aggregates, irregular contours, hard packing of erythrocytes);

2) dextrin-like (different sizes of aggregates, round-shaped, hard packing);

3) amorphous granule-like (a lot of aggregates as the granule, consisting of some erythrocytes).

There are some factors in the development of aggregation:

a) damage of the capillaries wall, causing the increase of filtration of liquid, electrolytes, and proteins. As the result the concentration of globulins and fibrinogen increases, this is the most important factor of aggregation.

b) Income of chemicals and their action on the erythrocytes, causing the changes in their physic and chemical properties.

c) The speed of the bloodstream in capillaries, is caused by the functional state of adductive arteries. Their constriction leads to slow down of bloodstream of capillaries (ischemia), promoting aggregation.

**Effects of stasis**

The bloodstream can be restored after removing the cause of stasis. But in some kinds of damage to the vessel walls and erythrocytes, the stasis of blood becomes irreversible, causing the necro-sis. The spasm or closing of adductive arteries promotes this so does the ischemia of that area of tissue.

**The role of endothelial factors in the pathogenesis of local disorders of blood stream**

Sympathetic cholinergic nerves widen the small arteries and arterioles of skeleton muscles, face, tunica mucosa of mouth and intestine. Its mediator is acetylcholine. In some cases, hyperemia is the result of the synthesis of prostaglandins – the derivative of polyunsaturated fatty acids. Prostaglandins E and A carry out the vasodilating activity. In the muscular wall of vessels, the prostaglandin $\mathbf{I_2}$ carries out huge angiotensin action to thrombocytes.

Widening of vessels causes decreasing pO2, increase of pCO2, excess of nonspecific metabolites, etc. In the development of reactive and working arterial hyperemia, the special role plays adenosine. The source of adenosine is smooth tissue and endothelial cells of vessels. Adenosinedezami-naze carries out destroy of adenosine, that's why the balance of adenosine intra- and extra cells stays still.

Under the local humoral factors, endothelial cells of vessels produce the substance called the factor of relaxation of endothelial origin. The shoved factor of relaxation acts on smooth tissue cells of the vessel walls and causes their hyperpolarisation. Carbon oxide is transported into the cells by the nitrozotioles. Activating the guanylate cyclize and ATP-rhiboziltransferaze, CO2 influences the intracellular amount of cAMP and Ca2+ ions. So carbon oxide is considered the secondary mediator like a universal regulator of cellular metabolism in many organs and tissues. In the arterial system, it acts as a smooth tissue relaxant and inhibitor of aggregation and adhesion of thrombocytes.

An important role in increasing of bloodstream in the local vascular reaction is after the pH tissue reaction – moving of reaction to the acidosis promotes widening of vessels due to enlargement of sensitivity to adenosine of smooth tissue cells. The main factor of local changes in venous hyperemia is hypoxia of tissue, which leads to the release of huge amounts of bioactive substances.

One of the main factors is changes in sensitivity of muscular elements of the vessel wall to nor-adrenalin and vasoactive peptides. Potassium ions, accumulating into the muscular fibers of the vessel, increase its sensitivity to pressor substances – catecholamines, vasopressin, and angiotensin. Damage to endothelium deprives it of the property to excrete factors of relaxation, so the spastic reactions increase. Type of exchange, functional and structural changes in the area of ischemia are defined by the level of hypoxia, the severity of which depends on speed and type of ischemia, its long, localization, type of collateral bloodstream, etc.

Particular importance is to bioactive substances and acidotic shift of pH to its colloid state. As the result, there is an increase in penetrability of the vessel wall, and vasodilatation, leading to an increase in viscosity, slowing of the bloodstream, and stasis.

**Changes in tissues cause by disorders of local bloodstream**

Prolonged widening of veins leads to expansion of its wall, which can be accompanied by hypertrophy of its muscular part and by phlebosclerosis. Prolonged venous stagnation is accompanied by heavy changes in functional elements of the wall, their atrophy, and death. E.g. cirrhosis of the liver

in heart insufficiency, caused by venous stagnation. AS it was shown the factor promoting the local changes in venous hyperemia is the hypoxia. Primary it depends on limited blood supply, then the action on tissue ferment systems of metabolites. Hypoxia in venous hyperemia promotes metabolism disorders and causes the atrophy changes and growth of connective tissue. In the area of ischemia, there are some stages of tissue disorders. Disorders of energetic exchange are the decrease of the effectiveness of the Krebs cycle and tissue breathing. Disorders of energy creation in that area are connected to oxygen insufficiency, which is needed to oxidize substrates. Disorders of energy-needing processes in cells cause a decrease in energy generation. In the end, there develops the damage of cells and necrotic changes that often ends with infarction. Increasing of biosynthesis of collagen, glycoproteins, and glycosaminoglycans is the basis of the next sclerosing of an area of ischemia of tissue or organ.

**Syndrome of reperfusion and ischemic toxicosis.** The destruction of cells arises as a consequence of the deprivation of cells of power supplies and oxygen. The variety of pathogenic factors seems boundless. Invaluable value has the fact that irrespective of the type of the damaging factor molecular-cellular changes are identical. It is important to distinguish between hypoxemic damage of the cell which mechanism is started by any influences causing hypoxemia, and is free-radical damage when it can be exposed to destruction without hypoxemia. At the restoration of perfusion, an ischemic site probably occurrence so-called reperfusion syndrome. It consists in an organism intoxication, because of the hit in the blood of products of metabolism, and as ammonia formed owing to the disintegration of amino acids which at ischemia are used as a power material. The absorption in the blood of the aforementioned substances and other products at ischemia leads to an ischemic toxicosis. The specified mechanisms can be combined. For example restoration of blood supply of an ischemic site of the myocardium is accompanied by the production of active oxygen radicals in damaged ischemia of mitochondrion. At acute poisoning with oxygen, the basic mechanism of damage is considered the action of active oxygen radicals on membranes. However, the final stage of damage of destruction of mitochondrion leads to the impossibility to utilize oxygen and to the development of accompanying deep tissue hypoxemia.

**Thrombosis**

Thrombosis – lifetime adjournment of a clot of the stabilized fibrin and forming elements of blood on an internal surface of blood vessels with narrowing of their opening and an obstacle to a blood groove. During thrombosis dense deposits of blood are formed and they adhere to sub-endothelial structures. In the arterial system, blood clots consist of thrombocytes with an impurity of erythrocytes and leukocytes, in the venous system - from erythrocytes, leukocytes, and a small number of thrombocytes that gives to a blood clot red color.

Besides independent genesis, thrombosis can appear at diseases of the cardiovascular, respiratory, digestive system, shock, and inflammation, trauma periods, at the action of poisons, toxins, etc.

In the last century it was possible to generate an accurate representation about major factors of thrombosis in the form of a triad of Virhov:

1) damage of a vascular wall under the influence of pathogenic factors;
2) disorder of activity of the system of fibrillation and a vascular wall;
3) blood-groove delay.

**Mechanisms of thrombosis in arteries**

***Key mechanisms of thrombosis in arteries:***

1) damage of vascular endothelium;
2) local angiospasm;
3) adhesion of thrombocytes to a subendothelium;
4) aggregation of thrombocytes;
5) activation of coagulation ability of blood.

Damage of endothelium can have traumatic or metabolic character.

In the first case, there is an exposure to thrombogenic component of basal membranes (collagen, elastin, and microfibril) to the subsequent adhesion to them thrombocytes. In the second case – endothelium isn't damaged, but loses abilities:

a) to synthesize antithrombus, anticoagulant, and fibrinolytic substances (the activator plasminogen, prostacyclin, etc.);
b) to inactivate procoagulative substances (V, VIII, IX, and X factors); metabolize BAS;
c) influencing the hemostasis system (prostaglandins etc.).

At traumatic damage of a vessel, the thrombosis begins with the adhesion of thrombocytes to endothelium. Includes three stages:

1) activation of thrombocytes' membranes;

2) fixing activated thrombocytes to galactose groups of a molecule of collagen;

3) reduction of thrombocytes with the occurrence of pseudopodia.

Activation of thrombocytes depends on chemical modification of thrombocytes membranes and induction of glycosyltransferase, acting with specific receptors on the collagen molecule providing the adhesion of thrombocytes on subendothelium. A lot of membrane ferments become active. For "joining" the factor of Villebrandt and plasma fibronectin is obligatory.

So, the adhesion of thrombocytes to subendothelium is the first stage of the formation of an arterial blood clot. The second stage is an aggregation of thrombocytes, and consists of two subsequent phases:

1. Degranulation and emission of thrombocytes contents of dense little bodies (adrenaline, noradrenaline, histamine, Ca2+);

2. Emission of contents of alpha granules (lysosomal enzymes).

It leads to the activation next intact thrombocytes, to their gluing to each other and to a surface adhesive cell, and, hence, to the formation of the large units. Simultaneously there is the spasm of a vessel caused by the local allocation of thromboxane A2. The final (third) stage of thrombogenesis is connected with the activation of contact factors of plasma hemostasis. They are adsorbed on a surface aggregated тромбоцитов and start «the internal cascade» fibrillation. All comes to the end with the loss of threads of the stabilized fibrin and blood clot consolidation. Along with it joins and «the external cascade» the fibrillation, connected with liberation forming of thromboplastin.

Besides, thrombocytes are capable to start «the internal cascade» (without contact with the XII factor) by interacting with the V factor being on their surface with the X factor, and it quickly catalyzes pro-thrombin transition in thrombin. Erythrocytes and leukocytes participate in the forming of thrombi. In leukocytes there synthesize the products of lipoxygenase way of metabolism of arachidonic acid. From other intracellular products, important role prays superoxide and hydroxide anions, ferments dissolving heparin. The cause of arterial thrombosis is erythrocytosis, leading to increasing viscosity and stasis of blood, etc.

**Mechanisms of thrombosis in veins**

Venous thrombosis appears as the result of activation of the plasma chain of hemostasis. Activation is promoted by the hemodynamic state near venous valves. There the adsorption of contact factors (XII factor of Hageman, high molecular kininogen, prekallikrein, and XI factor) to negative structures of subendothelium starts an inner cascade of blood coagulation. Activated XII factor dissolves located near prekallikrein, connected with kininogen, making it to kallikrein, and activates the XI factor. The last one activates the IX factor, cooperating with activated factor VIIa. This complex VIIIca-IXa dissolves and activates near molecules of factor X, connected with phospholipids through the rest of gamma-carboxyglutamate. After it factor, Xa is fixed on the surface of thrombocytes and connects the molecules of activated factor V (Va). Molecules of the V factor are ad-sorbed by thrombocytes of plasma or are released in active form from alpha-granules. On the surface of the thrombocytes complex, Xa-Va is near molecules of prothrombin (factor II). Under the factor, Xa prothrombin in that complex dissolves into two parts. The first contains the rest of gamma- carboxyglutamate and the second – gets to the bloodstream. In the end, thrombin removes two peptides from a molecule of fibrinogen and transforms it into the monomer form of fibrin, after it – into polymer form. There appears typical venous thrombus, stabilized with the net of polymerized fibrin. Thrombin and polymers of fibrin can be generated also by the outer way. It is initiated by in-coming phospholipoproteids of membranes of dead cells and tissues. The last ones connect by Ca2+ bridges molecules of gamma- carboxyglutamate rests of vitamin K-dependent preferment of factor VII and transforms it to active factor VIIa. At the final stage of blood coagulation under the action of thrombasthenin of thrombocytes there occurs the contraction of fibrin fibers. The clod becomes solid. The process of forming thrombi in veins is limited by the system of inhibitors of coagulation.

**Effects of thrombosis**

They can be considered from biological positions as an adaptive phenomenon. At the same time, the thrombosis causes blood circulation infringements (ischemia, ve-nous stagnation, hypostasis development). The blood clots formed in veins can cause a reflex angiospasm. If the blood clot corks an artery gleams, and collateral bloodstream doesn't develop, necrosis appears. The separation of a blood clot or its part leads to emboli. Aseptic or septic fusion, organization, and recanalization can be thrombosis outcomes. Clinical variants of arterial thrombosis are thrombotic and thrombocytopenic purple and demolition-uraemic syndrome, venous – DIC syndrome, and deficiency of antithrombin.

## Embolism

**Embolism** – closing of blood and lymphatic vessels by particles brought by flow. Those particles are called emboli.

**Embolism** can be exogen and endogen character. The most frequent are **endogenic embolism:**

a) thromboembolism – the most frequent. The source is new, soft thrombi, separated from the place, where they were formed.

b) tissue – pieces of tissue in trauma, atherosclerotic masses, etc.

c) fat – drops of fats in fractures of pipe bones or crushing of fatty tissue.

d) amniotic fluid – if they get into the damaged vessels of the uterus while childbirth.

**Exogenic factors:**

a) Air – by the vials of air getting from the surrounding atmosphere at wounds in large veins, which walls aren't fallen down (jugular, upper cava veins) in which the blood pressure can be below atmospheric. A sharp expansion of alveoli and rupture of a wall.

b) Gas – the vials of gas formed in blood at a fast fall of barometric pressure (Kasson illness), at a gas gangrene

c) Bacterial or parasitic – conglomerates of bacteria or parasites from any center of an infection; parasitic – at the drift of trichinellas from intestines in a lung through lymphatic vessels and a chest lymphatic channel.

d) Foreign matters – at the hit of these bodies in vessels during wounds.

**Embolism can appear in:**

1) in arteries of a small circle of blood circulation;
2) in arteries of a big circle of blood circulation;
3) in the portal system of the liver.

It is necessary to consider the possibility of movement of embolus not on a flow of blood, and against it – retrograde embolism. It is caused by weight emboli. There is a paradoxical embolism – when they from the veins of the big circle, get into the right heart, get, and pass a small circle, directly in the left auricle and a ventricle, and further to the big circle.

Hemodynamic infringements depend on reflex influences from a hit place of embolus, and from conditions of distribution of vascular branches, quality of embolus, and forces of a blood groove. The direction of emboli is often defined by the activity of the nervous system. In this respect, the big role belongs to receptors of vessels. Irritation of angioreceptors can influence the speed of a blood-groove and blood circulation process as a whole and by that on carrying over of embolus. The most important functional shift at embolism of vessels of a small circle of blood circulation is the acute decrease in arterial pressure in the big circle. Certain value in decrease of arterial pressure at embolism of to a pulmonary artery is given to easing of function of heart owing to a myocardium hypoxemia that grows out of increase in loading at the right half of heart and sharp decrease in arterial pressure. In irritation of receptors of pulmonary vessels can result pressure increase in arterioles lungs, mechanical irritation of vessels by emboli, blood-groove reduction etc.

For embolism a pulmonary artery are characteristic: pallor of the person as result of a reflex angiospasm, a reflex spasm of bronchial tubes, and sometimes and suddenly arising insufficiency of coronary blood circulation. Infringements of external breath at embolism is the reflex reaction arising as with receptor field of a small circle, as well as owing to irritation reflexogen zones of the big circle blood with the lowered maintenance of oxygen.

**Embolism of big circle of blood circulation** can be from the income of embolus from the left heart, arterial system of the big circle.

The direction of the embolus depends on many factors: its size, the character of a blood groove, etc. The consequences of embolism of the big circle of blood circulation are the infringements of food of corresponding sites of tissues.

The level of a clinical picture is in each specific case defined mainly by the interrelation of two factors – a reflex angiospasm and the development of collateral circulation. Embolism of branches of a portal system of the liver. The income from branches of the portal vein.

In a communication in the big capacity of a portal channel corking by an embolus, the main trunk of portal vein or branching leads to increase blood income bodies of an abdominal cavity and to development of a syndrome of portal hypertension. There is a clinic triad (ascites, widening of surface vein of abdomen, increase of spleen), a decrease of inflow of blood to heart, the minute volume of blood, a decrease of arterial pressure, apnea, etc. The basis of those disorders is the decrease in the

volume of circulating blood, caused by its accumulation in the portal sinus. Those disorders of hemodynamics often are the cause of death of the sick.

The effect of embolism depends on the place of embolism itself. The most dangerous is the embolism of coronary vessels of the heart and vessels of the brain. Embolism in insufficiency of collateral circulation is accompanied by infarction. Also, the quality of emboli is important. Some signs develop of simple embolus, others – of embolus from the tumor, and the third – from the income of infected embolus.

## TYPICAL MICROCIRCULATION DISORDER

According to the standard classification, microcirculation frustration divides into intravascular Disorders, frustration connected with change of vessels, and extravascular Disorder.

Intravascular Disorders of microcirculation can be connected with changes in viscosity and rheology of blood, aggregation, and pasting of erythrocytes, thrombocytes, and Disorders of fibrillation. Changes in the fluidity of blood are one of the principal causes of Disorder of microcirculation. Such changes influence the blood flow on the microcirculation channel, I promote blood-groove delay, already to a stop.

The factors causing Disorders of rheology and fluidity of blood in microvessels are:

1. The strengthened intravascular aggregation эритроцитов.

2. Deformability Disorder of erythrocytes depends on changes in mechanical properties of their membranes. It has great importance at a flow in capillaries. The diameter of a gleam of capillaries is less than erythrocytes and at a normal flow of blood, they move on in the deformed condition.

3. Their concentration. In the conditions of an organism's concentration of erythrocytes can influence the fluidity of blood indirectly because the increase in their quantity promotes the formation of units.

4. The structure of a stream of blood is the important factor that defines the normal fluidity of blood on microvessels. At ischemia, the stream structure changes so that fluidity decreases, promoting blood-groove delay in all streams.

Reduction of the size of a negative charge of erythrocytes leads to a decrease in suspense stability of blood, and aggregation of erythrocytes and other blood cells. A decrease in the speed of a blood groove aggravates this process. It has received the name sludge.

Depending on the character of influence sludge can be reversible and irreversible. Agglutination of erythrocytes in the latter case takes place.

The process of formation of units has a certain sequence. First minutes after damage units from thrombocytes and chylomicrons are formed. They are densely fixed to a wall of vessels, forming a white blood clot, or are carried away in other departments of the vascular system to the new centers of a thrombosis. Erythrocyte units are formed during the first hours after damage, at first in venules, then in arterioles. It is caused by a decrease in the speed of a blood groove. 12–18 hours after it development of the specified Disorders progress. Also, the return development of the process is possible. Disorder of balance of a hemostasis and antihemostasis leads to loss of locality of a thrombosis, coagulation, and their system character. It accepts especially dangerous forms of disseminated intravascular clotting (DIC). Pathogenesis is connected with an avalanche increase of quantity active thrombin in a system blood groove.

The etiology of DIC is reduced to several typical situations.

1. Distribution and massive damages of a fabric (burns, traumas). In blood, it appears a lot of forming of thromboplastin and collagen.

2. An emergency obstetric pathology (rupture of a placenta, etc.). In this case, it is a question of distribution forming of thromboplastin and other coagulants from placenta and fruit bodies where it is a lot of them.

3. Polianion molecules in the blood (sepsis, etc.). In this case, they make coagulation in a system blood-groove, and lipocarboxydrates activate leukocytes, endothelium, and thrombocytes, as a result of it cages aggregate.

4. Malignant tumors. In that case blast cells are a source of procoagulants and proagregants, mucine, and activating factor X.

5. Total activation of kinin systems and complement (at poison action, anaphylaxis).

**Four stages of development of DIC are described:**

1. Hypercoagulation (owing to activation of contact factors of hemostasis or occurrence in blood-activated fabric thromboplastin).

2. Accruing coagulopathy of consumption (in connection with the strengthened expense of factors of curling).

3. Hypocoagulation (in connection with the exhaustion of stocks of fibrinogen and it is frequent hyperfibrinolysis).

4. Restoration (against gradual normalization of the process of coagulation).

Clinical displays of stages are imposed against each other. At fast development of a syndrome prevail hemorrhagic, at sub-acute – thromboplastin symptoms. The great value has emboli by micro cloths, breaking microcirculation. In case of successful treatment or not heavy current there comes a phase of reconvaliscention when remaining residual occlusive the phenomena and insufficiency of functions of organs.

**Capillary (true) stasis**

As it was shown the stasis can appear as the result of increased pressure in the venous till it's equal to arterial. In that case, it's after the venous hyperemia and it's called venous. If arterial pressure falls to the venous level, the bloodstream may stop. That stasis is called ischemic. And the sta-sis can appear as the result of difficulties in the bloodstream in capillaries. This stasis is called true or capillary. While stasis inflow and outflow of blood in the area are absent. Arteriovenular difference of pressure decreases in venous and ischemic stasis, but it is the true one. True stasis differs by a huge increase in capillary resistance of viscosity.

If we look microscopically we see the homogenous character of blood masses in microvessels and changes in vessels. It appears in dehydration and the last stages of leukocytosis, in macroglobulinemia, polycythemia, and sicklemia. As the result there is a huge increase in viscosity, leading to stasis. The danger is the probability of thrombi. While blood stops the thrombocytes are separated by plasma bloodstream contact with the endothelium. Also, the factors are the absence of inactivation of procoagulants, income of fresh anticoagulants, the trauma of endothelium, etc.

So in true stasis, the central chain is early and deep changes in rheological properties of blood: deformation and sticking of its elements, increasing of viscosity, and the shift of balance of hemostatic and antihaemostatic factors.

**Disorders of microcirculation connected with changes of vessels**

Changes in vessels wall leading to disorders of microcirculation can be connected with the disorders of tone, mechanical integrity, and penetrability of microvessels.

Changes in basal tone of arteries promote deviation in the content of vasoactive substances – catecholamines, histamine, etc. The constrictor effect of catecholamines weakens then the level of histamine and serotonin increases. The action on the tone of arteries is made by changes in the pH of sarcoplasm. Alkalosis increases the concentration of calcium and potassium ions in the sarcoplasm. Positive deviation of those ions increases the contraction of smooth muscles of arteries. Increasing H+ ions in acidosis decrease the contraction of smooth muscles. Changes in the tone of smooth muscles in alkalosis and acidosis don't depend on the activity of alpha-adrenoreceptors of the sarcolemma. A decrease in the basal tone of vessels appears if there is an excess of vasodilators: through receptors in smooth tissue, the synthesis of cAMP decreases, and the cGMP grows. This increases the K+ and decreases the potassium penetrability and causes the repolarisation of the sarcolemma. In the regulation of the tone of vessels acts the important role endotheliocytes, releasing the vasodilating and vasoconstriction substances. The endothelial factor of relaxation – $CO_2$ – and those substances have a similar mechanism of action: they activate diluted guanilatecyclaze but increasing intracellular cGMP leads to relaxation of smooth muscles of vessels.

In pathology, we often see the changes in the intensity of substances passing through vessels wall due to both changes of the bloodstream and intensive disorders of vascular penetrability. In morphology – the increasing penetrability is characterized by enlargement of openings between endotheliocytes due to constriction and strengthening of vesicular transport. In the functional view – increases the passage of proteins.

**Extravascular disorders of microcirculation**

The main are two types of disorders. The first type is the reaction of base cells of connective tissue to the damaging agents. The second type is the change of perivascular transport of interstitial liquid together with diluted substances. In pathology, while base cells degranulate they free a lot of bioactive substances. They increase the anticoagulative activity of blood and change its rheological properties, causing vasoconstriction and vasodilation, and changes in the velocity of the bloodstream. According to the theory of Starling the pass of liquid from blood to tissue is carried out through a semi-impermeable membrane of capillaries under the filtration pressure (FP);

$$FP = (HPB + OPT) – (HPT + OPB).$$

There is the HPB – hydrostatic pressure of blood on the capillaries wall (32,5 mm Hg); OPT – oncotic pressure of tissue (4,5 mm Hg); HPT – hydrostatic pressure of tissue (3 mm Hg); OPB – oncotic pressure of blood (25 mm Hg). In arterial capillary effective filtrate pressure equals 9 mm Hg. It provides the passing of liquid from blood to tissue. In venous capillary and venules, the hydrostatic

pressure falls much due to the partly passing of liquid to the interstitia (down to 17,5 mm Hg). As the result FP = (17,5 + 4,5) – (3 + 25) = -6 mm Hg, that causes partly resorption of liquid from tissue to blood. Part of the interstitial liquid is spent on lymph forming and gets into lymph vessels.

Strengthening of transudation appears in increasing of hydrodynamic pressure of blood onto microvessels, decreasing of oncotic pressure of blood. While stasis of potassium ions in organisms due to primary or secondary hyperaldosteronism the accumulation of liquid in the interstitial is caused by both increased transudation and relocation of it from intracellular space. Increasing transudation can be connected with increasing vessel penetrability.

**Changes of perivascular transport interstitional liquid**, forming and transport of lymph can be connected with the development of mesenchymal dystrophies. The transport systems suffer first. So that the dyscircular-hypoxic mechanism is very important.

Often mucoid degeneration, fibrinoid degeneration, and hyalinosis are the logical stages of the disorganization of connective tissue. Amyloidosis differs from those processes. It has the protein-carbohydrates complexes that include the fibril protein, which is synthesized by amyloidoblasts.

Mucoid degeneration and fibrinoid degeneration – are the types of mesenchymal protein dystrophy, which characterize the process of disorganization of dysproteinoses. While this mucoid degeneration is described as surface disorganization, fibrinoid degeneration – is the process of deep disorganization of connective tissue. The change of mucoid degeneration to fibrinoid de-generation isn't obligatory. However fibrinoid degeneration can appear independently.

## Capillary trophy insufficiency

Due to the stasis of terminal arterioles by the high quantity of erythrocyte aggregates the capillary vessels admit only plasma. While this wall damages. The process worsens by acid reaction, local metabolites, and bioactive substances, coming into the blood due to the general degranulation of basophils. Appearing increased penetrability of veins and capillaries promotes the coming out of liquid, increasing blood viscosity. Those pathophysiological disorders of microcirculation in the final stage of sludge development, characterized by metabolism and organ and tissue disorders, and the insufficiency of trophy supply are called capillary trophy insufficiency. It has the system character. This is the generalized reaction of an organism.

## Typical disorders of the lymph circulation

The function of the lymphatic system is connected with the function of micro circular and venous systems. The lymphatic system carries out the homeostasis of extracellular liquid by its constant refreshing. In organs and tissues, the lymphatic vessels are formed as the closed nods, there the water can go in. The lymph formation is the most active in the postcapillary parts of the venous circulation system. In the open communication ways, the lymph gets in by filtration of the liquid part of blood through interendothelial openings and the activity of transport mechanisms of the endothelium. Lymphatic vessels have capacitive, drainage, and transport functions, but the main function is the removal of substrates, coming into the intercellular liquid from the microcirculation system.

In organ damage of any etiology, the system is always involved. While medium damage, is accompanied by increasing blood circulation volume in the microcirculation, lymph formation increases, and so does the volume of intercellular space and the drainage.

The most marked disorders of lymphatic system function appear while hard changes of organs and tissues independently from their etiology. In damaged structures, the processes of lymph formation grossly change due to disorders of microcirculation, in intercellular liquid metabolites and poisonous substances begin to accumulate. Income of tissue lymph to the blood system can promote general toxicosis.

**Insufficiency of lymph circulation** – this is the state then lymph vessels don't carry out their main function – constant and effective drainage of interstitial. There are some forms:

1. Mechanical insufficiency. Develops by difficulties of lymph outflow because of some organic or functional causes.
2. Dynamic insufficiency. Appears then the volume of transudation increases the capacities of the lymphatic system to carry out its main function.
3. Resorptive insufficiency. Develops after structural changes of interstitial tissue, accumulation of proteins, and their precipitation in the interstitial.

The main display of the lymph circulation insufficiency in the acute stage is the edema, proteins, and their metabolites accumulation in the interstitial. In the chronic stage – fibrosis and sclerosis develop.

| The full student's name | The date | The marks | Teacher's signature |
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## PRACTICAL LESSON № 8 (9–10 stomat.)
## Topic: INFLAMMATION. THE VASCULAR PHENOMENA AT THE INFLAMMATION

**Relevance of the topic.** Inflammation as the standard pathological process which developed in the course of evolution and arises in response to any damage to tissues of an organism is the cornerstone of many diseases of the infectious and noninfectious nature of the person and animals. The knowledge of the main external manifestations of inflammatory reaction, the essence of processes which are the cornerstone of inflammation, of mechanisms of their development and consequences is necessary for timely and correct diagnosis of diseases of an inflammatory character, carrying out rational pathogenetic therapy at any stages of development of the inflammatory process. Studying in the experiment of a condition of microcirculation in the inflammation center in dynamics of its development allows opening more deeply internal essence of both an external manifestation of inflammation and many regularities of development and a current of actually pathological and protective and adaptive phenomena which are the cornerstone of an inflammation.

**General aim** – to be able to characterize an inflammation as a local vascular and tissue reaction of an organism to damage, to characterize its external signs, and explain the mechanism of their emergence. An experimental model of inflammation to reveal regularities of development of vascular reaction and changes of hemodynamics in the inflammation center, to interpret their mechanisms.

**For this it is necessary to be able to (specific objectives):**

1. To open a concept of "inflammation" essence.
2. To characterize the main processes which are its cornerstone.
3. To call the main external signs of inflammation and explain the mechanism of their emergence.
4. To prepare the preparation of a mesenterium of a frog.
5. To study dynamics of changes of microcirculation, the main stages of vascular reaction at an inflammation.
6. To explain the mechanism of disorders of microcirculation at different stages of development of the vascular reaction.
7. To connect blood circulation changes that are observed, with processes of exudation and emigration of leukocytes and other phenomena at an inflammation.

**Required to achieve the learning basic knowledge – skills.**

**To be able to:**

1. To immobilize and fix a frog, to carry out on her the elementary surgeries
2. To determine microscopically different types of blood vessels in tissues by their structure and nature of blood circulation.

### THE QUESTIONS FOR THE LESSON

1. Concept "inflammation" definition.
2. Main signs of inflammation
3. Inflammation etiology.The general pathogenesis inflammations
4. Metabolic disorder in the inflamed tissue.Inflammation mediators.
5. Sequence of the vascular phenomena of the center of an inflammation.
6. The mechanism of arterial hyperemia at an inflammation
7. The mechanism of venous hyperemia at an inflammation.Vascular theory pathogenesis U. Kongeym inflammations.

### EXPERIMENTAL PART OF LESSON

**Object of experiment:** Frogs

**Apparatus and reactives:** Boarels, pins, pinceps, needles, microscopes, physiological solution.

**The conduction of experiment:** Fix the frog on the board lying on its stomach that the lower third of its stomach lies on the edge of the side opening of the board. Cut the skin by the lateral surface of the stomach. Cut open the abdominal cavity (length of the incision 0,5–0,7 cm). With the help of pinceps carefully bring out a ring of the small intestine. Spread the mesenterium over the opening of the board with the help of pins. View under the microscope (small and average magnification) the development of the main vessel phenomena during inflammation. Draw the vessel changes you see under the microscope and white down their results.

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

## THEORETICAL MATERIAL FOR PREPARATION TO LESSON
## INFLAMMATION

### General knowledge about inflammation

Inflammation is the most often pathological process, which arises in a human organism. It is a typical pathological process, which arises after the damage to tissues and consists of three main vessel-tissue components: alteration, violation of microcirculation with exudation, and emigration of leucocytes and proliferation. Inflammation, as a typical pathological process has common regularities, which always are present and don't depend on the cause, localization, species of an organism, and its individual features. The inflammation can arise in various organs. Each concrete case has its own features, but the scheme of the inflammatory reaction response will always be identical, which is typical. The inflammation is the local process, but all organism reacts definitely too. The Immune, endocrine, and nervous systems are the main engaged systems in inflammation. Inflammation protective tissue response to injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissues. The classical signs of acute inflammation are pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function (function laesa).

### Classification of an inflammation

Depending on the clinical course, there are two kinds of inflammation: acute and chronic. During the acute inflammation, the pathological agent is destroyed completely and the process ends in the liquidation of the inflammation and reparation of full value. Chronic inflammation develops as the result of the persistent influence of the pathological agent on an organism, organ, and tissue, which cannot be destroyed and eliminated by the organism. There is normoxic, hyperergic and hypoergic inflammation when taking into account intensity of local and general changes in the organism. The normoergic inflammation is characterized by the adequate reaction of organism, as the response to the invasion of the pathological agent; the hy-perergic inflammation is characterized by a very strong reaction of the organism even on an insignificant influence of the pathological agent, the hypoergic inflammation is characterized by insignificant changes in tissues. During the inflammation one of the stages of inflammation can prevail, therefore there can be alterative inflammation, exudative inflammation, and proliferative inflammation. The alterative inflammation is characterized by hard damage of tissues (dystrophy, necrosis), the exudative inflammation is characterized by derivation of big quantity of exudates, and the proliferative inflammation is characterized by reproduction of cells.

### Etiology of Inflammation

In many cases the causes of inflammation are obscure, and this applies mainly to internal organs whose actions are greatly hidden from our view. Inflammation is producible artificially, and if we study the modes of production we shall find that agents are used to which the general name of Irritants is applied. The inflammation is produced, it is said, by irritating the part in some way. The name irritant is apt to be misleading, as it embodies the conception of a stimulating action: whereas the so-called irritants, in their nature and action, possess characters rather of a deadening than of a stimulating kind. Such agents as croton oil, nitrate of silver, and chloride of zinc, have a damaging action on the tissues, and they are some of the commonest in use when inflammation is to be produced. Again, traumatic causes produce inflammation; a direct injury inflicted may kill, but acting less vigorously it may produce inflammation. The agents, however, although their direct action is deleterious, may yet induce a reaction in the tissues, and in this sense stimulate them.

The nervous system itself can scarcely act as an irritant, but it may so alter the tissues that agents which normally would produce no such effect will irritate and produce inflammation. The case of Urticaria may here be cited. This condition is primarily an affection of the nervous system, but the

more definite inflammatory changes are brought about by friction, by the clothes, or otherwise so that a normal stimulus produces under the abnormal nervous conditions a pathological result. As an example of how local conditions may determine the occurrence of inflammation, the fact may be cited that a mild inflammation of the bone marrow produced by caustics may be converted into an intense septic inflammation by causing the animal to eat putrid food. Here an existing damaged state makes the tissues unable to resist the attack of a further damaging agent which normally they are able to withstand. It may be added that besides conditions brought about through the nervous system there may be Individual peculiarities, hereditary or acquired, rendering different persons variously liable to the action of irritants, and even in the same person, the various organs of the body may show different degrees of resistance.

The character of the inflammation will also, to some extent, be influenced not merely by the nature of the agent causing it, but also by the state of the individual. In studying individual cases of inflammation it will be important to consider by what path the irritant has reached the part which has become inflamed. In many cases, it reaches it by the blood, and as the blood is distributed in every part of the organ, the inflammation will not probably show any special localization. And so, when we find two symmetrical organs, both of which are attacked in every region, we infer that the agent causing the inflammation has come from the blood, or, at least, by a path common to both. Of course, there may be local differences in the organ itself of such a character that every part will not be equally susceptible to the action of an agent calculated to produce inflammation, and so the disease may develop more in one part of the organ than in another, although the general character of its distribution will generally still suggest the path by which the agent has come.

## The response to injury and infection

Inflammation is the body's reaction to invasion by an infectious agent, antigen challenge, or even just physical, chemical or traumatic damage. The mechanism for triggering the response of the body to injury is extremely sensitive. Responses are to tissue damage that might not normally be thought of as injury, for example when the skin is stroked quite firmly or if some pressure is applied to a tissue. Depending on the severity of the tissue damage resulting from an injury, the integrity of the skin or internal surfaces may be breached and damage to the underlying connective tissue and muscles, as well as blood vessels, can occur. In this situation infection can, and frequently does result because the normal barrier to the entry of harmful organisms has been broken. The inflammatory reaction is phylogenetically and ontogenetically the oldest defense mechanism. The cells of the immune system are widely distributed throughout the body, but if an infection or tissue damage occurs it is necessary to concentrate them and their products at the site of damage. Three major events occur during this response: An increased blood supply to the tissue "in danger". It is performed by vasodilation. The inflamed tissue looks like containing a greater number of vessels. Increased capillary permeability is caused by the retraction of the endothelial cells. This permit larger molecules than usual to escape from the capillaries, and thus allows the soluble mediators of immunity to reach the site of inflammation. Leukocytes migrate out of the capillaries into the surrounding tissues. In the earliest stages of inflammation, neutrophils are particularly prevalent, but later monocytes and lymphocytes also migrate towards the site of infection. For the possibility of surrounding tissue damage, inflammatory responses must be well ordered and controlled. Therefore, a wide variety of interconnected cellular and humoral (soluble) mechanisms are activated when tissue damage and infection occur.

The development of inflammatory reactions is controlled by cytokines, by-products of the plasma enzyme systems (complement, the coagulation clothing, kinin, and fibrinolytic pathways), lipid mediators (prostaglandins and leukotrienes) released from different cells, and vasoactive mediators released from mast cells, basophils and platelets. These inflammatory mediators control-ling different types of inflammatory reactions differ. Fast-acting mediators, such as vasoactive amines and the products of the kinin system, modulate the immediate response. Later, newly synthesized mediators such as leukotrienes are involved in the accumulation and activation of other cells. Once leukocytes have arrived at a site of inflammation, they release mediators which control the later accumulation and activation of other cells. However, in inflammatory reactions initiated by the immune system, the ultimate control is exerted by the antigen itself, in the same way as it controls the immune response itself.

The nervous system can also participate in the control of inflammation, especially axon reflexes, but inflammation may be realized in denervated tissues as well. Inflammation can become chronic. In certain settings, the acute process, characterized by neutrophil infiltration and edema, gives way to a

predominance of mononuclear phagocytes and lymphocytes. This probably occurs to some degree with the normal healing process but becomes exaggerated and chronic when there is ineffective elimination of foreign materials as in certain infections (e.g. tuberculosis) or following the introduction of foreign bodies (e.g. asbestos) or deposition of crystals (e.g. urate crystals). Chronic inflammation is often associated with the fusion of mononuclear cells to form multinucleated gigantic cells, which eventually become granuloma. Chronic inflammation is seen under conditions of delayed hypersensitivity. The main humoral and cellular components involved in the amplification and propagation of both acute and chronic inflammation.

There are two categories of factors capable to induce the damage of cells and tissues – endogenous and exogenous. Endogenous damaging factors include immunopathological reactions and some neurological and genetic disorders. Exogenous factors can be divided into:

- ***mechanical*** (traumatic injury),
- ***physical*** **(**extremely low or high temperature, ionising irradiation, microwaves),
- ***chemical*** (caustic agents, poisons, venoms, genotoxic and proteotoxic compounds),
- ***nutritive*** **(**deficiency of oxygen, vitamins and basic nutrients),
- ***biological*** **(**viruses, microorganisms, protozoan and metazoan parasites).

Immunopathological reactions may be also triggered by exogenous antigens. Genetically caused alterations leading to inflammation are manifested by the destruction of membrane structures, derangement of transport mechanisms, or by the defective activity of some enzymes and mediators. Cell damage also occurs during aging. It is a very complicated process in which genetic, metabolic, immunologic, neurological, and other factors are involved. In aging cells, probably metabolic intermediates such as different free radicals, aldehydes, ketones, and their reaction products, or on the contrary non-degradable compounds are accumulated. This results in a serious defect in the integrity and physiological homeostasis of cells and tissue. Extremely **low temperature** is able to form crystals inside the cell. Mild decrease in temperature causes paralysis of vasomotors and an increase in permeability of vessels. Blood viscosity rises proportionally with the lowering temperature and cells are destroyed by hypoxia. Low temperature acting for a longer time provokes the destruction of myelin in exposed area. Microthrombi are produced in vessels and they are the cause of *gangrene*.

**High temperature** increases the permeability of cell membranes. Very high temperature is responsible for the coagulation of vessels and denaturation of vital biopolymers, especially proteins.

According to the dose and the way of exposition ionizing irradiation may primarily damage hematopoietic, gastrointestinal, or neural tissues. Whole-body irradiation produces nonspecific immunosuppression which is the cause of increased sensitivity to infection. The infection is developed mainly due to leukopenia and the loss of physical integrity of mucosal membranes, especially in the gastrointestinal tract. Whole-body irradiation eliminates most of the mature lymphocytes of the immune system while preserving the more radiation-resistant elements such as the thymic epithelium. Ionizing radiation is also used for the treatment of patients with cancer and sometimes in the form of local graft irradiation. An alternative form of radiation therapy is total lymphoid irradiation e.g. for the treatment of Hodgkin's disease. Lethally irradiated persons can be given immature bone marrow cells to reconstitute their immune systems. On the cell level, irradiation destroys important biopolymers (DNA, proteins) and biological membranes. At first, the degenerative changes in the nucleus and chromosomal aberrations can be seen. The increased membrane permeability and activation of hydrolytic lysosomal enzymes disrupt cell structures and compartments. Irreversible damage of irradiated cells causes their complete destruction, necrosis**.** Some **chemicals**, namely caustic agents and mineral acids are able to damage tissues directly, other such as heavy metals, poisons and venoms mainly derange important enzymatic reactions. Metabolic homeostasis of cells and tissues is also disturbed by the action of genotoxic and proteotoxic agents. The often observed defects belong destruction of cell membranes, a decrease of intracellular pH, the release of lysosomal enzymes, and changes similar to hypoxia (decrease of oxidative phosphorylation). Lysosomal enzymes and free radicals derived from oxygen (reactive oxygen intermediates – ROI) or from nitrogen (reactive nitrogen intermediates – RNI) have an essential role in the damage of cell structures, especially during injury inflammation.

The **oxygen deficiency** is manifested in 3–5 minutes. In mitochondria, oxidative phosphorylation is very quickly impaired and insufficient production of ATP appears. Deficiency of ATP activates anaerobic metabolism in which ATP is formed from glycogen. But the reserves of glycogen are again quickly depleted. Because of persistent ATP insufficiency the sodium-potassium pump loses its operating capacity. This leads to the intracellular accumulation of sodium and the leakage of potassium

from cells. Accumulation of sodium induces the transfer of ions and water into cell. It is the reason of endoplasmic reticulum dilatation. The dilatation provides complete damage to ribosomes and blocks proteosynthesis.

If the hypoxia continues, the whole cell is overfilled with water, sodium, and chlorides. This state is still reversible, after the renewing of oxygen transport, the cell should recover. In the others cases, vacuoles in the cytoplasm and the damage of mitochondrial membrane appear.

**Infections** are often involved in cell damage. Virulence of microorganisms and the induction of inflammation depend on their ability to replicate in the human or animal bodies and to destroy cellular structures. During growth and multiplication, microorganisms can produce and release different exotoxins which are potent injuring agents. Other microorganisms, after destruction or lysis, release from phospholipid and lipopolysaccharide envelops toxins known as endotoxins. The term "endotoxin" is generally used to refer to the thermostable polysaccharide toxin, firmly bound to the bacterial cell, in contrast to the thermolabile protein " exotoxin", secreted into the external environment. **Endotoxin** (lipolysaccharide, LPS) is responsible for many pathophysiological symptoms observed during gram-negative bacterial infections. They include pyrogenicity (the ability to cause an increase in body temperature), changes in the number of circulating leukocytes (leukocytopenia, leukocytosis), complement activation, activation of macrophages, aggregation of platelets, increase of capillary permeability and others. In addition, LPS induces an immune response. Administration or release of a higher dose of endotoxin may produce lethal shock. All these biological activities are mediated through the endogenous mediator – tumor necrosis factor-α (TNF-α).

Viruses do not produce exotoxins or endotoxins. They are typical intracellular parasites and use cells for their own replication. During this, damage to cell structures leading to the death of cells is observed. In addition, viruses may be responsible for the tumorous transformation of cells.

It follows that cell damage following the inflammatory reaction may be useful or harmful. The useful activities include:

1) destruction of injuring and infectious agents and their elimination from the site;
2) limitation of spreading of injuring factors;
3) stimulation of the specific immune response;
4) help in the healing process.

To the *harmful* inflammatory reactions belong autoimmune and other immunopathological processes.

## The phases of inflammation

The main purpose of inflammation, this immensely complex response seems to be to bring fluid, proteins, and cells from the blood into the damaged tissues. It should be remembered that the tissues are normally bathed in a watery fluid (extracellular lymph) that lacks most of the proteins and cells that are present in blood, since the majority of proteins are too large to cross the blood vessel endothelium.

The main features of the inflammatory response are, therefore: **vasodilation**, i.e. widening of the blood vessels to increase the blood flow to the infected area; **increased vascular permeability**, which allows diffusible components to enter the site; **cellular infiltration** by chemotaxis, or the directed movement of inflammatory cells through the walls of blood vessels into the site of injury; **changes** in biosynthetic, metabolic, and catabolic **profiles** of many organs; and **activation** of cells of the immune system as well as of complex enzymatic systems of blood plasma Of course, the degree to which these occur is normally proportional to the severity of the injury and the extent of infection. Inflammation can be divided into several phases. The earliest, gross event of an inflammatory response is temporary vasoconstriction, i.e. narrowing of blood vessels caused by contraction of smooth muscle in the vessel walls. This is followed by several phases that occur over minutes, hours and days later, as outlined below.

The **acute vascular response** ollows within seconds of the tissue injury and lasts for some minutes. This results from vasodilation and increased capillary permeability due to alterations in the vascular endothelium, which leads to increased blood flow (hyperemia) that causes redness (erythema) and the entry of fluid into the tissues (edema). This phase of the inflammatory response can be demonstrated by scratching the skin with a fingernail. The "wheal and flare reaction" that occurs is composed of (a) initial blanching of the skin due to vasoconstriction, (b) the subsequent rapid appearance of a thin red line when the capillaries dilate; (c) a flush in the immediate area, generally within a minute, as the arterioles dilate; and (d) a wheal, or swollen area that appears within a few minutes as fluid leaks from the capillaries. It is usually terminated after several ten minutes. If there has been sufficient damage to the tissues, or if infection has occured, the **acute cellular response** takes place over the next few hours. The hallmark of this phase is the appearance of granulocytes, particularly neutrophils, in the

tissues. These cells first attach themselves to the endothelial cells within the blood vessels (margination) and then cross into the surrounding tissue (diapedesis). During this phase, erythrocytes may also leak into the tissues and a hemorrhage can occur (e.g. a blood blister). If the vessel is damaged, fibrinogen and fibronectin are deposited at the site of injury, platelets aggregate and become activated, and the red cells stack together in what is called "rouleau" to help stop bleeding and aid clot formation. The dead and dying cells contribute to pus formation. If the damage is sufficiently severe, a **chronic cellular response** may follow over the next few days. A characteristic of this phase of inflammation is the appearance of a mononuclear cell infiltrate composed of macrophages and lymphocytes. The macrophages are involved in microbial killing, in clearing up cellular and tissue debris, and they also seem to be very important in remodelling the tissues.

Over the next few weeks, **resolution** may occur, meaning that the normal tissue architecture is restored. Blood clots are removed by fibrinolysis, and if it is not possible to return the tissue to its original form, scarring results from in-filling with fibroblasts, collagen, and new endothelial cells. Generally, by this time, any infection will have been overcome. However, if it has not been possible to destroy the infectious agents or to remove all of the products that have accumulated at the site completely, they are walled off from the surrounding tissue in granulomatous tissue. A granuloma is formed when macrophages and lymphocytes accumulate around material that has not been eliminated, together with epithelioid cells and giant cells (perhaps derived from macrophages) that appear later, to form a ball of the cell. Inflammation is often considered in terms of **acute inflammation** that includes all the events of the acute vascular and acute cellular response (1 and 2 above), and **chronic inflammation** that includes the events during the chronic cellular response and resolution or scarring (3 and 4). In addition, a large number of more distant effects occur during inflammation. These include the production of acute-phase proteins, including complement components, by the liver; fever, caused by pyrogens acting on the hypothalamus in the brain; and systemic immunity, resulting in part from lymphocyte activation in peripheral lymphoid tissues.

## General pathogenesis of inflammation

**Inflammation**- the reaction of the body to injury, but its **effector system** is the system of blood microcirculatory bed and connective tissue. Blood system plays a crucial role in inflammation, since leukocytes are major effector cells in the process and the whole system provides the appearance and maintenance of leukocyte infiltration the main component of inflammation, connective tissue is the trigger system inflammation and microcirculatory bed provides a link between the blood and connective tissue.

The **initial effectors** of inflammation are vegetative neurons, C-fiber sensory neurons containing neuropeptides, connective tissue cells (tissue basophils, resident macrophages, fibroblasts), the factors of tissue fluid (kininogen, complement) and other components of connective tissue. In outline flogogenous is causing induces activation and damage of the stated cells and biochemical factors of tissue fluid (primary alteration), resulting in the release or formation of the mediators of inflammation. The later realize killing and lysis of microbes, while damaging its own tissues (secondary alteration to the release and the formation of secondary mediators of inflammation). Secondary alteration is aimed at containment and elimination flogogenous a and (or) damaging tissue to them. At the same time increasing vascular permeability, causing chemotaxis of leukocytes, activation of fibroblasts and the like, run a standard mechanism mediating reinforcement from the plasma and blood cells, the surrounding connective tissue (the phenomenon of exudation, proliferation and emigration). Mediators of plasma and blood cells are coming to the center with the exudate and blood leukocytes. Because of this the fighting with flogogenous and damaging of tissues increasing (expansion of secondary alteration), that, in turn, increases and prolongs the exudation and infiltration. First, leukocytic infiltration is carried out by circulating leukocytes, and then supported by the strong red blood cells. The destruction of flogogenous and rests its own tissues is also achieved by phagocytosis. As the purification of the inflammatory focus and damaged tissue from flogogenous exudation and emigration are subsiding, proliferation is increasing and tissue regeneration and tissue defect compensation are going on. Thus, inflammation is an automatic reaction, that provides its own deployment, maintenance, and subsided.

## Alteration

**Alteration** (Latin alteratio – change), or **dystrophy** – tissue damage, it’s alimentation (trophic), metabolism, structure and function malfunction.

Primary and secondary alteration is distinguished. The primary alteration is a consequence of the damaging effect of the inflammatory agent, so its evidence of other equal conditions (organism reactivity, localization of inflammation) depends on the properties of flogogenous. The primary alteration is not a component of inflammation, since the latter is a reaction to injury caused by flogogenous, i.e. to the primary alteration. However, practically it's almost impossible to separate the primary and secondary alterations from each other. However, the primary alteration is very transient and insignificant compared to the total of its volume.

Secondary alteration is not directly dependent on the inflammatory agent, for its development the future presence of flogogenous in the nidus is not necessary. It is a reaction of the organism to the damage already caused by flogogenous, i.e. is an integral part of the inflammatory reaction. Moreover, secondary alteration is a necessary component of inflammation as a protective-adaptive reaction. As mentioned, it is refused to localization and elimination flogogenous and (or) tissue that is damaged by it. By the way of secondary alteration, any other inflammatory reactions are reached. It initiates exudation, emigration, and proliferation, through them, provides its own regulation, that creates inflammatory response automaticity. As a result issues, repair, or reimbursement of tissue defects are reaching. Thus, secondary alteration is to be understood more widely, rather than as "the first phase of inflammation": a unity of damage and protection in inflammation is not only that it is a reaction to the damage caused by flogogenous, or reaction with the concomitant destruction of self-harm microbes that usually invest in the concept of "defense costs (through) injuries", but mainly in the fact that damage is an integral part of all the inflammation effects as protective phenomena. Secondary alteration is a consequence of the action on the connective tissue, blood microvessels and inflammatory mediators that having damaging effects, lysosomal enzymes (especially proteinase of polymorphonuclear leukocytes, collagenase, elastase, cathepsins G, B1, etc.), active forms of oxygen and nitrogen, the released extracellularly, and lytic complex of complement – C5b-C9. Alteration involves the disintegration of tissue and enhanced metabolism ("fire exchange"), that lead to a series of physical and chemical changes of the inflamed tissue – accumulation of acidic products (**local acidosis, or H+-hiperiony**), increased of osmotic pressure (**osmotic blood pressure** hypotension**, or hyperosmy**) or colloidal – osmotic or oncotic pressure (**hyperoncy**).

Depending on the strength of the damaging agent, the intensity and localization of inflammation morphological manifestations of inflammation vary widely from barely noticeable structural changes to the complete destruction and loss of tissue. Observed cloudy swelling of the cytoplasm of cells, the phenomenon of protein, fat, and other types of malnutrition. Dramatically increases the permeability of cell membranes and cell organelles. Changes in subcellular structures relate primarily to the mitochondria, lysosomes, ribosomes, and endoplasmic reticulum. Mitochondria swellor shrink and their cristae are destroyed. Increased permeability and damage of the membranes of lysosomes followed by the release of various enzymes that degrade subcellular structures. Change shape and size of tanks, the endoplasmic reticulum, vesicles in the cytoplasm appear concentric structures, etc. Marked boundary arrangement of chromatin, nuclear membrane damage. In the stroma tissue observed in mucoid and fibrinoid swelling up to fibrinoid necrosis, dissolution of collagen and elastic fibers.

An increase in metabolism during inflammation occurs primarily due to carbohydrates. First amplified as their oxidation and glycolysis that is connected with activation of the tissue enzymes. Markedly increases the oxygen consumption of the inflamed tissue. With the accumulation of leukocytes in the hearth, lysosomal enzymes that break down carbohydrates predominantly anaerobic infections, and injuries and reduce the number of mitochondria in the course of alteration, oxidation phenomena noticeably weaker, and glycolysis- is amplified. Accordingly, the splitting of carbohydrates is not always reached the end-products-carbon dioxide and water. Respiratory rate decreases. Oxidized products of carbohydrate metabolism are accumulated in the tissue producing lactic acid and tricarboxylic.

Furthermore, due to metabolic disorders of fats, proteins and nucleic acids in the nidus in-creases the content of fatty acids, ketone bodies, polypeptides, amino acids, nucleotides, and nucleo-sides. As a result, develop acidosis. Depletion of the buffer systems slowing the blood circulation and lymph flow means a lot in the growth of acidosis. If the rate of hydrogen ion concentration in the tissue is $0.5 \times 10^{-7}$, i.e, pH was 7.34, then the inflammation can be $25 \times 10^{-7}$and pH - 5.6 and lower. Thus, during acute purulent inflammation ph is 6,5-5,39, and chronic – 7,1-6,6. Acidosis has some significance in the development of inflammation, particularly in increasing vascular permeability. It creates favorable conditions for the realization of the damaging effects of lysosomal enzymes, in

particular, glycosidase, that break down carbohydrate components of the connective tissue matrix. Along with the H+-hyperiony the content of other ions - potassium, sodium, and calcium is growing in focus. This is due to the destruction of cells and dissociation of electrolytes that is enhanced in the acidic environment. Due to the advanced incising level of potassium, its relation to calcium increased (diziony). At the same time, the molecular concentration increases, because in the process of tissue decomposition and enhanced metabolism the splitting of large molecules into many small ones occurred. Due to increased concentrations of ionic and molecular hyperosmia develops.

As a result of physical and chemical changes in the inflamed tissue, splitting proteins into polypeptides and amino acids with a higher concentration of the latter the dispersion of colloids, their ability to pull up and retain water is increasing hiperonkia is developing.

Changes in osmotic and oncotic pressure are important factors in exudation and, thus, in inflammatory edema. Forced metabolism in inflammation is the basis of increased heat production, which, by turn is a major cause of such an external local sign of inflammation, as fever.

**Inflammatory mediators**

The large quantities of various biologically active substances that becomes mediators (vehicle) of inflammation are released or produce during the primary and secondary alterations, i.e. cause or maintain these or other inflammatory conditions.

Mediators are the main link of the inflammatory response. They provide the origin and interrelation of all inflammation, cellular phase shifting the focus of inflammation, the transition from the deployment of the reaction to its subsided.

All of the known mediators of origin can be divided into two types: 1) **humoral** derived from tissue fluid and plasma, and 2) the **cellular** that are linked to tissue cells and blood. In addition, they can be divided into 1) the **pre-existing** or existing in body fluids and cells before the activation; here are all humoral mediators (located in the tissue fluid and blood plasma in the form of precursors that are usually activated by proteolysis) , and from cellular mediators – containeding in specific granules of certain cells, they are called – granule associated, and 2) spin-off, or originating from the membranes; here are those cellular mediators, that are produced by direct activation of cells of the components of the membranes.

The main source of the most inflammatory mediators is white blood cells and their products – the major mediators of inflammation. First of all such mediators are those that have damaging effects – lysosomal enzymes, reactive oxygen, and nitrogen, that provide the killing and lysis of microbes and the development of secondary alteration. This is in line with the role of leukocytes as the main cells-effector of inflammation. The most important humoral mediators are the active components of complement, particularly lytic (membrane attacking) C5b-C9 complex, since it jointly with leukocyte factors has relevant lysis of microorganisms and damaging of its own tissues.

Other neurotransmitters (most of them) are carrying out their biological activity by binding with the specific receptors on target cells.

It is clear that mediators may act on one or many types of cells, having different targets or effects on different cell types. However, despite a large number of neurotransmitters and their effects, according to their main influences, it is possible to divide to a potentially responsible for 1) vascular and smooth muscle reaction (including the increased permeability of blood vessels) – **vasoactive – spasmogenic mediators**: kinin, vasoactive amines, lysosomal factors, neuropeptides, acetylcholine, prostaglandins, leukotrienes, C4, D4, E4, factor that activates platelets, reactive oxygen and nitrogen, and 2) leukocyte chemotaxis – **chemotaxic mediators** or **mediators of infiltration** – the active components of complement, clotting factor, leikotrien B4 and other eikozanoids, monokines, lymphokines. This number of mediators with the same type of effects correlated with the phenomenon of **tachyphylaxis**, or "desensitization" of blood vessels and cells to them, i.e. with a decrease in their sensitivity to the further action of the mediator, limiting the duration of the mediator. Tachyphylaxis is obviously related to the blockade of the existing and limited synthesis of the new receptors. This by-turn, causes a different mechanism, complexity of the sequence, and the inclusion of mediators, that makes it easy to compensate for the absence of one or some of them: inflammation in evolutionary and biological terms is a protective-adaptive reaction, and breakage or strong artificial oppression of it is not appropriate. It is also "agreed" with the fact that most mediators have a short life. They are rapidly degraded (eg, arachidonic acid metabolites) inactivated by enzymes (kinins, etc.) are removed (eg, reactive oxygen species are removed by antioxidants), and inhibited (eg, enzymes). All this also shows the presence of a checks and balances system in the regulation of the effects of neurotransmitters.

In addition, being the true mediator of one of these inflammation phenomena, the same substances are modulators of the other, i.e. can enhance or diminish its intensity. This is caused by the interaction of inflammatory mediators and the relationship of the phenomena. Thus, increased vascular permeability is a condition contributing to emigration. The release of neurotransmitters and formation of a cascade reaction, i.e. a mediator provides the appearance of other mediators, that in turn serves as one of the manifestations and mechanisms of automaticity of inflammation. Thus, the active components of complement cause degranulation of tissue basophils, leukocytes interact synergistically with prostaglandins and substance P. Histamine via H 1 receptors may increase the degranulation of monocytes, activation of fibroblasts, and inhibit the degranulation by H-2 receptors of granulocytes. Vasoactive amines potentiating interact among themselves and bradykinin, adenine nucleotides, and substance P in increasing vascular permeability. Vasodilator action of histamine enhanced in combination with acetylcholine, serotonin, and bradykinin. Lysosomal enzymes activate the complement system, kallikrein-kinin, coagulation and fibrinolysis, tissue basophils, macrophages, endothelial cells, leukocytes, and fibroblasts. Cationic proteins cause degranulation of tissue basophils. They cause degranulation of tissue basophils, enhance degranulation of leukocytes, and increase the sensitivity of nociceptors to PGE2 and prostacyclin while making a difference in inflammatory pain. Prostaglandins potentiate the development of edema induced by histamine or bradykinin. Leukotrienes synergistically interact with histamine, acetylcholine, prostaglandin, and thromboxanes, stimulating the formation of cyclooxygenase derivatives. Lymphokines regulate the degranulation of tissue basophils, macrophages, leukocytes, and the activity of fibroblasts. Reactive oxygen species release and inactivation of lysosomal enzymes, enhance the formation of mono-and lymphokines interact with nitric oxide to form highly reactive products. Nitric oxide reacts in the regulation of vascular tone with vasoactive amines, kinins, and eicosanoids.

**Changes of the blood flow in inflammation nimbus**

Vascular reactions develop after the influence of the inflammatory agent, as the initial ones are reflexive. They are easily traced under a microscope in a classic experiment by J. Kongeym inflamed mesentery of the frog (1867) and are characterized by the following sequence:

1. **Short-term ischemia** caused by spasm of the arterioles. It is consequence of reflex excitation of the direct action of vasoconstrictors inflammatory agent. Depending on the severity of damage varies from several seconds to few minutes, so that it cannot always be noted.

2. **Arterial hyperemia** caused by the expansion of the arterioles, that mechanism, on the one hand, is associated with axon-reflex stimulation of vasodilators, and on the other – with direct vasodilator effect inflammatory mediators: neuropeptides acetylcholine, histamine, bradykinin, prostaglandins, nitric oxide, etc.

Arterial hyperemia can be observed for half an hour and is the basis of two major external local signs of inflammation – redness, and fever.

3. **Venous congestion**. In the extensive damage it may be developed after few minutes after exposure to an inflammatory agent. It is characterized by a significant duration – is accompanied by the further course of the inflammatory process. Accordingly, when it carried all the major involvement of inflammation.

Therefore, it is **true inflammatory hyperemia**.

I **There are three groups of factors in the mechanism of venous congestion:**

1) violation of the rheological properties of the blood and its proper circulation. These include: a) increase in blood viscosity due to its thickening, loss of albumin due to exudation, increased globulin that contents in the synthesis proteins of the acute phase, changes in the colloidal state of proteins, and b) increased resistance of the bloodstream as a result of the regional standing of white blood cells, swelling and erythrocyte aggregation, c) thrombosis due to the activation of coagulation and platelet-vascular hemostasis components, d) violation of the nature of blood flow – slow blood flow in the axial zone, reducing of the marginal plasmic zone;

2) changes in the vascular wall, which includes: a) loss of vascular tone due to paralysis of the neuro-muscular vessels and b) decrease of vascular wall elasticity, and c) endothelial swelling and increase of its adhesiveness, resulting in the lumen of blood vessels narrowing, the conditions for adhesion of leukocytes and platelets to endothelium;

3) tissue changes, that consist of a) compression of the venules and lymphatic vessels by swollen, infiltrated tissue, and b) elasticity reduction of connective tissue.

It should be noted that many of these factors are, on the one hand, the proximate causes, but on the other – at the same time consequences of developing venous congestion. They are connected to the mechanism of true hyperemia in inflammation and enhance its development. Inflammatory hyperemia differs from other types of congestion in considerable weakening and even distortion of vessels reaction of inflamed tissues to the action of vasoconstrictor agents (adrenaline, caffeine) and to stimulation of sympathetic nerves. This phenomenon can also be associated with tachyphylaxis of vasoconstricting vessels to stimuli. Other differences in the inflammatory hyperemia are more intensive blood supply inflamed tissue, expanding and increasing number of functioning capillaries, the intensity of microcirculation, the backlog linear blood flow velocity, etc., thus considered inflammatory hyperemia as a special kind of infringements of microcirculation.

4. **Stasis**, that may be developed in some vessels ramifications of the inflamed tissue. A common stasis characteristic of acute, rapidly developing, such as hyperergic, inflammation. The mechanism of stasis is in violation of the rheological properties of blood, that, in turn, are connected with changes in blood flow of microvessels, enhanced intravascular erythrocyte aggregation due to changes in physical and chemical properties of membrane protein in the blood, slowing blood flow. Stasis precedes **prestatic condition** characterized by pendulum motion of the blood, when, as a result of increasing congestion, loss of vascular tone, and a dramatic expansion of capillaries and venules during systole, it moves away from arteries to veins, and during diastole – in opposite direction. As a rule, the violation of blood flow in inflammatory stasis is temporary, but in event of damage to the vascular wall and blood clots, much vascular stasis becomes irreversible and leads to necrosis of surrounding tissue.

## Pathogenesis of inflammation

The inflammation, a typical pathological process, consists of three stages: the first is the alteration stage; the second is the violation of microcirculation with exudation and emigration of leucocytes in the center of inflammation and the third – is proliferation.

The first stage after the damage of tissues is characterized by the disorder of proteins, fats, and carbohydrates metabolism, physical-chemical and morphological changes of tissues. The more complicated protein fibrous derivations (collagen, elastin) can also be destroyed. Necrobiosis and necrosis can take place in tissues. It is the reversible (sublethal) damage of cells if they can adapt and restore their structure and function, and the irreversible (lethal) damage of cells, which is characterized by irrevocable change of cells structure.

There are two types of alteration: primary and secondary. The primary alteration is the result of the influence of the pathological (flogogenic) agent on a tissue. Metabolic and structural changes arise, therefore. Various cells react differently: some cells perish, others – remain alive, and others become activated. The activated cells are responsible for the creation of the following stages of inflammation. The secondary alteration is the consequence of the primary alteration and it arises even in the absence of the damaging agent.

The signs of cells damage are the following the lessening of $pO_2$; limitation or termination of $O_2$ consumption by cells; the decrease of ATP and ADP and the increase of the inorganic phosphorus concentration; the intensification of glycolysis, which causes the accumulation of lactic acid and pyruvate acid; the decrease of cells pH. The decrease of ATP concentration reduces the activity of ionic pumps of cell membranes, the parity of Na, K, Ca, and Mg in the cytoplasm is violated, and the activity of biochemical systems of cells is violated too.

The constant deficiency of energy provokes the rise of permeability of organelles membranes and swelling of the cell takes place. These changes are the result of the significant damage to cell membrane structures. Free radicals and peroxides play a significant role in this process. They are the result of hypoxia of the damaged tissues and the violation of biochemical processes in cells. The accumulation of free radical substances exceeds the possibility of the cell neutralizing them. Therefore these substances damage the membrane structures of the cell.

Especially dangerous is the damage to lysosomic membranes. Enzymes, which are localized in lysosomes, can act on all kinds of macromolecules of cytoplasm. Primary lysis of the cell can be a result of the lysosome membrane destruction by the pathological agent. Lysosome enzymes can get into the intracellular space. The secondary lysis of cells is the result of the destruction of the lysosomal membrane by free radicals. There is a protein complex in the blood of the man, which consists of 20 proteins (complement's system). These proteins are activated during the invasion of microorganisms, promote damage to cell membranes and stimulate the protective phagocytic response. The main task of

the complement system is the destruction of all foreign agents, which get or derivate from the human organisms. These proteins, as well as lysosomal enzymes, promote the development of the first stage of inflammation. The consumption of oxygen in this stage of inflammation is increased. But it lasts not for long (2–3 hours). Then the alteration of cells provokes the damage of mitochondrial membranes. The Krebs cycle is violated; the ATP derivation is sharply oppressed, so the energy deficiency and accumulation of toxic substances, such as polypeptides, fatty acids, and ketone bodies take place. Simultaneously derivation of $CO_2$ is violated, and the respiratory coefficient decreases.

The inflammation always begins with the rise of metabolism. The main characteristic of this stage is the activation of metabolism; this is a process of substance disintegration and as result destruction of glycoproteins and glycosaminoglycan complexes, the formation of free amino acids, and polypeptides. Some of these substances are mediators of inflammation and determine dynamics of the inflammatory process.

The accumulation of partly-oxidated products in the cytoplasm, as the result of a violation of the Krebs cycle, is accompanied by the development of metabolic acidosis (decrease of pH), and the conditions which are necessary for enzymes systems operation are also violated. The tissue destruction is accompanied by the release of Na+, K+, $Ca_2$+ out of the cells and the rise of osmotic pressure (hyperosmia, the increase of protein concentration, as the result of catabolism intensification, causes the oncotic pressure increase (hyperonkia). The swelling, pain, and violation of the organ's functions are the result of these changes. The secondary alteration is the result of disorder metabolism, the derivation of free radicals, the influence of lysosomic enzymes, local acidosis, hyperonkia, hyperosmia, and the influence of inflammatory mediators (biologically active substances, generate in the inflammation area). The main components of antimediators system: histaminase destroys the histamine; carboxypeptidase destroys the kinins; esterases inhibit the complement proteins; prostaglandin dehydrogenase de-stroys the prostaglandins; superoxyddismutase and catalase neutralize radicals of oxygen (eosinophils are the important cells, which generate and delivery anti -mediators). Cortisol, cortisone, and corticosterone have antimediators activity too. They weaken vascular reactions, stabilize membranes of microvessels cells, reduce the exudation and the emigration of leucocytes, weaken phagocytosis, reduce the excretion of histamine, stabilize lysosome membranes, reduce the activity of lysosomic enzymes and the derivation of kinins and prostaglandins. These effects of corticosteroids doctors use for patient's treatment.

The lymphatic system also participates in mechanisms of inflammation. In a healthy organism, the lymphatic system executes the drainage function. Their major functions are the extract of microparticles, macromolecules, detritus of the cells, and the exchange of liquid between blood and tissues. The inflammation involves many sites of the lymph system. Liquid comprises lymph capillaries and it changes local lymphatic circulation. The damage to cell membranes breaks the pump function of lymphatic collective vessels. The inflammation is accompanied by the increase of lymphatic capillaries' permeability and their overflow. The detritus of the damaged cells and proteins get into the lymph. The injurious factors can cause the inflammation of lymphatic vessels and lymphatic nodes. Due to the drainage function of the lymphatic system, the amplification of lymph circulation promotes the decrease of swelling and carries antigens to the lymphatic nodes. Besides the amplification of the drainage function of lymphatic vessels can promote the distribution of the infectious agent and the toxic products of proteins disintegration. Spasm of the lymphatic vessels, which usually arises proximately from the area inflammation and inflammation of the lymphatic nodes deepen the swelling in the area inflammation and evidence development of lymphatic circulation insufficiency. The principal value of the alteration and violations of microcirculation is the creation of unfavorable conditions for further penetration of the pathological agent into the organism.

**Exudative and proliferative processes**

The increase of vascular wall permeability provokes exudation (penetration of a liquid from the blood into the tissue), and emigration of leucocytes. The permeability of microvessels increases first of all (especially of venules). The amplification of exudation provokes rheologic properties of blood change and microperfusion as the result of blood condensation; laminar blood stream violation; plasma structure change after the output into the tissue proteins; of microvessels compression by the edematic liquid. These processes provide phagocytosis (a protective process); it is sufficient activity and restoration of the injured tissue. In a stage of arterial hyperemia and especially in venous hyperemia stage fluid with the proteins and salts, dissolved in it, penetrates the vessel. The high hydrodynamic pressure in vessels and the low colloid-osmotic pressure of blood increase the vessel's permeability and penetration of plasma proteins into the tissue.

There are three ways of penetrating of fluid through the vessel wall (exudation). The 1st way is inter endothelial (between nearby endotheliocytes). Histamine promotes the contraction of endothelial cells, the slots between nearby endotheliocytes extend, and the basal membrane is exposed. The second way of exudation is transendothelial (through the endoteliocytes cytoplasm). Vesicles pinocytosis activity (the catch of fluid) of the endoteliocytes increases. The blood plasma is inside vesicles, which move through the cell and sometimes form channels. Various substances can pass without any control through channels (microvesicles transport). The third way of the exudation is the vessel wall area, where are injured endotheliocytes.

The development of the inflammation promotes the amplification of the exudation and the output of blood plasma and the mediators outside the vessels. The main cause of the exudation is mediators of inflammation, but an amplifying disorder of the metabolism, the injury cells, and leucocytes promotes other pathological mechanisms, which increase vascular permeability. They are lysosomes hydrolytic enzymes of various phagocytes and parenchymal cells (collagenase, elastase) and bacterial enzymes (hyaluronidase), lactic acid, and pyruvate acid, other non-oxidated substances, which are the result of tissues hypoxia, adenosine, H+, and K+, especially during the decrease of $Ca_2$+ level. First of all albumins, then globulins and fibrinogen, which promote the formation of fibrin clots, penetrate outside the vessels.

The serious damage to the vascular wall is accompanied by the erythrocytes diapedesis (penetration through the vessel wall) and the bleeding.

The exudation peculiarity and its structure depend on osmotic, oncotic, and hydrodynamical factors of inflammation. Hyperosmia (high osmotic pressure) and hyperoncia (high oncotic pressure) of the tissue in the area inflammation) and osmotic-oncotic pressure of blood is differed, so fluid penetrates out the vessels and amplifies swelling. Hyperosmia is the result of the accumulation osmotic active particles (K+, Na+, salts, light-weight organic substances) of injurious tissue. Hyperoncia is the result of the macromolecules disintegration substances of the injurious tissue accumulation.

There are three types of microvessels permeability change. The first type is the second type – immediate-continuous, third type – is the deferred-prolonged increase of permeability of walls of vessels during inflammation. The first type is called the immediate-transient and occurs during weak damages. The main cause of it is the release of histamine, serotonin, and bradykinin. The contraction of endothelial cells and extension of interendothelial slots in small and average venues occur under the influence of histamine. The permeability of walls of capillaries does not change. Endothelial cells of the small and average venues have more histaminic receptors than the similar cells of capillaries and arterioles; therefore only venues are involved in the process of such type.

The second type of vessel permeability violation arises during hard tissue damages (for example, extensive serious burn). The sharp increase of microvessels permeability arises immediately after damage and lasts up to five days because endothelial cells of microvessels perish and are characterized by plasmorrhea.

The third type of vessel permeability change is characterized by the lasting latent period after the damage. After that, the permeability of vessels sharply increases and lasts for some hours or days. This type of vessel response is the most frequent in the human being (thermal damage, tissue injury by ionizing and ultra-violet rays, operation of bacterial toxins, delayed-type of the allergy). In these cases, endothelial cells don’t round, but the juncture between endotheliocytes of the capillaries and venules is broken. The combination of several mechanisms in dynamics the inflammation is possible.

Amplified exudation promotes the development of edema, pain, and function violation. The pain is the result of the nervous ending compression caused by exudates. The violation of the organ or tissue function is the result of the increase of diffuse distance between the capillary and parenchymal cells, and also their compression. The exudation deepens the negative effects of the inflammation: the disorder of metabolism and microcirculation of the injurious tissue, hemoconcentration, and derivation of thrombus. But at the same time, the pathological factor operation weakens due to injuries area.

Vascular changes and the bloodstream decelerationpromote the reallocation of blood cells: leucocytes move to the vessel wall and begin to attach to it. Then, leucocytes adhere to the endotheliocytes and form the cover along the vessel's walls. The process of the edge standing of leucocytes is necessary for two following conditions: the increase of endothelial cells' adhesive properties and the activation of leucocytes. The increase of adhesive properties of endotheliocytes is promoted by the lowering of their negative membrane charge (it’s the result of the accumulation in the area of inflammation H+, $Ca_2$+, $Mg_2$+, $Mn_2$+, cationic proteins, excreted by activated leucocytes). These ions reduce the leucocytes' negative charge too, and also activate leucocyte enzymes, which increase the adhesive properties of these cells.

Complement, fibronectin, immunoglobulins, histamine, interleukins, and leukotrienes are the most important initiators of the activation of leucocytes' adhesive properties. C5, IgG (Fc-fragment), and IL-8 (chemotactic factors) promote the activation of these cells and their movement to endothe-liocytes. Gradually leucocytes begin to pass through the vascular wall and to emigrate into the tissues (positive chemotaxis).

The penetration of leukocytes through the vessel wall is promoted by the alteration of leukocytes, endotheliocytes, interendothelial contacts basal membrane, and perivascular tissue states. After the adhesion of the leukocyte to the endotheliocytesmembrane it moves on its surface and goes to the interendothelial slot. The leukocyte forms a pseudopodium, which moves through the interendothelialslot into the underendothelial space. All contents of leukocytes move into the pseudopodium, and the leukocyte is placed in between the endothelial cells and the basal membrane of the microvessel. Then the leukocyte excretes collagenase and elastase, partly alters the basal membrane and passes through the vessel wall, and gets out of the vessel.

**Exudate kinds**

Serous exudate promotes the washing off of microorganisms and their toxins from the damaged surfaces. But the serous exudate in brain coats can squeeze the brain and violate its function. The serous infiltration of the lung alveolar septs can cause the development of acute respiratory insufficiency syndrome. The fibrinous exudate contains plenty of fibrinogen, which forms clots of fibrin in tissues. Such inflammation occurs when an organism is affected by corynebacterium diphtheria, pneumo-coccus, Friedlander's bacillus, Frencel'sdiplococcus, streptococcus, and mycobacterium of tuberculosis. Such type of inflammation occurs on mucous or serous coats more often.

The causes of purulent inflammation are staphylococcus, streptococcus, gonococcus, meningococcus, and Frenkel's diplococcus. Purulent exudate consists of many viable leukocytes and purulent bodies (perishing leukocytes), cells detritus, microorganisms, and plenty of proteins (especially globulins). The decaying inflammation develops after the invasion of decaying microflora into the purulent inflammation site. During this type of inflammation necrosis of injurious tissues progresses, the inflammation area doesn't localize, and this provokes the arrival of alien and toxic products into vessels and the development of intoxication due to which the patients usually die.

The hemorrhagic inflammation, as the form of the serous, the fibrinous, or the purulent inflammation, is characterized by the erythrocyte's impurity to the exudate (Siberian ulcer, natural small-pox, influenza). The combination forms of inflammation are characterized by the connection of one type of exudate to another. Any combinations are possible. Such forms usually develop as the result of the connection of a new infection to the lasting process. The tissue damage and the process of inflammation cause the restoration of broken structure and function (reparative regeneration).

**The inflammation proliferative phase**

The inflammation proliferative phase is simultaneously a phase of reparatory regeneration. The restoration of the structure of the damaged tissue depends on the interaction of connective tissues cells among themselves (fibroblasts, macrophages, labrocytes, lymphocytes, endotheliocytes), on the interaction of connective tissues cells with the intercellular matrix (collagen, proteoglycans, fibronectin), on the interaction of connective tissue cells with blood cells and parenchymal ones.

The process of cell proliferation is regulated by substances, which can stimulate (mitogens) or oppress (keilones) the reproduction of cells. Cambial cells are the tissues source of regeneratory material. The damage to tissues causes intensive proliferation of trunk cells. The reparative stage of inflammation begins when phagocytes actively swallow the microorganisms or the tissues detritus. At that time labrocytes activate interaction with macrophages, fibroblasts, and intercellular matrix, clotting the blood system and promoting the excretion and the synthesis of substances, which stimulate proliferative processes.

Thrombocytes produce substances, which strengthen the proliferation and the chemotaxis of fibroblasts to the injurious area: the thrombocyte factor growth of fibroblasts, the factor of epidermis and fibroblasts growth, the peptide, which activates connective tissue, etc.

The labrocytes excrete histamine and leukotriene B4, which activate fibroblasts proliferation. The neutrophiles excrete peptides, which activate the growth of fibroblasts and leukotriene, which cause the migration of fibroblasts into the injurious tissue.

The macrophages are the main cells, which regulate the reparative processes. Macrophages enclose (segregate)of the injurious tissue, and form neutrophile-macrophage, macrophages, and macrophage-fibroblasts barriers – the granulating tissue.

The macrophage-fibroblastic interaction conduces migration, proliferation, and differentiation of fibroblasts, synthesis, and secretion of collagen and other components of tissue matrix. The accumulation of fibroblasts in the inflammation site inhibits their growth and stimulates the biosynthesis of collagen. Fibroblasts' contact interaction stimulates the production of keilons.

The macrophages, lymphocytes, and neutrophils produce the intercellular matrix (collagen, fibronectin). The further stage of connective tissue growth autoregulation is characterized by collagen synthesis inhibition, the destruction of the majority of cells, and the transformation of the fibro-blasts into fibrocytes (inactive cells). The fibroblasts destroy unnecessary collagen fibers by means of their phagocytosis, or the secretion of collagenase. All of these promote the stop of connective tissue growth.

**Granulation tissue** one of the very important products of the inflammatory-reparative process is, that this is a young connective tissue with plenty of vessels. This tissue fills wounds and ulcers and skin defects; it is formed during the damage of mucous coats and internal organs, during bone fractures, hematomas organization, at necrosis and infarctions sites, and during chronic inflammation.

The functions of granulation tissue are as follows: mechanical (filling of the defect), trophic (microcirculation regulation, oxygen, and metabolites transport, filtering of substances), morphogenetic (influence on the epithelium and muscular tissue differentiation). But the main function of the granulation tissue is the protection against unfavorable influences of the external environment, against infection and intoxication, incapsulation (closing) of necrosis area and alien bodies, and also reconstruction of the anatomic and functional structure of injurious tissues. During the proliferative process activation, the cells, which are constantly stimulated by mitogens, become very sensitive to carcinogenic substances. Abnormal mitosis can lead to tumor formation.

The course of inflammatory reaction depends on the organism's reactivity, on the nervous, endocrine, and immune systems conditions. The meaning of the nervous system in the dynamics of the inflammation proves to be true in numerous cases of inflammation signs development in the patients under the influence of suggestion during hypnosis. The occurrences of hyperergic inflammation during the local action of the damaging factor at maniac excitement are often in psychiatric clinics, and at serious depressions, the inflammatory reaction proceeds very languidly. The change of nervous – impulse and nervous – trophic influences on the damaged tissue promotes the amplification of exudative processes and the violation of microcirculation.

Neuromediatorsand trophogens, activate phagocytosis and the free-radical processes. The violation of afferent innervation strengthens alteration processes and decelerates the reparation of parenchymal cells. Proliferative processes pass most actively on the periphery of the inflammation area because just there nervous fibers regenerate first and anabolic processes on the periphery proceed more actively.

Neuropeptides take an active part in the regulation of proliferative-regeneratory processes in tissues of organs, especially the opioid peptides. The stimulation of C-fibres opioid receptors by these peptides weakens the pain, reduces the release of noradrenaline from sympathetic nerve endings, the activation of labrocytes and thrombocytes stops, and the disorders of microcirculation and violation of hemostasis are eliminated.

The influence of the endocrine system on inflammation is proved by numerous clinical observations. Hyperthyroidism amplifies manifestations of inflammation and hypothyroidism is characterized by insignificant signs. Mineralocorticoids promote the development of inflammatory reactions and glucocorticoids weaken them. The ability of glucocorticoids to weaken the inflammation is constantly used in clinics because they reduce the number of tissue basophils, increase the activity of histaminase (enzyme, which destroys histamine), reduce serotonin formation, stabilize lysosome membranes and inactivate their enzymes. Glucocorticoids induce the synthesis of proteins, which block prostaglandins and leukotrienes synthesis. Mineralocorticoids are capable to strengthen the exudation, accelerating the reproduction of cells, the derivation of new capillaries, and synthesis of the connective tissue.

The inflammatory reaction in the process of phylogenesis has arisen as a protective response of the organism of hot-blood biological individuals. The organism protects itself from the influence of the pathological factor due to the limitation of the inflammatory area of the whole organism. The barrier is formed around the inflammation area; it allows various substances to flow in one direction (to the center of the inflammation site) due to blockage of lymphatic and blood vessels. The unfavorable conditions for microorganisms are created in the center of the inflammation. But in the conditions of significant tissue damage or microcirculation violations, the hard metabolism disorder in the damaged tissue or organ, hypoxia, and the common intoxication strengthening patient’s sufferings can be provoked. Inflammation is an example, which connects both the elements of injury and the elements of organism protective forces.

## Exudation and swelling

***Fluid exudate.*** In acute inflammation, the pressure in postcapillary venules may overcome the osmotic pressure of plasma proteins. Therefore fluid and low molecular substances have the tendency to penetrate into the surrounding area. The vascular permeability for proteins and some smaller molecules differs from tissue to tissue. For example, the brain and thymus vessels are less permeable. The sinusoids in the liver and sinuses in the spleen are highly open vessels even under normal conditions. The increased capillary permeability for plasma proteins is the key factor in the production of inflammatory exudate. In the interstitial area, high-molecular proteins may be split into smaller fragments that participate in the raising of the osmotic pressure of the interstitial fluid. In addition, the alteration of the general matrix is observed. It becomes more fluid which helps to make easier the diffusion of exudate. On the other hand, a sudden increase of pressure in tissue is thus prevented.

There are two phases of inflammatory infiltration. The **immediate temporary phase** with a peak between 8 and 10 min and duration about 30 min. It is developed by the release of fluid from venules mediated by histamine. This is followed by **immediate prolonged phase** which is similar, only the time of duration is greater – a few days. The second **delayed phase** needs a few hours for its development. The damage to capillaries and venules is observed.

In the fluid exudate, all components of plasma, including fibrinogen, kinins, complement, immunoglobulins, etc., are present. Fibrinogen is important for clot formation and the prevention of further loss of blood. Fibrin, which originated from fibrinogen, acts as the beginning of a scaffold on which tissues may subsequently be repaired and on which new capillaries can be constructed, a process is known as angiogenesis. Although the rapid response of the coagulation pathway is essential, the extent of blood clotting must be limited so that it does not progress to undamaged vessels. In addition, the clots must ultimately be removed from the area of damage. This is controlled by fibrinolysis (fibrin breakdown) due to the enzyme plasmin.

The kinins are important mediators of inflammatory responses. For kinin generation to proceed efficiently, the activated Hageman factor activates prekallikrein via a series of prekallikrein activators, resulting in the production of **kallikrein**. The generation of kallikrein triggers kinin production, including the formation of **bradykinin**, which is responsible for induction pain, increasing vascular permeability, and causing vasodilation.Kallikrein also activates the fibrinolytic pathway, leading to the removal of blood clots.

The **complement cascade**, as a part of the innate immune response, may be activated via the alternative and/or collectin (lectin) pathway to destroy some invading microorganisms. In addition, during activation of complement, important opsonins (C3b), chemotactic factors for neutrophils and mononuclear phagocytes (C5a), and anaphylatoxins (C5a, C3a) are formed. They all participate in inflammation during phagocytosis or immediate allergic reactions.

**Immunoglobulins** may act as specific or nonspecific opsonins facilitating thus the process of phagocytosis, or may participate in antibody-dependent cell-mediated cytotoxicity (ADCC) by which target cells are de-stroyed by killer cells.

In the fluid infiltrate, all components of plasma, including administered drugs, are present. Therefore it is important to administer effective antibiotics or other chemotherapy as soon as possible in order to reach the inflammatory area in a concentration similar to that in plasma.

Exudative infiltrate contributes to the general signs of inflammation. It is responsible for edema (swelling, tumor). The increased pressure in tissue may participate in the production of pain (dolor). Actually, the pain is observed before the occurrence of greater edema since also other factors such as the acidic pH of exudate, the accumulation of potassium ions, and the presence of bradykinin, serotonin, or other mediators take part in this process.

***Cellular exudate*** is formed during the second and the third phase of inflammation – acute and chronic cellular response. During the former, neutrophils are prevalent, whereas mononuclear cells (macrophages and lymphocytes) overcome later. Cell composition of exudate differs not only depending on the phase of inflammation but also on the type of inflamed tissue and factors triggering the inflammatory process. Central effector and regulatory functions in acute inflammation possess neutrophils. They are also dominant when a pyogenic bacterial infection or local deposition of immune complexes containing IgG are the cause of inflammation. Mononuclear phagocytes represent the main infiltrating cells in the subacute and chronic phases of the majority of inflammatory reactions, and in the case of infection with intracellularly parasitizing microorganisms as well. Eosinophils and basophils are predominant when inflammation has been initiated by immediate allergic reactions or by parasites.

**Professional phagocytes** (neutrophils, eosinophils, monocytes and tissue macrophages) are essential performing phagocytosis, lymphocytes are involved in the specific immune responses, endothelial cells in the regulation of leukocyte migration from the blood into inflamed tissue, and platelets with mast cells in the production of early-phase mediators.

The accumulation of leukocytes in inflamed tissue results from adhesive interactions between leukocytes and endothelial cells within the microcirculation. These adhesive interactions and the excessive filtration of fluid and protein that accompanies an inflammatory response are largely confined to one region of the microvasculature - postcapillary venules. The nature and magnitude of the leukocyte-endothelial cell adhesive interactions that take place within postcapillary venules are determined by a variety of factors, including expression of adhesion molecules on leukocytes and/or endothelial cells, products of leukocyte (superoxide and other ROI) and endothelial cell (nitric oxide) activation, and the physical forces generated by the movement of blood along the vessel wall. The contribution of different adhesion molecules to leukocyte rolling, adherence and emigration in venules will be discussed later.

This process is similar for granulocytes, monocytes, and lymphocytes, only different chemotactic factors, and cytokines may be involved in its initiation and control. The white blood cells leave the postcapillary venule by extending pseudopodia between opposing endothelial cells and pulling themselves into the subendothelial space and the adjacent interstitial compartment. This complex event, which is often termed leukocyte extravasation, emigration, or diapedesis, is dependent not only on an array of cellular processes including adhesion molecule expression and activation, but also on cytoskeletal reorganization, and alteration in membrane fluidity.

## Products of the complement system

Complement is a complex system containing more than 30 various glycoproteins present in serum in the form of components, factors, or other regulators and/or on the surface of different cells in the form of receptors. These are present in the blood serum in an inactive state and are activated by immune complexes (the classical pathway), carbohydrates (the lectin pathway), or by other substances, mainly of bacterial origin (the alternative pathway.

The components of the classical pathway are numbered 1 to 9 and prefixed by the letter C, e.g. C1, C2....C9. C1 is composed of three subcomponents C1q, C1r, and C1s. The early components of the alternative pathway are known as factors, and each molecule is named by a letter, for example, factor B, D, P. The lectin pathway is the same as the classical pathway, only C1q is omitted. All these pathways use in the later stages of activation of the same terminal components C5-C9 that form membrane attack complex (MAC) – C5b678(9)n. C3 also participates in all pathways.

Activation of each of the components results from a proteolytic cleavage event in a cascade mechanism that fragments the native molecule into two fragments. The fragment which participates further in the complement cascade is designated the b fragment (e.g. C3b) and is usually larger than the another a fragment (e.g. C5a) which possesses other biological activities.

Activation of the complement cascade, with the formation of the effector MAC unit, results in cytotoxic and cytolytic reactions. Target cells for MAC action may be heterologous erythrocytes, nucleated cells (autologous or foreign), bacteria (Gram-negative, susceptible to serum), microscopic fungi, viruses with a surface envelope, and virus-infected cells.

The result of cytotoxic complement reaction may be beneficial for the body (elimination of the infectious agent or damaged cells) or harmful (damage to autologous normal cells by immunopathological reactions).

Different fragments, released from individual components during complement activation, operate by a non-cytolytic mechanism through specific receptors present on various cell types. The direction and intensity of the biological response depend on the state of the receptors (affinity and density) and on the function of cells-bearing receptors.

The complement system is a potent mechanism for initiating and amplifying inflammation. This is mediated through fragments of complement components. To the most well-defined fragments belong anaphylatoxins. Anaphylatoxins are proteolytic products of the serine proteases of the complement system: C3a, C4a, and C5a. They are polypeptides containing approximately 75 amino acid residues and meet all the criteria which characterize local hormones. The C-terminal arginine in the molecule of C3a is of fundamental importance for its biological activity. As soon as arginine is removed, the biological activity disappears completely. In the case of C5a, the removal of C-terminal arginine (C5adesArg) only decreases its biological activity.

The production of anaphylatoxins follows not only from complement activation but also from activation of other enzyme systems which may directly cleave C3, C4, and C5. Such enzymes include plasmin, kallikrein, tissue, and leukocyte lysosomal enzymes, and bacterial proteases.

The anaphylatoxins have powerful effects on blood vessel walls, causing contraction of smooth muscle and an increase in vascular permeability. These effects show specific tachyphylaxis (i.e. repeated stimulation induces diminishing responses) and can be blocked by antihistamines; they are probably mediated indirectly via the release of histamine from mast cells and basophils. C5a is the most powerful, approximately 100 times more effective than C3a, and 1000 times more effective than C4a. The smooth muscle contraction in the lungs is primarily mediated by LTC4 and LTD4.

This activity decrease in the following order: C5a > histamine > acetylcholine > C3a >> C4a

C5a is extremely potent at stimulating neutrophil chemotaxis, adherence, respiratory burst generation and degranulation. C5a also stimulates neutrophils and endothelial cells to express more adhesion molecules. Ligation of the neutrophil C5a receptor is followed by mobilization of membrane arachidonic acid which is metabolized to prostaglandins and leukotrienes including LTB4, another potent chemoattractant for neutrophils and monocytes. At the same time, C3b and C4b fragments act as opsonins enhancing phagocytosis. In addition to inducing phagocytosis, ligation of complement receptors on neutrophils, monocytes and macrophages may also stimulate exocytosis of granules containing powerful proteolytic enzymes, and free radical production through the respiratory burst. The complement cascade also interacts with another triggered-enzyme cascade: coagulation, kinin generation and fibrinolysis. There is another connection between these systems: the regulatory protein, C1 inhibitor, inhibits not only C1r and C1s but also Factor XIIa of the coagulation system, kallikrein of the kinin system and plasmin of the fibrinolytic cascade. Under some circumstances, the consequences of complement activation in vivo may be deleterious rather than beneficial. The state of shock that may follow bacteraemia with Gram-negative organisms may, in part, be mediated by complement, which is extensively activated by endotoxin. The large quantities of C3a and C5a which result from this cause activation and degranulation of neutrophils, basophils and mast cells. These anaphylatoxins may stimulate intravascular neutrophil aggregation leading to clothing and deposition of emboli in the pulmonary microvasculature. At this site neutrophil products, including elastase and free radicals, may cause the condition of shock lung. This condition is characterized by interstitial pulmonary oedema due to damage to small blood vessels, exudation of neutrophils into alveoli, and arterial hypoxaemia. Tissue injury following ischaemic infarction may also cause complement activation. Abundant deposition of membrane attack complex may be readily seen in tissue following ischaemic injury. A possible pathophysiological role for complement activation following tissue ischaemia was demonstrated in experimental models of myocardial infarction: complement depletion reduced the size of tissue injury and infusion of soluble CR1 has recently been shown to have a similar effect. The activation of complement by immune complexes is normally beneficial. Immune complexes bearing C3b are efficiently removed from tissues and from the circulation by monocytes and other phagocytes. However, there are circumstances in which immune complex production continues at a high level; complement activation by immune complexes may then prove deleterious. Such complexes may form in tissues, for example in glomeruli of patients with autoantibodies to the glomerular basement membrane (Goodpasture's syndrome) or at motor end-plates in patients with autoantibodies to acetylcholine receptors (myasthenia gravis). Alternatively, immune complexes may become trapped in blood vessel walls having travelled through the circulation. This occurs, for example in systemic lupus erythematosus, and in bacterial endocarditis in which an infected heart valve provides the source of immune complexes which deposit in the kidney and other microvascular beds.

Complement mediates inflammation in these diseases by two major pathways:

1) by activated leukocytes, which are attracted to sites of immune complex deposition by locally-produced anaphylatoxins C5a and C5adesArg and which bind to C3b and C4b fixed to the immune complexes;

2) by the membrane attack complex (MAC), which causes cell lysis and thus stimulates prostaglandin synthesis from arachidonic acid, mobilized from perturbed cell membranes.

These two mechanisms of damage are well exemplified by considering two types of glomerular disease. Autoantibodies to the glomerular basement membrane cause inflammation which can be inhibited by either complement depletion or by neutrophil depletion. In contrast, membranous nephritis, (which may be induced experimentally by antibodies to subepithelial antigens), is unaffected by neutrophil depletion, but almost totally abrogated in animals deficient in C5. In this disease, the basement membrane is

presumed to act as a physical barrier to neutrophil exudation, so the heavy proteinuria is caused by the deposition of the membrane attack complex. The blood clotting system of the coagulation pathway, like the complement system, is a proteolytic cascade. Each enzyme of the pathway is present in the plasma as a zymogen, in other words in an inactive form, which on activation undergoes proteolytic cleavage to release the active factor from the precursor molecule. The coagulation pathway functions as a series of positive and negative feedback loops which control the activation process. The ultimate goal of the pathway is to produce thrombin, which can then convert soluble fibrinogen into fibrin, which forms a clot. The generation of thrombin can be divided into three phases, the intrinsic and extrinsic pathways that provide alternative routes for the generation of factor X, and the final common pathway which results in thrombin formation.Clot formation. The end result of the clotting pathway is the production of thrombin for the conversion of fibrinogen to fibrin. Fibrinogen is a dimer soluble in plasma. Exposure of fibrinogen to thrombin results in rapid proteolysis of fibrinogen and the release of fibrinopeptide A. The loss of small peptide A is not sufficient to render the resulting fibrin molecule insoluble, a process that is required for clot formation, but it tends to form complexes with adjacent fibrin and fibrinogen molecules. A second peptide, fibrinopeptide B, is then cleaved by thrombin, and the fibrin monomers formed by this second proteolytic cleavage polymerize spontaneously to form an insoluble gel. The polymerized fibrin, held together by noncovalent and electrostatic forces, is stabilized by the trans-amidating enzyme factor XIIIa, produced by the action of thrombin on factor XIII. These insoluble fibrin aggregates (clots), together with aggregated platelets (thrombi), block the damaged blood vessel and prevent further bleeding. There is an interrelationship between the coagulation pathway and other plasma enzyme systems. Contact activation of the coagulation pathway, in addition to promoting blood clotting, results in the generation of plasminogen activator activity, which is involved in fibrinolysis or clot removal. The activated Hageman factor and its peptides can also initiate the formation of kallikrein from plasma prekallikrein, and this triggers the release of bradykinin from kininogens in the plasma.

***Fibrinolysis.*** Once haemostasis is restored and the tissue is repaired, the clot or thrombus must be removed from the injured tissue. This is achieved by **fibrinolytic pathway**. The end product of this pathway is the enzyme *plasmin*, a potent proteolytic enzyme with a broad spectrum of activity. Plasmin is formed by activation of the proenzyme, *plasminogen* by either plasma or tissue activators. Tissue plasminogen activators are found in most tissues, except the liver and the placenta, where they are synthesized by endothelial cells and are found concentrated in the walls of blood vessels. The two best characterized are vascular activator (commonly known as *tissue plasminogen activator* – tPA) and *urokinase*. There is great interest in using tPA as a therapeutic agent for dissolving blood clots: the gene for tPA has now been cloned and the expressed gene product is avaible for clinical trials. Plasminogen activator is also a product of macrophages. The level of tissue activator in the plasma is normally low, but can be increased by exercise and stress. Two forms of plasminogen are present in the plasma; one has a glutamic acid at the N-terminal of the polypeptide chain, and is called native or glu-plasminogen, and the other a lysine. The latter form arise as a result of partial degradation of the parent molecule by autocleavage. Triggering of fibrinolysis occur when the plasminogen activator, plasminogen, and fibrin are all in close proximity.

***The kinin-forming system.*** The **kinins**, *bradykinin* and *lysylbradykinin*, are important mediators of inflammatory responses. They are liberated from precursor molecules, **kininogens**, by the action of various proteases, collectively known as **kininogenases**. Three types of kininogen have been identified: high- and low-molecular weight kininogen (HMWK and LMWK respectively), and T-kininogen. These molecules are synthesized by hepatocytes and are released into the plasma, where in addition to releasing kinins, they function as (1) cofactors in the coagulation pathway; (2) inhibitors of cysteine protease enzymes; and (3) part of the acute phase response. The kinins are potent vasoactive basic peptides and their properties2 are wide ranging, including the ability to increase vascular permeability, cause vasodilation, pain, and the contraction of smooth muscle, and to stimulate arachidonic acid metabolism. Three different pathways may lead to kinin formation during inflammation. As bradykinin is such a potent vasoactive peptide, its activity and its formation must be carefully controlled. Activation of the pathway is controlled internally by the presence of inhibitors for each of the active components. C1 inhibitor controls the activity of the activated Hageman factor, while $\alpha_2$-macroglobulin and C1 inhibitor act as kallikrein inhibitors. There are a variety of enzymes in plasma that control bradykinin activity, including carboxypeptidase N, which removes the C-terminal arginine residue, thus inactivating the peptide.

*Kallikrein* also act directly on the complement pathway with direct cleavage of the chemotactically active peptide C5a from the complement component C5. Cleavage of fibrinogen by plasmin results in

a number of products including fibrinopeptide B, which potentiates the action of bradykinin and has also chemotactic activity for phagocytic cells.

## Chronic inflammation

**Chronic inflammation** – an inflammation that occurs as a result of elimination and is characterized by elongated flogogenous duration (weeks to decades), the simultaneous presence of attempts to heal and re-manifestation of secondary alteration.

In turn, the difficulty arises from the elimination of flogogenous its features or to reduce reactivity. Accordingly, the distinction is made between primary and secondary chronic inflammation. Primary chronic inflammation develops as a chronic from the outset, often begins gradually.

Its reasons are:

1. Persistent infection i.e. microorganisms that are poorly eliminated, such as tuberculosis bacteria, treponema pallidum, some fungi.These microorganisms cause the development of the immune response – delayed-type hypersensitivity. Morphologically inflammation sometimes seen specifically – as granulomatous (see below).

2. Foreign bodies, that are practically not destroyed, such as particles of silica, with long-term inhalation of whom develop chronic inflammatory lung disease - silicosis.

3. Constant irritation fabric – mechanical or chemical. For example, atherosclerosis is a chronic inflammation of the arterial wall, caused, in particular, the toxic components of the plasma lipid levels. Another example might be a stomach ulcer or duodenal ulcer.

4. Development of autoimmune process leading to autoimmune diseases such as rheumatoid arthritis, lupus, etc., that is a chronic inflammation.

Secondary chronic inflammation caused by the transition of acute inflammation in chronic. This is due to lower reactivity. An example would be the transition of acute pneumonia or chronic (due to excessive tissue damage) in chronic lung abscess.

Chronic inflammation is characterized by exacerbations and remission change, generally less severe local and general manifestations than acute. During the period of remission, it can be asymptomatic. In contrast to acute inflammation, manifested severe vascular changes, exudation and neutrophil infiltration mainly in chronic inflammation of these conditions are mild. Observed persistent infiltration of mononuclear cells – macrophages, lymphocytes, plasma cells, that periodically amplified, repeated attempts to heal by replacement of damaged tissue by connective tissue, re-secondary alteration – that is product exactly of inflammatory cells, mainly macrophages.

Macrophages play a crucial role in the pathogenesis of chronic inflammation. In acute inflammation, when flogogenous eliminated, macrophages tend to disappear (or die are carried away by a current of lymph in the lymph nodes), chronic inflammation, accumulation of macrophages is supported. In this persistent accumulation of macrophages is mediated by different mechanisms, each of them dominates depending on the type of reaction:

1. The continued attraction of monocytes from the bloodstream due to persistent expression of adhesion molecules and chemotactic factors. It is quantitatively the most important source of macrophages. Chemotactic factors are C5a, chemokines, that are made by activated macrophages, lymphocytes and other cells types (eg, MCP-1), some growth factors such as platelet-derived growth factor and T-lymphocyte growth factor-β; cleavage fragments of collagen, fibronectin, fibrinopeptidy. Each of them may play a role in certain circumstances, for example, chemokines are involved in almost always delayed-type hypersensitivity.

2. Local proliferation of macrophages after their emigration from the bloodstream. If previously it was considered unusual, now known as an outstanding event in atheromatous plaques.

3. Immobilization of macrophages to the site of inflammation. Some cytokines (factor inhibitory macrophages) and oxidized lipids can cause such immobilization.

As indicated, the macrophages are responsible for re-tissue destruction in chronic inflammation. They are a source of large amounts of reactive oxygen species, lysosomal enzymes, the main source of nitric oxide, cytokines in inflammation.

In acute inflammation of the usual course of lymphocytic reaction is not expressed, it is not necessary, since this is the optimal course of inflammation, that is realized most evolutionary adaptive and protective function of this process. On the contrary, the number of lymphocytes in the inflammation is less than in the tissue is normal, although after the rapid decline in the first hours of inflammation and then gradually recovered. Lymphocyte content in the source increases, compared with the usual course of inflammation, with any unusual it flow, because they are regulatory cells in

relation to all other inflammatory cells i.e. lymphocyte response is compensatory and is aimed at restoring cellular dynamics, characteristic of the optimum flow of inflammation. It is more pronounced in the immune than nonimmune, inflammation, especially in cell-mediated immune (chronic).

Lymphocytes stimulate other cells in the focus of chronic inflammation, including macrophages and fibroblasts, and, in turn, are the opposite regulatory effect of other cells. However, because the complete or timely elimination flogogena impossible, a vicious circle of repeated attempts to heal and re-tissue destruction that occur simultaneously.

Repair of chronic inflammation occurs in the form of fibrosis – that is, in the form of deposits of connective tissue in repeated attempts to damage and heal that exist simultaneously. In a broader sense, the term "fibrosis" refers to any abnormal deposition of connective tissue, regardless of cause.

Fibrosis involved the same mechanisms as fibroplasia (scar formation). However, if they are arranged in fibroplasia, the fibrosis – no, because chronic inflammation is a persistent flogging, the development of immune and autoimmune responses, constant interaction lymphocyte-monocyte, that supports the synthesis and secretion of growth factors, fibrogenic cytokines, proteases, and other biologically active substances. As a result repair in fibrosis is excessive and distorted. For example, the degradation of collagen, collagenase, which is important in the normal remodeling in wound healing, rheumatoid arthritis causes marked joint destruction. In cirrhosis of the liver caused by chronic alcoholism or arising out of hepatitis B or C, the activation of stellate cells and collagen production. Collagen deposition in the parenchyma of the liver and changes in the structure of the sinusoids due to deposits of the components of ECM, strongly violate the structure and function of the liver, leading to cirrhosis. In chronic interstitial lung disease, pneumoconiosis – pulmonary macrophages activated by the absorption of particles of coal, asbestos, or silica, secrete cytokines and growth factors that promote fibrosis. Granulomatous inflammation is a distinctive kind of chronic inflammation, in that the predominant cell type is activated macrophage in a modified epithelial (epithelioid) form. Granuloma consists of microscopic clusters of macrophages, epithelioid cells turned into, surrounded by lymphocytes, among that plasma cells. Granulomatous inflammation is observed with a relatively small list of diseases, but common – chronic immune and infectious diseases, such as tuberculosis, sarcoidosis, Hodgkin's disease, leprosy, brucellosis, syphilis, and some fungal infections, berylliosis, etc.

There are two types of granulomas, that differ in their pathogenesis: foreign body granulomas and immune granulomas.Formation of **foreign bodys granuloma** causing relatively inert foreign bodies, such as particles of talc, thread for sewing wounds, etc. Since they do not undergo phagocytosis by macrophages, the immune response does not occur.

Epithelioid cells and giant cells of foreign bodies are attached to the surface, surrounded by foreign body and delimit.

**Immune granulomas** are formed insoluble particles that can cause a cell-mediated immune response. Macrophages absorb foreign material, process it, and display antigens corresponding to T-lymphocytes by activating them. T-cells produce cytokines such as IL-2 that activate other T-cell responses to the deployment, as well as INF-γ which is important for the conversion of macrophages into epithelioid and multinucleated giant cells. Granulomas are not static. Cytokines not only provide formation but also support the existence of granulomas. A classic example of immune granuloma is tuberculous granuloma (tuberculoma).

**Outcomes of inflammation**

The outcome of the inflammation depends on the type and flow, location, and prevalence. Possible outcomes of inflammation:

1. Almost complete restoration of the structure and function (return to normal). There is insignificant damage when there is a restoration of specific tissue elements, i.e. regeneration.

2. Scarring (return to normal with incomplete recovery). Occurs in the healing of connective tissue by replacing the (at fibroplasia) with a significant defect on the site of inflammation, inflammation in tissues that do not regenerate, and fibrinous inflammation, when not carried out complete resorption of fibrinous exudate and is its organization. The scar may not affect the function or result in impairment of function due to a) deformation of the organ or tissue (eg, cicatricial changes of heart valves) or b) removal of organs (eg, light due to the formation of adhesions in the thoracic cavity in the outcome of pleurisy).

3. The death of the body and body - with necrotizing inflammation.

4. The death of the organism at a specific localization of inflammation - such as suffocation due to the formation of films on diphtheritic laryngeal mucosa. Alarming is the localization of inflammation in vital organs.

5. Complications of the inflammatory process:

a) intake of fluid in the body cavity with the development, such as peritonitis with inflammatory processes in the abdominal cavity;

b) the formation of pus from abscesses, cellulitis, empyema, Pius (sepsis) – especially observed in pyogenic infections;

c) multiple sclerosis or cirrhosis of the body as a result of diffuse proliferation of connective tissue by proliferative inflammation.

6. The transition of acute inflammation to chronic.

In the clinical outcome of inflammation is of great importance underlying disease, if the appearance of foci of inflammation associated with it.

**Features of inflammation in its failure mechanisms**

As the leading role in the immune and inflammatory reactions are leukocytes, particularly inflammatory in any way connected with the violation of the functional state of white blood cells - a primary or secondary, hereditary or acquired. Currently, a number of known clinical manifestations of a genetic deficiency of white blood cells are caused by defects in various cell functions.

1. Violation of chemotaxis observed during the so-called failure specific granules of neutrophils, which is characterized by the absence of neutrophils in these granules and, therefore, susceptible to recurrent bacterial organism infections.

2. Violation of leukocyte adhesion. There are two known types of genetic disease leukocyte adhesion molecules - LAD (leukocyte adhesion deficiency) and LAD-2. LAD-1 is associated with failure (violation of biosynthesis) of beta-integrins (CD18), which leads to disruption of adhesion of neutrophils, spreading, phagocytosis, and generation of oxidative explosion and is characterized by recurrent bacterial infections and impaired wound healing. LAD-2 is caused by mutations in fukozil-transferase (forming part of carbs), generalized violation in exchange fucose, absence of neutrophils stabilizing oligosaccharide sialyl-lewis X-selectin ligand to endothelial (see above). It is also characterized by recurrent bacterial infections but is clinically more moderate to LAD-1.

3. Violation of phagocytosis. One of them – is Chedyaka – Higashi syndrome. It is an autosomal recessive disorder caused by disturbances in the membrane-bound protein of leukocytes, that are involved in anchoring organelle and membrane fusion, resulting in reduced leukocyte degranulation and transfer of lysosomal enzymes to phagosomes, slowing killing germs. The number of neutrophils in the blood is reduced. Neutrophils and other white blood cells contain giant granules, that can easily be identified in peripheral blood cells and that are probably the consequence of an abnormal fusion of organelles. Lytic granule secretion by cytotoxic T-lymphocytes is also impaired, which explains the severe immune deficiency in this syndrome. Due to the reduced release of lysosomal enzymes, their entry to the phagosome, melanocytes, neurons, and platelets, is characterized by increased susceptibility to infection, albinism, nerve disorders, and bleeding.

4. Violation of microbicidal activity. There is a group of disorders of killing microbes, that collectively are called chronic granulomatous disease and that patients are susceptible to recurrent bacterial infections. It is the result of inherited disorders in the genes responsible for several components of NADF oxidase, and superoxide generator.

The most common variants of this disease is an X-linked defect of one of the associates with the plasma membrane components (gp91phox) NADF oxidase and autosomal recessive disorders in the genes encoding two cytoplasmic components (p47phox and p67phox) NADF oxidase. It is also a possible hereditary defect of myeloperoxidase, that consists in the absence of the MPO-$H_2O_2$ system in leukocytes, thus, reducing the oxygen-dependent bactericidal mechanism.

As for the acquired deficiency of white blood cells function, the violation of chemotaxis observed during the thermal damage, diabetes, cancer, sepsis, these and other secondary immunodeficiencies; adhesion – after dialysis, diabetes, phagocytosis, and microbicidal activity – with leukemia, anemia, sepsis, diabetes, malnutrition.

Lysosomal protease inhibitor deficiency (antiprotease) in serum and tissue fluid, in particular, α1-antitrypsin, which is the main inhibitor of neutrophil elastase, may lead to the maintenance of leukocyte proteases, the released extracellularly. Leukocyte-dependent tissue damage underlies many acute and chronic human diseases: acute respiratory distress syndrome, transplant rejection, asthma,

glomerulonephritis, reperfusion injury, septic shock, vasculitis, arthritis, atherosclerosis, chronic lung disease, etc.

Often, especially inflammation may be associated with hereditary disorders of the complement system. The latter usually due to lack of inhibitors that control the complement system. For example, if **paroksizmal nocturnal hemoglobinuria** cells lose their ability to express the phosphatidylinositol-linked membrane proteins, including factor, accelerating the destruction of C3 - convertase, that, by C3b education plays a key role in both the classical and the alternative ways of splitting C3 (a cascade of the complement system). The disease is characterized by recurrent episodes of intravascular hemolysis, which is the result of complement-mediated lysis of erythrocytes and leads to chronic hemolytic anemia.**The syndrome of hereditary angioedema** associated with deficiency of a specific C1-inhibitor, that blocks the first step of the classical path, where C1 is associated with immune complex and is characterized by episodic edema of the skin, extremities, larynx, and mucosa of the intestine, that is triggered by emotional stress or trauma.

## The value of inflammation for the body

In general biological importance of inflammation is a protective and adaptive response that emerged during evolution as a way to preserve the whole organism at the cost of damage to part of it. It is a way of emergency, extreme (in the form of pathology) defenses applied in the case when the body is unable to cope with the harmful agent through its elimination and physiological damage occurred. Inflammation is a kind of biological and mechanical barrier, that is providing with containment and elimination of the inflammatory agent and (or) damaged tissue and its restoration or compensation of tissue defect. Biological barrier properties are achieved by adhesion, killing, and lysis of bacteria, the degradation of the damaged tissue. Mechanical barrier function is carried out by deposition of fibrin coagulation of lymph in the hearth, the blockade of blood and lymph vessels, and connective tissue cells of reproduction on the border of the damaged and normal tissue (demarcated). All this prevents the absorption and distribution of microbes, toxins, metabolic products, and decay.

The inflammatory focus has not only a barrier but also the drainage function: on the exudate from the blood into a hotbed of metabolic products out the toxins. Inflammation is one of the methods of the formation of immunity. However, the usefulness of inflammation as a protective adaptive response is absolute only in the evolutionary-biological terms, i.e. not always realized. And as a local process at a specific location and extent, and given that inflammation may be associated with common pathological manifestations, such as intoxication, abnormal reactivity of the common adaptive and compensatory reactions, that are not indifferent to stress to the body and that may be "hard" links of the disease, even in the ordinary course, it can acquire harmful value. In addition, changes in reactivity in practice are very often encountered with the current form of unusual complications and inflammation.

## Principles of antiinflammatory therapy

Traditionally, anti-inflammatory therapy is only understood as pathogenetic therapy, i.e., aimed at the mechanisms of the inflammation. Therefore, in the ordinary course, non-threatening location and extent of inflammation is sufficient causal treatment (with a bacterial inflammation – antibiotics and other chemotherapeutic agents), "help" inflammation in his fight against the harmful agent. The main question is the presence of disease entities and the underlying disease. In the unusual forms of inflammation and its complications, that threaten the localization and ubiquitous anti-inflammatory therapy is required. At the same time when sluggish during inflammation is appro-priate proinflammatory therapy aimed at sharpening process, helps to restore and protect the unity of damage in inflammation, the realization of its protective and adaptive abilities and can be viewed as anti-inflammatory therapy in the broadest sense of the word.

Since the outcome of inflammation depends on the reactivity of the organism, form, flow, location and distribution process, the following basic general principles of anti-inflammatory drugs:

1. Accounting for the main pathogenetic link inflammation. Since this link is the mediator regulation, the most effective anti-inflammatory drugs are antagonists and agonists of neurotrans-mitters. The widespread use of purchased antihistamines anticyclikoxugen drugs, inhibitors of pro-teinases, anti-oxidants.

2. Accounting reactivity. In the hyper-inflammation and hypergich, other than the local mechanisms for inflammation, are necessary measures to normalize the reactivity. This explains, for example, the effectiveness of immunomodulators in allergic inflammation - glucocorticoids, that is inherent not only the anti-inflammatory, and desensitizing effect.

3. Accounting types of inflammation. When excessive alterative, exudative-proliferative or infiltrative events than measures to normalize the reactivity of the organism, requires the use of antagonists of the neurotransmitters that mediate these phenomena.

4. Accounting for the flow of inflammation. Optimum is the usual acute during the process. In subacute inflammation of the necessary measures to prevent its chronicity. As mentioned, for the effective treatment of chronic inflammation, especially infectious, it is advisable to relapse. Along with efforts to normalize the reactivity of the organism, with prolonged inflammation may be effec-tive pro-inflammatory mediators or their agonists, the stimulation of polymorphonuclear leukocytes and, on the contrary, the antagonists of products monocyte-macrophages and lymphocytes, inhibition of these cells.

5. Accounting for the localization and prevalence of inflammation. On this depends not only need, but also the intensity of anti-inflammatory therapy.

6. Accounting forecast the outcome of inflammation. On this depends both the nature and intensity of anti-inflammatory therapy.

| The full student's name | The date | The marks | Teacher's signature |
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## PRACTICAL LESSON № 9 (11 stomat.)
## Lesson topic: FEVER

**Relevance of the topic.** As a typical pathological process, a fever accompanies many diseases. It has similar features and a unified mechanism of development for various infectious and noninfectious diseases. Knowledge of the causes, development mechanisms, clinical manifestations, and biological significance of febrile reactions is necessary for the doctor on behalf of correct performance in the symptomatic and pathogenetic treatment of diseases that are accompanied by fever. Along with the development of proper pathological phenomena in the organism during fever is activated by a number of protective and adaptive reactions, which allows its use in practical medicine in the complex therapeutic measures in such diseases as furunculosis malignant hypertension, polyarthritis, and a number of traumatic injuries of the nervous system and scar contractures of the skin. The study of fever in the experiment allows visually to trace the manifestation of feverish reaction regularities of its development and course.

**General aim** – be able to characterize fever as a typical pathological process, to explore the functional changes in the organism the main mechanisms of their development, and the principles of treatment during fever.

**For this it is necessary to be able to (specific objectives):**

1. Interpret the notion of "fever", "hyperthermia", and "pyrogenic substances."
2. Classify fever and pyrogenic substances.
3. To model fever using the pyrogenal, explain the mechanism of fever.
4. Use the measurements of body temperature, and other functional parameters for judgment about the state of the body's heat transfer during experimental fever.
5. Reveal the basic manifestations of febrile reactions to explain the mechanism of their occurrence in the dynamics of the development process.
6. Explain the difference in the pathogenesis of fever and hyperthermia.
7. Decide what conditions in the organism during fever are proper pathological, and what – protective and adaptive nature, in order to substantiate the symptomatic and pathogenetic therapy of fever.

**Required to achieve the learning basic knowledge – skills.**

**To be able to:**

Define differences poykilo- and homeothermic animals.

2. Explain how the production of heat occurs.
3. Describe the ways of heat transfer.
4. Describe thermoregulation and explain to her the types and mechanisms.
5. Interpret the changes in temperature homeostasis in normal.

### THE QUESTIONS FOR THE LESSON

1. Mechanisms thermoregulation disturbances and increasing of body temperature in fever.
2. Stages of fever. The relationship between heat production and heat emission in various stages of fever.
3. Types of temperature curves.
4. Changes in metabolism and body functions during fever.
5. Damaging and protective and adaptive value of fever.
6. The role of national scientists in the study of fever. Comparative pathology of fever.

### EXPERIMENTAL PART OF LESSON

**Experiment:** To produce fever in animals by injecting pyrogenic substances – "pyrogenal" (Pyrogenal: high molecular lipopolysaccharide received from a culture of gramme negative microorganisms).

**The object of the experiment:** Rabbits.

**Apparatus and reactives:** thermometer, medical syringes, solution of pyrogenal containing two units in 1 ml (1 unit = minimum pyrogenic dose), vaseline.

**The conduction of the experiment:** Measure the body temperature, and determine the respiratory rate and the heart rate of the rabbit. Measure the temperature in the rectum. Carefully smear the end of the thermometer with vaseline. After measuring the original values, inject 1ml solution of pyrogenal subcutaneously into the hind third of the rabbit's thigh. Measure the respiratory rate and the heart rate every 10, 20 30, and 40 minutes.

Draw the dynamic graph of temperature changes in the animal, heart rate, and respiratory rate.

Table

| Time | Temperature | Respiratory Rate |
|---|---|---|
| | | |
| | Injection 1 ml pyrogenal | |
| | | |
| | | |

**Results:**

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_____

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## THEORETICAL MATERIAL FOR PREPARATION TO LESSON FEVER

**Fever (febris)** – is the general reaction of warm-blooded animals and humans to harmful effects, often infectious, agent, developed through evolution and is a disorder of thermal regulation of the accumulation of heat in the body and fever that does not depend on fluctuations of ambient temperature.

In contrast to hypothermia, coming under the influence of increased ambient temperature and characterized by a loss in the long run the capacity for thermoregulation and fever may develop under normal conditions, and temperature control is retained (see the difference between fever and hyperthermia). Severe fever decreased stamina to changes in ambient temperature, which narrowed the limits of the regulation of heat – a little easier for a febrile body to be exposed to overheating and cooling. An increase in body temperature is possible only if the prevalence of heat production overheats. The nervous system causes the rate of change in heat balance. For example, a fever in individuals with an excitable nervous system, metabolism increases stronger than in those with a balanced nervous system. Age is also important in the manifestation of the febrile process. In infants, the ability to regulate heat balance is relatively weak. They easily come with hypothermia and hyperthermia, a violation of the chemical regulation of heat compared with adults.

Fever is characterized by an active delay of heat in the body due to displacement at a higher level of "set-point" under the influence of the thermoregulation center of pyrogenic factors. For a long time regarded as a symptom of fever of various infectious and inflammatory diseases.

However, to a true fever should be attributed not every increase in body temperature. The temperature may rise when muscle work (1–2 degrees), during menstruation, and during overheating.

Fever can occur only in those animals in which the central nervous system has achieved a high degree of development and formed thermoregulation as the process of maintaining body temperature at a constant level regardless of fluctuations in ambient temperature. A typical febrile process is observed only in higher animals homoiothermal having sufficiently stable temperature (people, dogs, guinea pigs, rabbits). Newborn babies are able to regulate body temperature immediately after birth. They are fully developed vasomotor response and secretion of sweat but lack the ability to increase thermogenesis through involuntary muscle contractions.

The increased heat production is carried out in newborns due to the amplification of oxidative processes in brown adipose tissue. In infants and young children because of the heat transfer process is enhanced by a large specific surface area of the body and under severe subcutaneous adipose tissue, so the imbalance between heat production and heat loss occurs in them more often. In infants, infectious diseases may not be accompanied by a fever, but when it occurs, it indicates the seriousness of the disease.

## Physiological Mechanisms of Temperature Regulation

### The etiology of fever

Distinguish between infectious and noninfectious fever.

**1) infectious fever** occurs the most frequently. They arise as a result of the action of bacteria, viruses, protozoa, their toxins and waste products, as well as special pyrogenic substances derived from microbes or contained in the products of bacterial origin and decay of tissue, such as pus, extracts their focus of inflammation, decaying tissues (lipopolysaccharide, nucleoproteins).

**2) Non-infectious fever**: protein, salt, from the action of pharmacological substances and bulimia:

***a) Protein fever*** is caused by parenteral administration of foreign proteins or by the action of different high endogenous protein decomposition products formed during the hemorrhage, necrosis of tissue, bone fractures, hemolysis of red blood cells, cancer, burns. This kind of fever is also called the action of toxic products of protein nature, absorbed through the intestinal mucosa as amended, with a decrease in function of the excretory organs that produce these products in the norm;

b) salt fever is caused by the introduction of hypertonic solutions of sodium chloride. Apparently, it occurs as a result of salts produced by osmotic disturbances, destructive changes and subsequent stimulation of the central nervous system due to receipt of blood pyrogen.

c) fever of action of pharmacological substances occurs after injection of epinephrine, thyroxine, cocaine, nicotine, alpha-dinistrofenola, and others, besides the activation of leukocytes, some of them are directly excited sympathicotrope and heat-regulating center, while others, such as alpha-dinitrophenol and thyroxine, are directly on tissue metabolism, causing an increase in oxidative processes and excessive heat generation;

d) neurogenic fever arises from damage and brain contusions, puncture wounds caused by the thermal, intermediate brain tumors, epilepsy, mental trauma, hemorrhages in the III ventricle, and reflex stimulation of the thermoregulatory center (renal and hepatic colic).

**The immediate cause of the fever are pyrogenic substances.**

Pyrogens enter the body and/or formed there in, stimulate the formation of true leukocyte pyrogens, which cause a reaction. They are divided into:

a*) infectious and noninfectious;*

*b) natural and artificial;*

*c) the exogenous and endogenous;*

*d) primary and secondary.*

**Pyrogenic infectious origin** are the most common cause of fever. For infectious pyrogens at-tributed lipolisaharidy, lipoteichoic acid, as well as endo- and exotoxins acting as superantigens. The most pyrogenicity have lipolisaharides (LPS). LPS is part of the membranes of bacteria, mainly Gram-negative. Of the three components of LPS – Lipid A, proteins and polysaccharides – pyrogenic effect peculiar to lipid. Microbial pyrogen is heat-labile, has no toxicity and specificity of the group. Toxicity and pathogenicity is determined by other components of microbes. Thus, highly cholera, tetanus, botulism, do not have a significant pyrogenic properties. Pyrogenic lipid A property is used in medicine for therapeutic purposes in the application of pharmacological agents "pirogenala" derived from the shells of certain bacteria. Gram-positive bacteria contain lipoteichoic acid and peptidoglycans possessing pyrogenic properties.

Multicellular endo- and exotoxins of staphylococci and streptococci act as superantigens – polyclonal activators of T-lymphocyte receptors, followed by numerous effects such activation, including release from macrophages and neutrophils of various cytokines.

**Pyrogens non-infectious origin** can also cause fever. According to the structure they are likely to be proteins, fats, nucleic acids, or less nucleoprotein, steroid substances. More or less marked febrile reaction is always observed under aseptic injury, necrosis of the organs and tissues (heart attack, lung, spleen), stroke, tumors, decay, hemolysis of red blood cells, infection inflammation, and allergic reactions.

Naturally called pyrogens, which exist in nature or are formed naturally from no pyrogenic substances. Artificial pyrogens are produced by the treatment of bacterial toxins and are used with curative intent (pyrotherapy).

Exogenous pyrogens act or are imposed from outside. With the introduction of exogenous pyro-gen parenteral fever occurs in 45–90 minutes. Endogenous pyrogens are produced in the body. These are products of primary and secondary alterations produced in the inflammation, the products that enter the bloodstream of necrosis, steroid hormones, metabolites, complexes, "antigen-antibody"; leukocytic pyrogen – products of the activity of neutrophils and macrophages. After ingestion or education in him

above infectious and/or non-infectious pyrogenic agents in the blood for 30–40 min increased the content of peptides with pyrogenic activity is a negligible dose. These substances are formed mainly in phagocytic leukocytes (granulocytes and agranulocytes: neutrophils, monocytes/macrophages, as well as in lymphocytes, although in smaller numbers in them). Thus, pyrogenic agents indirectly cause the expression of genes coding for the synthesis of cytokines. Trapped in the body or produced in him pyrogenic substances designated as primary pyrogens.

Formed in leukocyte cytokines (cytokines) called secondary or leukocytic pyrogens. Leukocytic pyrogens belong to a class of cytokines, factors of intercellular information exchange. Among a large number of cytokines, only a few are highly pyrogenic activity. Among pyrogens include IL-1, IL-6, TNF, and y-IFN.

The process of leukocyte pyrogen formation has two stages. In the first stage are activated Enzymatic mechanisms of pyrogens. This occurs within 20–30 min after exposure of leukocytes to the stimulus – the primary pyrogens. The first stage is characterized by increased oxygen consumption, metabolic activation, and increased synthetic processes in activated leukocytes.

The second stage begins with leukocyte pyrogen exocytosis 30–60 min after exposure to the stimulus. Excited granulocytes can interact with the cake for 16–19 h, and mononuclear cells – up to 35 hours of pyrogens exocytosis coincides with the increase in body temperature. Unstimulated micro-and macrophages do not contain pyrogens in the form of pre-existing and acquire the ability to synthesize them only when activated.

When inflammation of leukocyte stimulants is most often by bacteria, fungi, and viruses. Activated phagocytic leukocytes interact with pyrogens in conjunction with other active substances – cationic proteins, enzymes, prostaglandins, etc. Pyrogenic cytokines synthesized by leukocytes from the blood penetrate the blood-brain barrier and in the preoptic area, the anterior hypothalamus interacts with receptors on nerve cells' thermoregulation center. As a result, activates phospholipase A2 membrane-dependent and included a metabolic cascade of arachidonic acid. In neurons of the thermoregulation center significantly increases the activity of cyclooxygenase. The result is an increase in the concentration of PGE2 in neurons. PGE2 formation – is one of the key elements in the development of fever. This argument is the fact that preventing the synthesis of PGE2 and as a consequence – the development of febrile reactions in the suppression of cyclooxygenase nonsteroidal anti-inflammatory drugs (for example aspirin). PGE2 activates adenylate cyclase and catalyzes the formation of neurons in the cyclic 3',5'-adenosine monophosphate (cAMP). This, in turn, increases the activity of cAMP-dependent protein kinases and other enzymes. Developed in connection with this change in metabolism in neurons leads to a decrease in excitability threshold cold receptors. Thanks to a normal temperature of blood are seen as reduced: cold-sensitive impulses of neurons to the effector neurons in the posterior hypo-thalamus increase significantly. In this regard, the so-called temperature "mounting point" is shifted to the center of the thermoregulation higher level.

**Stages of fever**

I. **The stage of temperature increase (stadium incrementi),** typically brief. The temperature increase is because the heat production starts to rise, but primarily because the heat is lowered due to spasms of the cutaneous vessels, especially the extremities of the skin, and reduces sweating. These autonomic responses are associated with activation of the sympathetic nervous system. The ratio of heat production to heat transfer is increased. The gap between education and the impact of heat in the event of a rapid rise in temperature accompanied by chills - feeling cold and shivering, pallor of the skin, "gooseflesh." At the same time due to increased muscle tone and contractions of individual muscle groups thermotaxis is even stronger, and the body temperature rises. Chill explained irritation of nerve endings of the skin due to the decrease of temperature caused by a spasm of surface vessels. It creates a gap between the temperature of the internal environment and the temperature of the skin that causes a shudder reflexively.

The more developed a fever, the more pronounced the gap between physical and chemical regulation of heat, and the more pronounced chill. Heat production at the same time always dominates the heat transfer, primarily by reducing heat transfer.

There are various options for raising body temperature in the fever stage: 1) a rapid rise in temperature due to the sharp decrease in heat transfer and a small increase in heat production (influenza, lobar pneumonia), accompanied by a fever, pallor of the skin, increased blood pressure, tachycardia, and 2) a slow increase in temperature significant increase in heat production and less than in the first case, the reduction of heat transfer (pneumonia, typhoid fever).

II. **The stage of standing at a higher temperature damage (stadium fastigii)** is characterized by a steady relationship at a certain level of heat production and heat transfer, these processes balance each other, and the fever stops. The increase in heat transfer due to the expansion of peripheral (skin) blood vessels due to excitation of the parasympathetic nervous system centers and shortness of breath. Heat production compared with the first stage may remain the same, but the balance between production and release of heat set at a level higher than a healthy person. Organism retains the ability to thermoregulation, ie ability to regulate the newly established temperature. With the expansion of blood vessels followed by her pale skin erythema, skin temperature increases, shivering ceases and is replaced by a feeling of heat.

III. **The stage of temperature decrease (stadium decrementi)** is characterized by intensification of heat transfer, the predominance of its heat production, which remains somewhat elevated. Enhancing heat transfer is due to sweating and a significant expansion of peripheral vessels. The ratio of heat production to heat transfer is opposite to that observed in the first stage of fever.

Lowering the temperature can occur gradually over several days ("lytic") or very quickly within a few hours ("critical"). The critical temperature drop, especially when failure of the cardio-vascular system, is dangerous because of falling blood pressure and collapse as a result of vasodila-tation of the skin.

At various stages of febrile reaction in the heat balance may be noticeable fluctuations, explained the upcoming compensation of disturbed functions, which in turn is associated with a protective physiological role of the central nervous system. For various periods of fever is not only causative factor, but also the state of the organism, its reactivity, metabolism, and the intensity of oxidative processes.

**Pathogenesis of fever**

The constancy of body temperature in heat and provides the process heat transfer, which are regulated by the central nervous system. In the middle of the XIX century. It was shown that the most important part of the brain that have functions of the thermal center is the hypothalamus.

According to modern concepts, the main focus of thermoregulation in the preoptic area anterior hypothalamus near the bottom of the W ventricle. In this section identify several anatomically and functionally separate units:

1) *the heat-sensitive area ("thermostat"),*

*2) thermal installation area ("mounting point"),*

*3) heat production and heat-transfer centers.*

Neurons "thermostat" record temperature flowing through the brain arterial blood and receive impulses from thermoreceptors of the skin and other tissues, as well as from various parts of the central nervous system. Based on the integration of these pulses is determined by body temperature. Information is transferred in the "set point", which regulates the function of heat production and heat-transfer centers and thus supports the body temperature at a certain level. If the neurons are "set point" determined that the body temperature below the desired, they activate the center of heat production and inhibit heat transfer center, and with an increase in body temperature is a re-structuring of the reverse nature. Centers for heat production and heat dissipation, located in the preoptic area anterior hypothalamus, as well as in the posterior part of the hypothalamus, are clearly separated, but interconnected units.

Center for thermoregulation exerts influences on the processes of heat generation and heat transfer through the autonomic nervous system and endocrine glands (pituitary, adrenal glands, thyroid gland). In the excitation of the sympathetic nervous system is a spasm of cutaneous blood vessels, decreased sweating, increased inflow of blood and tissue adrenaline, noradrenaline and thyroid hormones that contribute to the formation of heat in the cells. The result is a reduction in heat transfer and heat generation increase. In the excitation of the parasympathetic nervous system increases the amount of heat transfer through increased sweating, vasodilatation of the skin and mucous membranes. In thermoregulation centers involved the spinal cord, but they are subordinated to the main hypothalamic center.

Apparatus for thermoregulation affects the cerebral cortex. It is known that fever can be invoked using suggestion. This is confirmed by data on the possibility to influence the temperature of the animals by a conditioned reflex (repeatedly combining with pyrogenic stimulus can be conditioned reflex increase in temperature). Body temperature may rise by emotional excitation (at artists, speakers, etc.).

Reactivity of the thermoregulation center may change under the action of thyroid hormones, especially pituitary gland, which is associated with the activity of the adrenal cortex. Thus, in hyperthyroidism, the reaction is enhanced, while in hypothyroidism and pituitary hypofunction – weakened. Parenteral administration of norepinephrine and epinephrine also causes fever.

**Neurotransmitters thermoregulation.** Synaptic neurons to mediate "thermostat" is serotonin and norepinephrine, acetylcholine plays a mediating role in the neurons' set-point. The last is very sensitive to the ratio of local concentration of sodium and calcium. At the same time increasing the concentration of sodium ions in the preoptic area of the hypothalamus causes a rise in body temperature and increased concentration of calcium ions – her fall. In the process of restructuring the functions of neurons "set-point" under the action of endogenous pyrogen mediator role played by prostaglandins. In maintaining body temperature at normal levels, they do not participate.

Increased body temperature can cause the introduction into the cavity of the ventricles of the brain peptide synthesized in the hypothalamus and in the intestinal mucosa - is somatostatin, neurotensin, vasoactive peptide.

**Change mechanism of the thermoregulation during fever.** Changing the heat of fever is that thermotaxis "switches" (P.N. Vesselkin) at a higher temperature level above 37 °C, higher than normal.

The essence of the mechanism of development of neurogenic fever is that under the action of endogenous pyrogenic "mounting point" in the area of the hypothalamus adjusted to a higher temperature level than normal, and perceives as normal body temperature is very low. As a result of this change in perception of "mounting point" sends impulses to the centers of the autonomic system, regulating the processes of heat generation and heat transfer. Under the action of these pulses increases thermogenesis, and heat transfer is reduced. In the future a new equilibrium is reached between heat production and heat loss at a higher level.

Increased body temperature is closely related to the excitation of the sympathetic nervous system centers, located in the posterior part of the hypothalamus, with the participation of which is an increase in heat production, vasospasm skin and mucous membranes, contributing to reduce heat transfer. Against the background of blockade of central alpha-adrenergic receptors endogenous pyrogen fever is. However, the development of fever is inhibition of the parasympathetic nervous system centers that promote the processes of heat transfer.

Effects of endogenous pyrogen in the neurons' set-point", as indicated, via prostaglandin E1 and E2 in particular. Suppression of enzyme activity prostaglandinsintetazy aspirin or paracetamol reduces body temperature during fever, but does not alter the normal body temperature. The transition to the new regime thermoregulation in the development of fever accompanied by dysfunction of the calcium pump. Was found that cooling the preoptic area of the hypothalamus increases the yield of $Ca^{2+}$ from the neurons in this area, and when heated it delayed output of nerve cells. All agents that cause fever also cause the output of $Ca^{2+}$ from neurons located here.

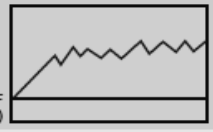
**Types of febrile reactions**

According to the degree of temperature are distinguished fever:

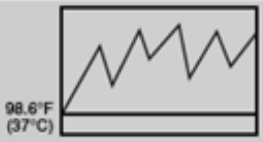
1) **subfebrile** (rise in temperature to 38 °C);
2**) moderate** (increase in temperature to 39 °C);
3) **high** (rise in temperature from 39 °C to 41 °C);
4) **an excessively high** – hyperpyretic (higher than 41 °C).

**By the nature of the temperature curves distinguish the following basic fever:**

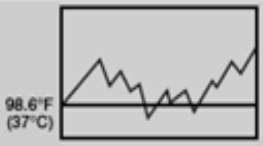
1. **Fever of constant type (febris continua)** is characterized by the fact that the temperature rose, while kept at a high level, the difference between morning and evening temperature does not exceed 1 °C. End of fever may be sudden (crisis) or gradual (lysis). This type is typhoid fever, set in the first half of the disease, fever with lobar pneumonia, typhus and other infectious diseases.

| Pattern | Description | Illustration |
|---|---|---|
| Continuous fever | Body temperature fluctuates minimally but always remains elevated<br>*Occurs with:*<br>Scarlet fever<br>Pneumococcal pneumonia |  |

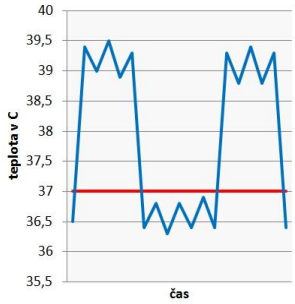
2. **Remitting fever (remittent) type (febris remittens)** is characterized by the difference between morning and evening temperatures in excess of 1 °C (1–2 °C), but reducing it to normal is not happening. These include temperature curves observed in most viral and many bacterial infections, in the second half of the course of typhoid fever, catarrhal pneumonia, tuberculosis, pleural effusion, and sepsis.

| | | |
|---|---|---|
| Remittent fever | Wide range of temperature fluctuations occur, all of which are above normal<br>*Occurs with:*<br>Influenza<br>Pneumonia<br>Endocarditis |  |

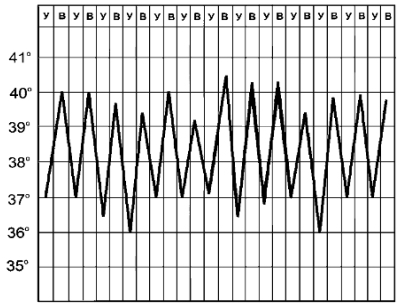
3. **Intermittent fever (intermittent) type (febris intermittens)** is characterized by regular alternation of short bouts of fever (fever paroxysm) with afebrile periods (periods apyrexia).High temperature is a few hours, then drops back to normal and below, then rises again. The duration of fever-free periods may be different. This type of temperature curve is characteristic of malaria. The individual may experience bouts of fever every third (***febris quartana***) or day 2 (**febris tertiana**), or repeated daily (***febris quotidiana***). In addition, this type is characteristic of suppurative infections, tuberculosis, juvenile rheumatoid arthritis, lymphoma, etc.

| | | |
|---|---|---|
| Intermittent fever | Body temperature alternately rises and falls and at times returns to normal or becomes subnormal<br>*Occurs with:*<br>Bacterial infections<br>Viral infections |  |

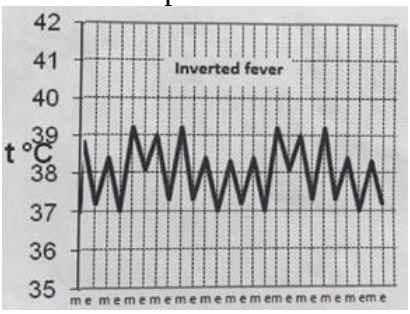
**4. Fever is the return type (febris recurrens)** is characterized by comparison with intermittiruyutsey longer periods of fever (5–8 days) between periods of normal temperature. The duration of these corresponds to the duration of febrile apyrexia attacks. This curve is typical of relapsing fever.



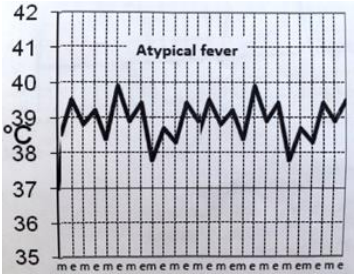

**5. Debilitating fever (depleted, hectic) (febris hectica)** lasts a long time with large daily fluctuations (3–5 °C). Characteristic of severe tuberculosis.




**6. Perverted fever (febris inversus)** is characterized by a rise in temperature in the morning and fall of the evening. It occurs in some forms of sepsis and tuberculosis.




7. **Atypical fever (febris atypical)** is characterized by several scale of temperature during the day with a complete violation of the circadian rhythm. It occurs in sepsis.Additionally, you may see a slight transient increase in body temperature not exceeding 37,5–38 ° C with the irregular fluctuations – the so-called **short-term (ephemeral)** is incorrect, with an uncertain course of fever **(febris ephemera)**, observed in various neuro-endocrine disorders, chronic infections.




**Involvement of the nervous, endocrine, immune systems in the development of fever**

The development of febrile reaction is closely related to the functional state of the cortex and subcortical centers of thermoregulation. In a classic experiment with thermal injection into the region of the gray hill proved participation in the central nervous system in temperature rises. The body temperature may increase a person under the influence of hypnosis, and mental illness, hysteria (psychogenic fever).There are cases of short-term increase in temperature from the speakers, artists, students examinees (emotional fever). In animals deprived cortex, thalamus and striatum, and retained the ability to thermotaxis fever.With deep ether anesthesia, when braking extends from the cortex to the subcortex, fever dramatically suppressed. Region of the hypothalamus considered the main automated thermoregulation center. All three groups of nuclei of the hypothalamus (anterior, middle and rear) complex involved in the occurrence of febrile reactions.

The rear and middle part of the hypothalamus part mainly regulate heat production and heat retention in the body through the sympathetic nervous system (increased metabolic oxidative processes, peripheral vasoconstriction) and somatic innervation of skeletal muscle (increase in muscle tone and muscular tremor). The front part of the hypothalamus regulates heat mainly through the parasympathetic innervation (vasodilation), cholinergic sympathetic fibers (sweating) and somatic innervation of respiratory muscles (rapid breathing).

During stimulation the anterior nuclei body temperature falls. With the destruction of their excessive temperature rise. Complete destruction of the hypothalamus or transection of the brain stem below the hypothalamus turns homoiothermal poikilothermal animals: they lose their thermoregulation and fever are not capable. Of hypothalamic thermoregulation center impulses are sent to the spinal cord. After transection of the spinal cord in the thoracic chemical thermotaxis is not broken, and the physical is lost.

It is known that under the influence of pyrogens activates the pituitary-adrenocortical system. Primary dysfunction of the endocrine glands may be affected by the nature of the febrile reaction due to the fact that endocrine disorders vary metabolism and reparative processes, the reactivity of the central nervous system, autonomic centers and the thermoregulation.

If hyperthyroidism is observed constant low-grade fever. The thyroxine increases the oxidative processes in tissues, and thermogenesis in the body increases. The deficit in the formation of prostaglandins thermostatic hypothalamic nuclei may be due to excessive concentration of glucocorticoids in the blood, neurological damage hypothalamic nerve centers with hemorrhages. Inhibition of prostaglandin production inhibits the development of febrile reactions when exposed to the body of pathogenic factors expressed even in the face of neutrophilic leukocytosis.

Change the excitability of the sympathetic-adrenal system in different ways affects the development of febrile reactions. Lack of activity of the sympathetic-adrenal system (toxic diphtheria, myxedema) is combined with the weakening of fever due to lack of production of catecholamines in the hypothalamic thermostatic centers, weak stimulation of uncontractile and contractile thermogenesis. Inhibition of development of fever does not allow the body to create effective mechanisms of nonspecific and specific defense. Increased activity of the sympathetic-adrenal system facilitates the development of fever, as noted in the overproduction of thyroxine (hyperthyroidism), hyperkateholaminemia (pheochromocytoma), taking sympathomimetic drugs. The rapid development of fever is due to stimulation of phagocytosis and the formation of pyrogens by leukocytes, enhancing education of neurotransmitters in the hypothalamic thermostatic centers, increasing mainly uncontractile thermogenesis and heat transfer limitations.

**Metabolic changes during fever**

***Metabolic diseases with fever caused by:***

1) the characteristics of the etiological factor, most infectious;
2) increase in body temperature;

3) fasting, which is usually accompanied by fever, as febrile body due to loss of appetite and digestive disorders, and consumes less assimilates food than usual.

In most cases there is increased metabolism, underlies the increased heat generation.

When fevers moderate **basal metabolic** rate may increase by 5–10 %. Oxidative processes increased somewhat mainly due to increase respiration and heart activity.

Basal metabolism is enhanced by activation of the sympathetic-adrenal and hypothalamic-pituitary-adrenal systems, release of iodine in the blood of thyroid hormones and temperature stimulation of metabolism. These processes lead to a generalized intensification and acceleration of the individual to the predominant limiting parts of metabolism. On the one hand, it provides energy and substrates for increased metabolic function of several organs and physiological systems, and on the other – improves the body temperature. In stage I, fever increase metabolic rate increases body temperature by 10–20 %. Basal metabolic rate decreases in III stage fever.

**Protein metabolism.** If fever with high fever spending a disproportionate expenditure of protein fat and carbohydrates. The strong decay of the protein leads to an increase in nitrogen excretion in the urine (negative nitrogen balance). People with mild fever part of the protein in the overall energy balance often remains within the normal range (15–20 %). In fevers with high temperature part of the protein can be 30 % or higher. In the urine increases the urea content. Especially increased breakdown of protein in infectious fevers (toxigenic collapse), such as pneumonia. The urine is increased ammonia and urea. In the strong decay of the protein are important degree of intoxication, degenerative and inflammatory changes in tissues, starvation due to reduced appetite and digestion of food deterioration.

**Carbohydrate metabolism** increased and changed, is characterized by a significant activation of glycogenolysis and glycolysis. Products of high carbohydrate decomposition are used in the activated oxidative processes. This is evidenced by regular increase of respiratory rate. However, activation of glucose oxidation combined with low energy efficiency of its. This greatly stimulates the breakdown of lipids.

There is a depletion of liver glycogen and hyperglycemia due to activation of the sympathetic nervous system and increased release of adrenaline, as well as more frequent than normal, the occurrence of alimentary glycosuria. The respiratory rate in stage I is a fever.

**Fat metabolism in fever** is characterized by a predominance of catabolic processes, particularly in the prolonged phase II. This is evidenced by reduction in respiratory rate to 0.5–0.7. Given the increased consumption of carbohydrates and advanced to the growing deficit in the body lipid oxidation is blocked at the stage of intermediate products, mainly – ketones, addition of metabolic disorders, it leads to increased acidosis. In this regard, during prolonged fevers, patients must consume a large amount of carbohydrates.

Markedly increased fat metabolism, especially with prolonged fever of infectious origin. With the depletion of carbohydrates increases fat oxidation, which often does not reach the end-products accumulate in the blood and ketone bodies (ketonemia) and acetone in the urine released (acetonuria).

**Water and electrolyte metabolism.** Water exchange is subject to considerable change. Under increased loss of fluids due to sweating and urine output.

As a result, increase metabolism and accumulation of incompletely oxidized products of metabolism in tissues is water retention, is of great importance, and renal dysfunction due to intoxication and the filter of the increase in temperature. In stage II of fever there is a delay in tissue water and chlorides, due to increased secretion of aldosterone decreased urine output. In stage III, along with a sharp increase in heat transfer and sweating is an increase of allocation of water by the kidneys, increase urine output, which is accompanied by loss of NaCI. In most cases of fever due to the collapse of the tissue increases the allocation of phosphates and potassium salts.

Exchange of electrolytes changed dynamically in the development of fever. In stages I and II in many tissues accumulate $Na+$, $Ca_2+$, Cl- and other irons. In stage III irons are excreted in large quantities due to increased diuresis and diaphoresis.

**Changes in the functions of internal organs during fever**

**The nervous system** effects are observed excitation followed by inhibition of the higher nervous activity: a headache, fatigue, apathy, fatigue, drowsiness, inhibition of conditioned reflexes. Infectious fever often accompanied by confusion, delirium, hallucinations. Children react to the rise in temperature more strongly excited than the adults. In malnourished patients with fever usually occurs with symptoms of depression of the nervous system. The autonomic nervous system function is dominated its sympathetic division.

**The cardiovascular system.** Heart rhythm quickens due to excitation of the sympathetic nervous system and direct the heated blood to the sinus node. Typically, increased body temperature by 1 °C is accompanied by an acceleration rate of 8–10 beats. In addition to heart rate, important for the assessment of cardiovascular activity has the character of the pulse wave (pulse hard, bisferious, etc.). Changes in the state of vessels associated with the disorder of physical heat regulation, such as a fever accompanied by a spasm of peripheral vessels and the rush of blood to internal organs. In II and especially in stage III fever vessels are dilated. Blood pressure in stage I may be somewhat increased by increasing the activity of the heart and stimulation of vasomotor centers in II - is normal or somewhat reduced, III, especially at the critical temperature drops - can dramatically decrease due to the fall of vascular tone (collapse).

**Breathing quickens.** Shortness of breath goes in parallel increased heart rate and raise body temperature. The function of the respiratory center also strengthened due to increased blood temperature and acidosis associated with the accumulation of incompletely oxidized products of metabolism.

**Function of the digestive system** changed: reduced secretion of digestive glands and the secretion of bile, there is dryness of the mucous membranes of the mouth and tongue, which is usually lined with white coating, developed spasms of the pylorus, inhibited gastric motility and emptying it inhibited, which causes vomiting. Reduced intestinal peristalsis, which leads to constipation with amplification processes of decay, flatulence and bloating development. For intestinal infections (dysentery, typhoid fever) is characterized by diarrhea. Formed in the intestine toxins acting on different parts of the central nervous system and peripheral tissues, help reduce blood pressure, weakening of the heart, headache, etc. The lack of digestion and absorption lead to a lack of appetite, decrease food absorption.

**Renal function** also changed, especially in infectious fevers (such as scarlet fever, septic conditions). The amount of urine at the height of fever significantly reduced. Water retained by tissues. The urine content increases nitrogenous substances, sometimes there is the appearance of protein (proteinuria) and an increase in products of protein metabolism.

**The endocrine system.** There is activation of the pituitary-adrenal cortex, with an infectious fever increases the release of thyroid hormone, which increases the basal metabolic rate. Excitation of the sympathetic nervous system in stages I and II is accompanied by fever, increased formation of adrenaline.

In fevers with high temperature sometimes observed degenerative changes predominantly in parenchymatous organs. Changes are in the nature of cloudy swelling, sometimes waxy degeneration, fatty infiltration. The phenomena of degeneration in the internal organs causing a violation of their functions, in turn affecting the course of the hectic process.

In general, at a fever function of organs and systems are changed due to effects on the primary pyrogenic agent of an infectious or noninfectious origin, fluctuations in body temperature, influence the regulatory systems of the body; involvement in the implementation of a variety of thermoregulatory responses.

## Protective value and pathological manifestations of fever

Fever is seen primarily as formed in the evolution of protective and adaptive reactions to the action of different pathogenic factors. However, like inflammation, it can provide, positive and negative effects on the body.

Fever – general thermoregulatory reaction to the impact of pyrogenic agents. This is a typical, stereotyped reaction. Each patient is accompanied by both adaptive (mostly) and, under certain conditions, pathogenic (less) effects. The leading criterion for evaluating the significance of fever is a useful criterion for achieving the body of adaptive outcome, which provides the inactivation and/or destruction of the media and pyrogenic properties usually increase the body's resistance.

The adaptive effects include fever, direct and indirect bacteriostatic and bactericidal effects, and potentiation of specific and nonspecific factors of immunobiological surveillance of non-specific activation of the stress response.

**Protective and adaptive value of fever is confirmed by the following observations:**

1) fever is an enhanced immune response due to the activation of T and B lymphocytes, the acceleration transformation of B lymphocytes into plasma cells that stimulate antibody production, and increases the formation of interferon;

2) a moderate degree of increase in body temperature can activate phagocytic cells and IR-lymphocytes;

3) activated by enzymes that suppress the reproduction of viruses;

4) slow proliferation of bacteria and decreases the stability of microorganisms to medicines;

5) increases the barrier and antitoxic liver function;

6) hepatocytes strongly produce acute-phase proteins, some of these proteins divalent cations bind necessary for the reproduction of microorganisms.

The negative impact of fever on the body is detected mainly in a pronounced and prolonged increase in body temperature. It is associated with stimulation of the heart's functions, which can lead to overload a form of heart failure. Poses a risk of collapse, and the possibility of a critical reduction in body temperature in the final stages of fever. With a high degree of fever may occur suppression of immune responses. Children with high fever may develop seizures, cerebral edema, or lability of the water-salt metabolism. A large part of the observed fever of metabolic and functional changes is a manifestation of the acute phase response, one component of which is itself a fever. A manifestation of this reaction is the development of stress, leukocytosis, synthesis in the liver of acute-phase proteins, and increased activity of the immune system. The major pathogenic role in the development of the acute phase response is secondary pyrogens – IL-2, IL-6, TNF, and interferon. Secondary pyrogens are responsible for the development of stress and other hormonal changes, for stimulating the synthesis of acute-phase proteins, the development of negative nitrogen balance, leukocytosis, and activation of phagocytes. With their activities related to anorexia, and muscle weakness.

**Pathophysiological principles of antipyretic therapy**

The main pathogenetic principle of antipyretic therapy is to reduce the "setpoint" center of thermoregulation, which is achieved by inhibition of prostaglandin E formation by cyclooxygenase inhibitors (acetylsalicylic acid, indomethacin, acetaminophen), and inhibitors of phospholipase A2.

Treatment of fever is built to meet the requirements etiotropic, pathogenetic and symptomatic principles. But it must be remembered that the increase in body temperature during fever has adaptive value, consisting of the activation of protective and compensatory adaptive reactions aimed at the destruction or weakening of the pathogenic agent. These reactions include the reaction of cellular and humoral immunity, metabolic, and plastic. Etiotropic treatment aims to eliminate and/or terminate the pyrogenic agent, inhibition of synthesis, and the effects of leukocyte pyrogen (IL-1, IL-6, TNF, Y-IFN).

**The use of fever**

Detected at a fever processes, the importance of which can be evaluated as a protective-adaptive. Thus, fever stimulates the production of antibodies, interferon, the processes of phagocytosis, hematopoiesis, and the antitoxic barrier function of the liver. It inhibits the development of certain allergic reactions. When the body temperature to 38–39 °C disrupted replication of certain viruses, bacteria and tumor cells, the influence of IL-1 on cellular and humoral immunity. Fever can lower the survival of microbes.Fever was used for the treatment of hypertension of renal origin (vasodilation, increased blood flow to the kidneys, leading to lower blood pressure).

As adaptation of the body, formed in the process of evolution, fever in cases of moderate temperature increases may be useful in the fight which caused her body to an infectious agent.

Artificial fever (pyrotherapy) is used in medicine since ancient times. Currently, medical pyrotherapy used in conjunction with other medical and non-drug influences the character. Pyrotherapy carried out by playing with fever pyrogens. Currently used for therapeutic purposes Highly drugs pyrogen – pirogenal, used to treat late-stage syphilis, osteo-articular tuberculosis.

**The main differences between fever and hyperthermia**

Fever should be distinguished from excessive hyperthermia. The mechanism of these states are different. First, when overheating is no effect of pyrogenic substances, the temperature increase is the result of external influence, limiting the heat transfer. Hyperthermia as a result of delays in the body heat is observed in the production of high ambient temperature, in hot climates, with an insulating clothing, etc. Compensation for overheating is to overcome the difficulties with regard to heat and maintain thermal homeostasis. Since the ambient temperature around 33 °C heat loss by radiation and convection practically ceases, then this process can only be performed by evaporation of sweat and moisture from the respiratory tract. However, at high ambient humidity it also becomes impossible, all the compensatory mechanisms are ineffective, and body temperature rises, but this is not a state of fever.

If fever does not occur violation, and alteration of thermoregulation. The body itself maintains a high temperature, since the "mounting point" thermoregulatory center is set to a higher level. When hyperthermia is disturbed thermoregulation. The body temperature rises in spite of the desire to maintain body temperature homeostasis. "Setpoints" thermoregulatory center does not change.

| The full student’s name | The date | The marks | Teacher’s signature |
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## PRACTICAL LESSON № 10 (12 stomat.)
## Topic: TUMORS

**Relevance of the topic.** The study of this subject introduces the student to the problem of malignant growth, which is very important. This is due to the fact of many people die from tumors. There is a tendency for a permanent increase in the incidence. This is a problem not only for clinical but also for Experimental Medicine. Spite of the long-term study of tumor growth in an experiment in with participation of representatives of various disciplines (genetics, cytology, immunology, chemistry, etc.). Many questions about the origin and development of tumors till now are not been fully investigated.

**General aim** – to introduce students to the methods of experimental reproduction of tumors with the peculiarities of tumor growth by demonstrating the different strains of experimental transplanted tumors and tumors induced by chemical carcinogens.

**For this it is necessary to be able to (specific objectives):**

1. Define the notion of "tumor growth."
2. To characterize conditions necessary for successful tumor transplantation.
3. Name the types of transplantation.
4. Self execute experimental tumor transplantation.
5. Name the cancerogenic environmental factors.
6. Explain the etiology and pathogenesis of tumor growth.
7. Explain the interrelation between of the tumor and the body.

**Required to achieve the learning basic knowledge – skills.**

**To be able to:**

1. Explain the mechanisms of cell division.
2. Determine the origin of the mutation
3. Explain the regulation of tissue growth
4. Explain the types of tissue growth
5. To characterize the biochemical processes and violations that take place during tumor growth
6. To characterize factors (chemical, physical, etc.), Which are important in the etiology of tumor growth.

### THE QUESTIONS FOR THE LESSON

1. The definition of "tumor growth."
2. Methods of experimental tumors playback. Strains of experimental tumors.
3. Morphological, biochemical and physicochemical properties of the tumor tissue.
4. The etiology of tumors. The mechanism of carcinogenesis. The role of the body in carcinogenesis.
5. The interrelation of the tumor and the body.
6. Precancerous condition.
7. The role of scientists in the development of experimental oncology.

### EXPERIMENTAL PART OF LESSON

**Experiment 1.** Transplantation of tumor – Ehrlich's adenocarcinoma.

**The object of the experiment:** white mouse

**Apparatus and reactives:** device for animal fixation, scissors, tweezers, sterile instrument, iodine, alcohol, sample of tumor tissue.

**The conduction of the experiment:** Narcosis chloroform

1. Preparation of the mouse. Fix the mouse in the abdomen down position. Cut the hairs (2 × 2,5 cm) in the upper and anterior part

2. Prepare for operation: wash hands with the brush in the running water for 5 minutes. Then keep hands in spirit and brush the finger with iodine;

3. Prepare for operation field: wash the operation part with iodine and put tissue paper.

4. Operation: cut the skin of the back with a length of 0,5 m. Make a pocket under the skin-deep of 1,5 cm with the bulbous-end probe. Take a small part of the tumor and plant it in the pocket and confront and bind skin edges and smear the skin with iodine.

**Result:**

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**Experiment 2:** Microscopic studying of ascites form of Erlich Adenocarcinoma.

**The object of the experiment:** slide from ascitec fluid of mice, microscope, emersion oil.

**The conduction of the experiment:** Microscopic samples, pay attention on the atypical cell division, dwarf cells, giant cells. Draw the preparation.

1. Polynuclear cells
2. Dwaft cells
3. Giant cells

THEORETICAL MATERIAL FOR PREPARATION TO LESSON TUMORS

In the organisms, the coordination of the cellular regeneration is made by central (nervous, endocrine, immune) and tissue systems of regulation, whose influence is put into practice by its own genes regulating the mechanism of cell division. Genes regulation leads to cell division only when the synthesis of nucleic acids, proteins, the process of doubling and disjunction of chromosomes, etc. is provided in the cell. Dysplasia is mostly related to changes in the central mechanism of regulation or in the intracellular complex. The system of genome regulation of the cell division remains intact and determines the regeneration of the normal tissue growth. The processes of this type are hyperplasia and regeneration. When the gene mechanism does not function normally the cell starts answering inadequately at central and tissue regulating influences, the feedback from effectors cell mechanisms is impaired, and cell division becomes unregulated. The process of this type is a tumor.

The processes of the growing lack and cell and tissue regeneration are called hypobiotic (hypoblastic). They are 1) atrophies; 2) dystrophies and degenerations.

The processes of excess growth and cell, tissue and organ regeneration are called hyperbolic (hyperblastic). They are 1) hypertrophy and hyperplasia; 2) pathological regeneration; 3) tumors.

**Hypobiotic processes**

**Atrophy** (Greek tropheo – nourish) – decrease of the volume of the cells because of the lack of nourishment or metabolic disorder. By the mechanism of development they can be distinguished:

1. Atrophy of disuse (dysfunctional). If the chorda of the skeletal muscles is cut and shorn of one of the points of reattachment as a result there will be decreasemeant in the volume because of the impossibility of its clonus.
2. Atrophy of the denervation of organs (neurotic atrophy). Nerves influence tissues the next way: a) regulate blood supply through vasculomotor nerves; b) influence trophycally activating metabolism; c) arose activation of functioning (clonus, secretion, etc.) In denervated organs or tissue, the metabolism is inhibited and the volume decreases.
3. Atrophy as a consequence of enduring prelum of organ or tissue interrupts normal nourishment and metabolism. The tumor putting pressure on the bone can arose its thinning and further destruction. Along with the blockage of the ureter, the urine is accumulated in it and in the kidney pelvis, leading to the atrophy of the tissues of the kidney (hydronephrosis).

**Cell degeneration.** Different pathologic processes are accompanied by the inhibited metabolism in the cells which is called dystrophy (degeneration, devolution). Protein, fatty lipidic and carbohydrate dystrophies are distinguished.

**Hyperbiotic processes**

**Hypertrophy** – is an excess tissue growth beyond its normal volume. It happens through the enlargement of separate cells (hypertrophy itself) or their quantity. They can be distinguished: physiological hypertrophy (hyperplasia), progressing in physiological conditions (enlargement of the mass of skeletal muscles during physical work, of the metra during the pregnancy, of the breast during lactation) and pathological hypertrophy (hyperplasia), progressing in pathological conditions; genuine (equal enlargement of all the composites of the organ, including specific parenchymal elements; the function of the organ rises) and false (enlargement of the organ because of the stroma – connecting tissue; parenchyma is usually atrophied, the function of the organ is decreased). Also, distinguish:

1. **Work hypertrophy** (hypertrophy of skeletal muscles and the muscles of the heart of sportsmen, of the breast during lactation, of the unstriated muscles of the metra during pregnancy). It usually combines with the hyperplasia of the cells.
2. **Vicarious (compensatory) hypertrophy** – enlargement of the volume of the remaining organ after the amputation of one of the paired organ (kidneys, lungs, atrabiliary capsules and others).
3. **Restoratory hypertrophy** – enlargement of the rest of the organ after the amputation of the part of it.
4. **Compensatory hypertrophy** – enlargement of the organ after the amputation of one of the functionally related organs (enlargement of the hypophysis after the amputation of the thyroid body).

**Regeneration** is the tissue growth, aroused in the organism by the lesion or destruction of tissue and, as a consequence, its full or partial recovery. Vertebrate animals have the processes of regeneration less apparent compared with invertebrate animals.

There is physiological, reparative, and pathological regeneration. **The first one** – is the process of continuing cell repair, dying in normal conditions (hair, epidermis, gland cells, blood cells); **the second one** – distinguishes the processes of organs and tissue regeneration after they were damaged, **the third one** – excessive or perverse regeneration.

***The process of regeneration is caused by the number of factors:***

1. The stimulation pulse for regeneration – is damaged. It is the products of damaged tissue (proteases, polypeptides, and low molecular weight proteins) that fulfill the function of stimulators of cell division.
2. The most important factor of healing and regeneration – are white blood cells (monocytes-macrophages).
3. The condition of body nourishment and its regulating systems influence regeneration. During the famine, the regeneration is very hypersthenic. The vitamins have got vital importance, especially vitamins C and A.
4. With an increase in age the regenerating possibility of all tissues decreases.
5. Endocrine glands are important. Mineralocorticoids stimulate and glucocorticoids inhibit regeneration.
6. The nervous system has got important as a stimulator of regeneration. Experimental damage of the cortex and destruction of the ventromedial hypothalamic nucleus suspend the process of wound healing and of engraftment.

## Tumor Growth

The problem of tumor growth (tumorigenesis)-is one of the most serious, facing the mankind. Cancerous growths as a reason of death are at the second place (20 % of the total mortality) after cardiovascular diseases.

***Tumor growth – is a typical pathological process based on the measureless, uncontrolled growth of the cells with the processes of proliferation predominating on the appearances of normal cell differentiation.***

The neoplastic process occurs under the influence of multiple endogenous and exogenous oncogenes (blastogenic) factors, which exercise their effects through the genetic apparatus of cells. During the multiplication of cells, the risk of somatic mutations and the appearance of tumor cells rises sharply so that tumor growth is likely to be a kind of "a price paid for multicellularity". The neoplastic process is widely distributed in various organs and tissues of living beings at all levels of evolution, regardless of age, sex, and constitution.

***It should be noted that unlike the above-mentioned types of tissue growth from tumor one is that:***

1) they arise as a reaction to tissue injury, changes in its functions and constitution;
2) tissue growth stops as soon as the stimulus ceases to act;
3) emerging cells, differentiating, acquire the qualities of the cells of the tissue from which they originated;
4) The newly formed tissue continues to be associated with the surrounding tissues and is subject to the regulatory influence of the body.

**Tumor (blastomatous, neoplastic) growth** – is a special kind of abnormal tissue growth that arises from the transformation of normal tissue in the tumor and is characterized by atypical structure and function, relative autonomy (lack of proper regulation of the growth), infinite growth, and progressive development. Distinguish benign and malignant tumors.

**Atypicality of tumors** is the atypicality of the tumor tissue – is the change in the structure and function of tumor cells compared with the tissue from which a tumor began. At the bottom of the Atypicality is anaplasia (cataplasia) – lowering of the tissue differentiation, as its reverse development and return to an embryonic state (dedifferentiation).

***The following types of anaplasia are distinguished:***

**1. Structural** – is reflected in the fact that the parenchyma of the tumor can be of different sizes (giant and dwarf cells) and forms of the cellular elements, increase in the number of chromosomes, appearances of hyperchromatism, an increase of centrosomes and Golgi apparatus, the discrepancy between weight and mass of protoplasm and mass of an increased nucleus rich in chromatin, large nucleolus, a decrease in the number of mitochondria and changes in their structure, atypical mitoses. The cytoskeleton of tumor cells and their microtubules undergo significant changes. In cancer cells, the number of intercellular contacts is greatly reduced, which facilitates metastasis. Contact inhibition

of cell growth disappears. Tumor bottles do not contain contractile elements, and the size of their lumen is not regulated by the body. The proliferation of endothelial cells is far behind the proliferation of cancer cells, so during the growth of the tumor, the capillary network is reduced, especially in the center, which becomes necrotic. The tissue of tumors in most cases is not innervated. The nerve endings are located in the stroma, but even here the innervation is insufficient.

In addition, morphological changes combine with the functional ones (functional anaplasia) (eg, synthesis of bile pigments stops in hepatoma).

**2. Biochemical anaplasia.** Tumors are able to synthesize and secrete embryonic proteins along with the usual adult proteins (alpha-fetoprotein in hepatomas, cancer embryonic antigen, etc.) that serve as markers of malignancy. In tumors there are also found fetal isoforms of some enzymes (pyruvate kinase, aldolase, thymidine kinase), there is an active gamma-glutamyl, the amount of DNA-polymerase 3 decreases, and the number of DNA-polymerase 2 increases. As a rule, the production of enzymes and proteins that allow cells to perform specialized functions, and activate enzymes that provide cellular division is repressed, and there is an increased ability to absorb amino acids from the environment. Some tumors synthesize and secrete ectopic hormones that are not

characteristic of normal tissues (squamous cell lung cancer - parathyroid hormone, and small cell cancer - corticotrophin, kidney cancer - erythropoietin, or thyroxin).

**Carbohydrate metabolism.** Was found a significant ability of energy metabolism of malignant cells - anaerobic glycolysis, the intensity of which is 10-15 times greater than that of homologous cells by particularly powerful enzymatic apparatus and increased glucose transport.

In tumor tissue, the activity of key glycolytic enzymes is also increased - Hexa, fosfo- frukto- and pyruvate- kinase. There is aerobic glycolysis observed, i.e., breakdown of carbohydrates to pyruvate and its conversion into lactic acid in the presence of oxygen, whereas in normal tissues in the presence of oxygen, this decay is slowed down and the rate of glycolysis is reduced. Accumulating oxidized metabolic products (lactic acid) lead to acidosis.

The tumor rapidly captures glucose from the blood. Due to a sharp catch rate of supply of glucose to the tumor from the body the glycolytic rate of its splitting up of lactic acid in malignant tumors is maintained close to zero, which causes significant changes in homeostasis.

A decrease in tissue respiration is proportional to the degree of dedifferentiation of cells. This is accompanied by the inhibition of the oxidation of glucose load.

**Lipid metabolism.** In tumors synthesis of fatty acids and acetoacetate is attenuated. The basic amount of lipids it needs it gets from the body in the form of low-density lipoproteins and free fatty acids in a complex with albumin. In tumors, fatty infiltration and increasing content of unsaturated fatty acids increased cholesterol and decreased phospholipids and reduced activity of lipases are observed.

**Nitrogen metabolism.** Processes that use the synthesis of proteins and nucleic acids in tumors predominate over the processes of their decay. The synthesis of proteins of the mitotic apparatus in cells grow, and the ability to re- and deamination acids are reduced. There is an especially great need for a tumor in glutamine and asparagine, which do not synthesize and gets from the body. For the synthesis of nucleic acids, the tumor also needs to receive from the body thymidine and uridine. A tumor synthesizes polyamines. All this allows us to consider the tumor as a "trap for nitrogen".

**3. Physico-chemical anaplasia.** Tumor tissue is characterized by an increase in water content, lactic acid, acidity, content of potassium and sodium ions, the swelling of colloids, reducing the amount of calcium and magnesium, changes in colloidal properties of the cytoplasm (increase dispersion of colloids, decreasing their surface tension). The osmotic concentration of the internal environment, the electrical conductivity are Increased, negative charge of tumor cells is increased, which is close to the charge of lymphocytes.

**4. Antigenic anaplasia.** Changes in the tumor antigens are parallel to the disruption of differentiation of tumor cells. Antigenic differences in tumor and normal cells are expressed in the increasing content of ones (antigenic "complication") and a sharp decrease in others (antigenic "simplification") antigens. In tumors, the synthesis of biospecific antigens is resumed and the synthesis geteroantigens is increased. In the process of neoplastic transformation of cells, the synthesis of some normal antigens that are characteristic of the initial normal tissues is reduced – species-and organ-antigens as well as isoantigens. The reduction in organ-antigens is emphasized, as they attributed a crucial role in vital processes of cells of differentiated tissues, especially because it is accompanied by a complete or almost complete loss of the tumor cells of specialized functions. Their degree is expressed more into malignant tumors.

Tumor growth is possible only as a result of its cells escaping from immunological surveillance, due to:

antigenic simplification (loss of antigens characteristic of normal tissue);

a. appearance of fetal antigens, to which there is immunological tolerance;

b. masking of antigens (cells of chorionepithelioma have a neutral polysaccharide capsule);

c. presence of antigenic determinants, stimulating T-suppressors, which leads to inhibition of immune responses;

d. suppression of the immune system (immunosuppression).

**Autonomy of the tumor.** Compared with other types of tissue growth, tumors are characterized by autonomous growth. The intractability of tumor cells is greater and, consequently, the tumor grows faster than its less differentiated cellular elements. However, the autonomy of the tumor is, of course, relative.

**Infinity tumor growth.** Tumors characterize by the infinite relative growth, i.e. potential ability to grow without apparent limit. In malignant tumors the body disappears before the tumor reaches a large size. Infinite growth is based on the fact that out-of-normal control of neurohumoral and genetic regulation, tumor cells do not respect the principle of contact inhibition and limit of cell division of Hayflick.

**Tumor progression** Tumor development occurs continuously through qualitatively different irreversible stages, that manifest in the genetic changes in one or more features (growth rate, invasiveness, anaplasia, and metastasis) in the direction of increasing its aggressiveness. One of the first phases of progression is considered benign. However, the facts of malignancy of normal cells at once are known (in the colon). Signs of malignancy arise and are amplified independently of one another, giving rise to a variety of combinations and infinite variability of phenotypes of tumors. This is the fundamental difference between tumor and normal progression of differentiation of tissue. Distinguish the primary sign inherent in any tumors - uncontrolled growth. Properties that characterize the malignant tissue should be considered secondary, arising in the course of progression. Among these properties distinguish mandatory, without which there is no cancer: invasive and destructive growth, systemic effects on the body, and metastasis formation (a feature of malignancy).

It is now recognized the monoclonal origin of the vast majority of tumors, focus consists of the descendants of a single transformed cell (tumor growth "of itself", i.e. without the involvement normal neighboring cells). This cell produces a clone of cells like themselves with the same phenotype. However, due to increased genetic variability of the transformed cells at a certain point of one clone, there are several clones that differ in their phenotype (population of heterogeneity of the tumor). This polyclone population becomes the object of the current in the internal environment of the organism of directed natural selection that favors the most rapidly proliferating, resistant to the immune defenses of the body, aggressive clones, i.e. the transition to malignancy.

**Benign and malignant tumors. Biological characteristics of tumor growth**

| Benign tumors: | Malignant tumors |
|---|---|
| Slower growth | Faster growth |
| Expansive growth (the exception – some of the fibroids and angioma). | Infiltrative growth. |
| The absence or minimal destruction of tumor tissue and surrounding normal tissue. | Severe destruction of the tumor tissue |
| Does not form metastases (exception – some thyroid adenoma, chondroma). | Forms metastases. |
| Very rarely forms relapse. | Often forms a relapse. |
| It does not cause cachexia | Causes cachexia |
| Biological irregularities are less pronounced. | Biological irregularities are pronounced |

Cells from benign tumors are morphologically identical or similar to normal progenitor cells and form characteristic high-differentiated for this tissue structure. Such tumors grow slowly and do not metastasize.

Cells from malignant tumors are morphologically different from the normal progenitor cells, grow rapidly; and individual cells form metastasis. From the clinical and prognostic point of view, the tumor is regarded as malignant.

**The following types of malignant tumors:**

*Carcinoma* – malignant tumor derived from epithelium,

*Adenocarcinoma* – malignant tumor derived from epithelium and having a glandular component

*Sarcoma* – malignant tumor originating from the tissues of mesenchymal origin connective, bone, cartilage).

**Expansive and infiltrative growth**

Some tumors grow more or less in isolation, separated from the surrounding tissue capsule from which the tumor penetrated only the nerves and blood vessels feeding it. This type of growth – an expansive growth – characterizes tumors, less atypical in structure, with less severe anaplasia with cells, with less potency of growth and reproduction. With respect to respiratory function, it is the type of growth characterized by blastomatosic anaerobioses.

Tumors with expansive growth do not grow into the surrounding tissue, and only push them, which often disturbs the function of compressing the tissue. For those tumors, the slow growth is characterized, sometimes by long pauses. The tissue of these tumors is more likely to retain the specific properties of the tissue elements, in which it occurred.

Another type of growth - is infiltrative (invasive). With this growth, the tumor increases into the surrounding tissue, and the boundary between tumor and normal tissue is unclear. Such a tumor can grow well in the lumen of the blood or lymph vessels through which cells of automatic tissue can be transferred to more distant places, giving rise to new tumor growth (tumor metastasis). Because of infiltrating growth characteristic of malignant tumors, complete excision or husking them in most cases is impossible in the tissues may be part of the tumor, which after some time, can to give the new growth. Infiltrative growth, giving a relapse and metaphase, the cellular elements of anaplasia characterized predominantly tumors with more malignant tumors of the same course with expansive growth, usually do not give metastases and recurrences are more benign. However, the clinical course is often impossible to distinguish sharply the two types of tumors can often be seen that the benign tumors (such as the brain) lead to death and that the infiltrative growth does not always determine the malignancy within the tumor (angioma). There is also a so-called transition from benign tumors (eg, certain types of angiomas) to the acquisition of malignant characteristics typical of malignant growth.

**Metastasis, its mechanisms**

Metastasis – one of the manifestations of fatal irregularities of tumor growth – moving cells at a distance from the main (parent) node and the development of tumors of the same biological structure to other tissue or organ.

**Ways of metastasis:**

*1. Lymphogenic* (with a current of lymph through the lymph vessels). This is the most common way of metastatic tumors, especially carcinomas. Even with a small amount of tumor, it is possible to transfer some of its cells to the lymphatic vessels and fix them in regional lymph nodes.

2. *Gematogenic* (with the blood flow through blood vessels). The cells of sarcomas metastasize mostly in this way.

3. *Tissue or implantation.* Metastasis in this way is carried out in contact of tumor cells with the surface of normal tissue or organ (eg, in contact of gastric cancer with the surface of the peritoneum or with pleura); implantation of blastic cells in body fluids such as a peritoneal, pleural cavity, the cerebrospinal fluid, spinal cord, and brain.

Often, tumors metastasize to multiple paths simultaneously or sequentially.

**Stages of lymph and Hematogenous metastasis are the following:**

Malignant tumors are extremally heterogeneous in their population structure, particularly in their metastatic potential. In the first stage of metastasizing the separate cells, processing such potential is torn off the primary tumor node, which is facilitated by characteristics of a transformed state of decreased adhesion, and increased mobility. These cells are attached to the basal membrane through receptors processing affinity to glycoproteins and collagen IV. By the production of hydrolytic enzymes (proteinases, collagenases, glycosidases) tumor cells pass through the basal membrane and endothelial cells and penetrate the blood and lymph vessels. With the help of hydrolytic enzymes, they penetrate from the vessels into the organs and proliferate with the formation of metastases, if the vascularised stroma grows into the new node. Many tumor cells have the tendency to the primary metastasizing into the definite tissues (adenocarcinoma of mammary gland metastases into bone and brain, and neuroblastoma into liver and adrenals).

Metaphases are characterized by organ selectivity of metastasis (tropism). Because cancer cells often metastasize to the bones, liver, and brain; stomach cancer – in the ovaries, tissues, and bottom of the pelvis; breast cancer – in the bones, lungs, and liver. Such factors determine the affinity of metastasis: the specifics of metabolism in the body, especially of lymph and blood supply, low efficiency of the mechanisms of antiblastomic resistance, and positive chemotaxis.

The assumption of the role of the nervous system in tumor metastasis says the need for its implementation of a secretive period, which is a characteristic feature of all neurodegenerative processes. The value of the nervous system in tumor metastasis is confirmed by the fact that the traumatic impact on it with bandages of the nerves or their irritation with chemicals can change the direction of metastasis.

## Experimental reproduction of the tumor

*Methods of experimental modelling of cancer are:*

**1. Induction of tumors.**

Chemical factors. In 1775, London surgeon, P. Pott described the professional malignancy-skin cancer of the scrotum in chimney sweeps. In 1915–1916 Japanese scientists Ishikawa and Yamagiwa for the first time were able to cause skin cancer in rabbits for 6 months lubricating the skin with coal tar. Later carcinogenic substances were obtained in pure form; carcinogenicity of substances belonging to different chemical compounds was established.

**Viruses.** In 1908, Ellerman and Bow for the first time caused leukemia in chickens by cell-free filtrate of their leukemic white blood cells, which they obtained by passing minced tumor tissue extract through porcelain filters.

In 1910, Rouse with cell-free filtrate from chicken sarcoma caused the development of sarcoma in healthy chickens. So for the first time, the proof of the evidence of viral leukemia and tumors was obtained. The milk factory was opened by Bittner (1936). There are lines of mice with a high incidence of breast cancer (high cancer) and low (low cancer). However, if the newborn babies until the first feeding are picked up from a female of high cancer line, and are given to be fed by the female of low cancer lines, the frequency of occurrence of cancer among them will be greatly reduced, and conversely, when a female of high cancer line feeds mice of low cancer line, the frequency of tumor is significantly increased. Bittner showed that in the milk of high cancer mice there is a factor causing breast cancer in offspring.

**Physical factors.** The tumor is produced by ionizing radiation, including X-rays, radioactive isotopes, as well as ultraviolet rays.

**2. Explantation of the tumor** – growing a tumor in the culture of tissue outside the body. Tissue culture-derived directly from an animal or human tumor called primary. In addition, in the laboratories, there is a large number of constantly passing strains of tumor cells, whose properties are well understood. Tissue culture makes it possible to induce tumors outside the body by chemical carcinogens and oncogenic viruses. This method allows us to study the induction of tumors and the role of tumor viruses in human tissues.

**3. Transplantation of the tumor.** For the first time scientists, Novinsky M A successfully transplanted tumors of adult dogs to puppies. This experience was the beginning of experimental oncology. There are strains of passing tumors with well-studied properties: Ehrlich ascites carcinoma in mice, chicken Rous sarcoma, rat sarcoma Jensen, and rabbit carcinoma of the Brown-Pearce.

**Types of Transplantation:**

A) Autochthonous – from one location to another location within the same organism;

B) Syngenic – from one animal to another within the same clean lines;

C) Allogenic – different lines of animals within a villa,

D) Xenogenic – transplantation of the tumor from one species to another.

The reason for successful transplantation of allogeneic tumors is an antigenic simplification of tumors as they are malignant, the masking of antigens in tumors, as well as immunosuppressive effect. The introduction of a small number (400 000) of tumor cells causes inhibition of the immune system.

## The etiology of tumor

Causes of tumors are the factors that cause the transformation of a normal cell into a tumor. They are called carcinogens (blastogenic). Carcinogens are capable of: a) directly or indirectly affecting the cell's genome, leading to mutations (mutagenicity) and b) penetrating through the outer and inner barriers, and c) causing little damage to cells, which allows them to survive; d) create conditions for the manifestation of some carcinogenic factors and unfavorable for others (organotropic) e) inhibit tissue respiration and the immune response, f) enhance tumor formation by the action of some carcinogens (in cancerogenesis); sometimes factors that are not carcinogens, can exacerbate the effects of carcinogens – cancerogenesis.

**The nature of carcinogens are divided into 3 groups:**

1) The matter of local action exerts its effects at the site of application (polycyclic aromatic hydrocarbons cause sarcomas at the site of subcutaneous or intramuscular injection or skin cancer in its flushing);

2) The substance of the remote organotypic action that induces tumors in certain organs and tissues, rather than in place of the primary administration (beta-naphthylamine, etc.) (organotropic of cancerogenic explain the formation of active substances from less active precursors in the affected body);

3) Multiple actions substances, causing a variety of tumors in organs and tissues from the same animal. Distinguish carcinogenic chemicals, physical and biological (mainly viruses).

**Chemical carcinogens**

According to WHO, more than 75 % of human malignant tumors are caused by exposure to chemical environmental factors. The appearance of tumors produces factors mainly of combustion of tobacco (40 %), chemical agents included in the meal (25–30 %), and compounds used in various fields of production (about 10 %). More than 1,500 known chemical compounds are carcinogenic. Of these, at least 20 definitely cause cancer in humans. For example, they include 2-naphthylamine, benzidine, 2-aminotiofenil causing bladder cancer in workers painting and rubber industry, the component of synthesis of polyvinyl chloride, which induces liver tumors, bis (chloromethyl) ether, leading to cancer bronchial tubes and lungs. Therefore they are called procarcinogens, or precancerous. In the body, they are exposed to physical and chemical reactions as a result of which they become the genuine, final, carcinogens. It is believed that the ultimate carcinogens are alkylating compounds, free radical forms of substances range. Apparently, they cause such changes in the genome of normal cells that lead to their transformation into a tumor one. There are two interrelated stages of chemical carcinogenesis: initiation and promotion. At the stage of initiation, there is an interaction of the end carcinogen with DNA loci that contain genes that control cell division and maturation of cells (such loci are often called proto-oncogenes). There are two possibilities of interaction: genomic and epigenomic.

The genomic mechanism is the protooncogene point mutation. An epigenomic mechanism is characterized by the derepression of the inactive proto-oncogene. Under the action of chemical carcinogens, the protooncogene is converted into an oncogene, which provides in the subsequent process of malignant transformation of cells. Although such a cell does not have a tumor phenotype (called latent tumor cell), the initiation process has become irreversible. The initiated cell becomes immortal (immortal, from the English. Immortality – eternity, immortality). It loses the so-called Hayflick limit: a strictly limited number of divisions (in the culture of mammalian cells there are usually about 50 of them). Various carcinogenic agents induce the process of promotion, as well as cellular growth factors. At the stage of promotion: there is the expression of an oncogene, there is an unbounded proliferation of cells, which became genotypically and phenotypically tumoral, and the tumor is formed.

**The classification of chemical carcinogens**

**Chemical carcinogens** - are substances which may cause the development of malignant tumors.

I. By origin may be distinguished natural and man-made carcinogens.

II. By chemical structure the carcinogens may be distinguished as:
   a) polycyclic aromatic hydrocarbons (PAHs);
   b) aromatic amines;
   c) nitro compounds;
   d) mycotoxins;
   e) aminoazo compounds;
   f) simple compounds.

III. In relation to the body chemical carcinogens may be exogenous and endogenous.

IV. On the mechanism of the carcinogenic effect distinguish carcinogens of direct and indirect action.

The **carcinogens of natural origin** are the waste products of certain fungi (mycotoxins) and products of volcanic activity.

The sources of **man-made carcinogens** are:

1) industrial emissions;
2) vehicle exhaust;
3) tobacco smoke;
4) products of improper food cooking (using refried fat, the violation of technology of smoking).

**Exogenous carcinogens are divided into:**

***1. Organic:***

a) polycyclic aromatic hydrocarbons (PAHs):
b) 5,10-dimethyl-1,2-benzanthracene;

c) 9,10-dimethyl-1,2-benzanthracene (DMBA);
d) 3,4-benzipren;
e) 1,2,5,6-dibenzanthracene (DBA);
f) 20 metilhlorantren (synthesized by treatment of bile acids).

a) Established the widest dissemination of PAHs in the environment, which are formed not only by human activity (being a product of incomplete combustion, they are contained in the smoke and tar of tobacco, in fried oil, the exhaust gases, in smoked products, in the bitumen, in the asphalt), but are also natural carcinogens – they are contained in the soil, oil, emissions of volcanoes. Aminoazo connections (usually cause hepatomas, and sometimes – adenoma of the lungs and thyroid epithelioma): dimetilaminoazobenzol (DAB);

b) orto-aminoazotoluol;

1) aromatic amines:
   a) beta-naphthylamine and benzidine (bladder cancer);
   b) 2 atsetilaminofluoren (tumors of the liver, breast, digestive system, etc.).
2) nitrosamines:
   a) dimethyl-and dietilnitrozamin (tumors of the liver, esophagus and stomach);
   b) methyl- and trimetilnitrozo urea (brain and peripheral nervous system, liver, kidney, lung tumors).

The particular interest in this class of compounds is detected due to the possibility of its endogenous synthesis in the body of nitrites (nitrates) and secondary amines in food. Secondary amines can also be formed in the colon, with the participation of the bacterial flora, which at the same time is able to convert nitrate to nitrite.

3) Other compounds:
a) mustard gas and its nitrogen analogues (lung tumors and others);
b) urethane (adenomas of the lungs and hepatoma);
c) carbon tetrachloride (liver tumors).

2. Inorganic:
1) Arsenic and its compounds (cancer of the skin, lungs, etc.);
2) beryllium oxide (osteosarcoma);
3) chromates (lung cancer, osteosarcoma);
4) cobalt (sarcoma);
5) nickel (osteosarcoma).

Endogenous chemical carcinogens include:

1) estrogens (tumors of the breast, uterus, kidney, etc.):
   a) natural - estrone, estradiol;
   b) synthetic – hexestrol, diethylstilbestrol.

Estrogens may cause a tumor due to the fact that: a) the frustrating of tyrosine exchange, cause the accumulation of the intermediate product of its metabolism – parafeniloksimolochnoy acid (p-HEB), which has strong carcinogenic properties; b) they cause chronic tissue proliferation.

2)deoxy cholic acid (a weak blastomogenic effect when injected subcutaneously);

3)cholesterol and its derivatives:

a) cholesterol dienes and hydroxy derivatives (adenomas lung, leukemia, hepatoma and skin cancer in mice);

b) lipin carcinomas (tumors in rats and mice).

4)benzene extracts of liver, bile, lung tissue of people who died from cancer – cause tumors in mice at 50 %, while similar extracts of deaths from other diseases – 2–4 times less.

5)tryptophan metabolites (3-oksiantranilovaya acid, 3-oksikinurenin) – a bladder tumor;

6)metabolites of tyrosine (p-HEB). p-HEB is detected in all patients with leukemia and induces 80 % of various tumors in animals. In experiments on mice it's found that p-HEB has a transplacental influence, and so this phenomenon in the development of congenital tumors in children is likely to have importance.

All chemical carcinogens can be divided into two main groups: pro-carcinogens and direct carcinogens. The vast majority of chemical carcinogens belong to the first group. To become a true, end-carcinogens, pro-carcinogens must undergo metabolic conversions of pre-catalyzed fabric enzymes (nonspecific oxidases), mainly localized in the endoplasmic reticulum and cell nucleus.

**Direct carcinogens** – are highly active chemical compounds, including lactones, hloretilamines, and epoxides. They are able to directly interact with the structures of cells and cause tumor development. These compounds do not require any transformations in the body to manifest their carcinogenic effects. With its high reactivity, direct carcinogens cannot accumulate in the environment as well as they are destroyed within the interaction with environmental carcinogens, and do not represent a great danger to humans as carcinogenesis factors.

**Indirect carcinogens** – are controversial in their chemical properties of the compound. These include PAHs, aromatic amines, nitroso compounds, and aflatoxins. With its low reactivity, these carcinogens may accumulate in the environment and therefore pose a greater danger to humans. These compounds are carcinogens in the body only after a series of chemical enzymatic reactions, resulting in the formation of their active forms – the actual carcinogens. Similarly, epoxides are resulting from PAHs, hydroxylamines of aromatic amines, and alkyl radical of nitrosamines. These forms of carcinogens affect the genetic apparatus of the cell and cause its transformation into a tumor.

Chemical carcinogens are capable of so-called transplacental blastomatosis – when small doses of chemical carcinogens harmless to pregnant female rats, act on the fetus so that tumors appear in young (not all) a few months after birth. The effect is achieved if the carcinogen enters the embryo itself, without being modified by the tissue enzymes of the mother. Such young have tumors in different locations, including in the brain. The nervous system of the fetus was at least 50 times more sensitive to carcinogens than in the adult rat.

**The role of hormones in carcinogenesis**

During the violation of the regulation of the secretion of tropic hormones of the adenohypophysis (in violation of the feedback mechanisms), their number in the blood may increase substantially. Affecting the organs – the targets, they can stimulate proliferation and tumor development.

**Physical carcinogens**

Carcinogenic agents of the physical nature are: radioactive emission of substances containing 32P, 131I, 90Sr; X-ray radiation, alpha, beta and gamma particles, ultraviolet light.

**Ionizing radiation** – is a universal cancer-causing agent. Described the radiation-induced malignant tumors of all organs. most often Occur tumors of the skin and bone, leukemia, endocrine dependent tumors (breast cancer and ovarian cancer). Skin and bone tumors occur predominantly in local irradiation, and the rest – in general. Radiation carcinogenesis is probably put into practice through the conversion of proto-oncogenes of cells into oncogenes as a result of a sharp increase in genomic instability induced by ionizing radiation. At the heart of the radiation, blastomycosis is the damage to the nuclear apparatus of the heredity of somatic cells after irradiation. They create a higher probability of the occurrence of new mutations in somatic cells. The violations of physiological regulatory systems of the body irradiation also play a role.

Nor is there a minimum threshold dose, so that any radiation at any dose is potentially dangerous. All other things being equal, long and constant exposure to low doses, in terms of carcinogenesis, is much more dangerous than short-term treatment with large doses.

In the mechanism of radiation carcinogenesis, a key role in plays the formation of free radicals, the amount of which is directly dependent on the dose of radiation. Active radicals have a damaging effect on DNA and stimulate chromosomal aberrations and mutational processes. The human body is usually able to resist the pathogenic effect only of weak (subthreshold) doses of ionizing radiation. This ability can be significantly enhanced by artificial activation of antioxidant protection in cells with the increased intake in the body of tocopherol, selenium, and ascorbic acid, and with the increased activity of enzyme systems - glutathione, superoxide dismutase, and catalase. In case of insufficient activity of antioxidant systems in the cell, there is a growing carcinogenic effect of ionizing radiation.

Carcinogenesis can be induced by foreign bodies. Introduction under the skin of mice with solid plastic plates causes (in 6–24 months), the formation of sarcomas from pericytes, closely connected with the surface of the implant. Carcinogenic properties of asbestos that cause tumors within the inhalation of its containing air are known (pleural mesothelioma, lung cancer). The degree of carcinogenicity of asbestos is associated with the length of its fibrous components and is increased due to its ability to adsorb on the fiber surface carcinogenic PAHs that enter the lungs during smoking.

The target of carcinogenic agents of the physical nature is also DNA. Their direct effects on DNA, or through intermediaries – a kind of mediators of carcinogenesis are allowed. The latter include oxygen-free radicals, lipids, and other organic and inorganic substances. The first stage of physical carcinogenesis – is the initiation of tumor growth. It has direct or indirect effects of agents of the

physical nature on DNA. This causes damage to its structure (gene mutations, chromosome aberrations) or epigenomic changes. Both the first and the second may lead to the activation of proto-oncogenes and subsequent malignant transformation of cells.

The second stage – is promotion. At this stage of carcinogenesis, the expression of oncogene and modification of a normal cell into cancer is put into practice. As a result of successive cycles of proliferation, the tumor is formed.

**Biological carcinogens**

It's found that some biological factors are also able to induce carcinogenesis, in particular, the products of fungi. For example, aflatoxin – a fungus synthesized by Aspergillum flavum (parasitic on peanuts, corn, rice, etc.) and sterigmatocystin (synthesized by the fungus Aspergillus nidulans) cause the development of liver tumors. However, the basic biological carcinogens are oncogenic viruses. Experimental evidence of the viral origin of tumors is their appearance after the introduction of cell-free filtrates of tumor tissue in an animal. These filtrates are prepared from a suspension of tumor cells by passing them through a porcelain filter that inhibits bacteria and tissue cells.

**Classification of oncogenic viruses**

By the type of viral nucleic acid, oncogenic viruses are divided into DNA-containing and RNA-containing. DNA genes of oncoviruses are capable of being directly introduced into the genome of a target cell. The plot of DNA oncoviruses (actually oncogene), integrated with cellular genotype may carry out a tumor cell transformation. Do not rule out also that one of the genes of norovirus may play a role as a cellular proto-oncogene promoter.

DNA-containing oncoviruses include some adenoviruses, parvovirus, and herpesvirus. For example, the Epstein-Barr virus causes the development of lymphoma, hepatitis B, and C which can cause liver cancer. RNA-containing viruses – are retroviruses. This means that the integration of the viral RNA genes in the cell genome is not direct but after the formation of DNA copies. This DNA copy is integrated into the genome of the cell, being expressed and causing its transformation into a tumor one.

**Oncogenic viruses include (by AI Ageenko):**

I) RNA-containing viruses of the spiral (multiply in the cytoplasm), or polyhedral shapes - more than 100 species (oncoviruses – oncogenic, RNA-containing, or retroviruses - convey information in the opposite direction - from RNA to DNA). These include leukemia viruses in mice and chickens, the Rous sarcoma, the Bittner milk virus, etc.

II) DNA-containing viruses (more than 55 types):

1. Popes-virus (propagated in cell nuclei) - rabbit papillomaviruses, polyoma, human papilloma, the vacuolating virus of monkeys – SV40).
2. Adenoviruses.
3. Viruses of smallpox (multiply in the cytoplasm, forming characteristic cellular inclusions) - Yaba virus that causes reversible human tumors.
4. Viruses of herpes [Epschteyna-Barr virus, the causative agent of lymphoma Berkita, herpes simplex virus type 2 (SH-2) - agent of cervical cancer].

Related to it the origin of the virus HTLV-III has two functions: 1) the destruction of T-Heller (AIDS) and 2) the induction of malignant tumors, mainly Kaposi's sarcoma and B-cell lymphoma, squamous cell carcinoma.

**According to another classification, oncogenic DNA viruses include:**

1) popes viruses. They cause the development of three types of animal tumors: papillomas, polyoma, and tumors, which originated from the vacuolating virus SV-40;
2) The Adenoviruses. Oncogenic for animals are adenoviruses of 12, 18, and 31 types;
3) Herpes viruses, including Epstein-Barr virus.

**As for human beings, for some tumors it's proved, but for others there is a reason to believe that the reasons are:**

11) Epstein-Barr virus (causes Burkitt lymphoma, nasopharyngeal carcinoma);
2) Hepatitis B virus (can cause liver cancer);
3) Human papillomavirus (causes benign tumors of the skin, female genitalia, and larynx).

**Depending on the carcinogenicity retroviruses are divided into two groups:**

1) Acute transformation retroviruses. Cause the development of tumors after a short latency period. These viruses have in their genome an oncogene, and therefore at the heart of cell transformation in the tumor, there is the epigenomic mechanism. This group, in particular, is related to the acute leukemia virus of birds, mice, and Rous sarcoma.

2) Slowly transforming retroviruses. Cause the development of tumors after a long latent period. These viruses do not have a part of an oncogene, and therefore the main mechanism of action of the transformation – is the mutation. This group of viruses includes lymphocytic leukemia viruses.

The oncogenic human virus is a virus of a T-cell lymphoma - leukemia. It is transmitted from a person to person through prolonged intimate contact, and blood transfusions. This lymphotropic virus has many similarities with the human immunodeficiency virus (HIV) that causes AIDS.

Viral carcinogenesis is associated with exposure to specific viruses on proliferating cells. Penetrating into the body of humans and animals, they, for the entire period of life, can not cause cancer and pass it on to their descendants. In the body, the action of oncogenic viruses depends on the state of immune surveillance, age, genotype, hormonal levels, and many other factors.

**Stages of viral oncogenesis**

1. Reception of the virus. The interaction of viral particles to specific structures of the plasma membrane of cells (receptors).
2. Splitting and penetration of the virus into the cell (internalization).
3. Association (integration) of viral genome with the genome of the cell. This is a central and obligatory stage of viral oncogenesis. In the case of DNA-containing oncoviruses there occurs the insertion of viral DNA in the cell's DNA, in the case of RNA-containing viruses – DNA provirus, which is formed under the influence of the enzyme revertaze is integrated.
4. Permanent residence (persistence) of the virus in the genome of the cell. The virus multiplies along with the cell. Such a course of viral infection is called abortive. The abortive course is essential for the transformation of cells into the tumor under the influence of the virus.
5. The transformation of cells.
6. Promotion.
7. Tumor progression.

**Factors determining the ability of viruses to transform cells**

1. The factors that are determined by the properties of the virus. These include the so-called structural deficiency virus. Structurally defective are called viruses that are in the process of reproduction and the formation of virus particles have lost part of their genome.
2. The factors that are determined by the properties of cells. These include the availability of appropriate receptors on the surface of cells during the cell cycle, during which the virus enters the cell. Integration of the virus genome with the genome of the cells is only possible in the synthetic phase (phase S), or in the period immediately preceding it (the end of phase G1). This explains the fact that the highly differentiated cells that have lost the ability to divide are resistant to oncogenic viruses.

**The concept of viral oncogenes, cellular proto-oncogenes, oncoproteins**

Viral oncogenes – are the genes of the virus, the operation of the transformation of normal cells in the tumor the functioning of which is associated with. Proteins - the products of viral oncogenes - violate the regulation of cell division and thus cause the transformation of cells (the epigenomic mechanism of carcinogenesis).

Proto-oncogenes – are gene's own cells, which carry information about the structure of proteins involved in the regulation of cell division. Proto-oncogenes are cellular counterparts of viral oncogenes. It is believed that viral oncogenes are proto-oncogenes caught in the genome of viruses as a result of a long evolution of the latter.

Proto-oncogenes are present in all cells.

**Classification of oncogenes and products of their activity**

Depending on the products, which the virus oncogenes and proto-oncogene cells carry information about, they are divided into the following groups:

1) Oncogenes coding the growth factor or their equivalents. For example, sis – an oncogene of apes sarcoma virus, and similar protooncogene of cells encode the structure of the platelet-derived growth factor origin;

2) Oncogenes that encode cellular receptors for growth factors. For example, an oncogene of chicken leukemia virus erb-B carries the information about a modified receptor for epidermal growth factor;

3) Oncogenes encoding protein structure, which transfer information from the receptor of the cell plasma membrane to the nucleus. An example is a ras – an oncogene of rats sarcoma virus;

4) Oncogenes encoding tyrosine-specific protein kinase. An example is the oncogene of the Rous sarcoma virus and the corresponding protooncogene of cells.

## Mechanisms of activation of proto-oncogenes

Cellular oncogenes (transforming genes) – these are proto-oncogenes, which acquired the ability to transform cells, i.e. to transform them into a tumor. The transfer of these genes to other, healthy cells causes the transformation of the latter.

***Now the existence of the mechanisms of proto-oncogenes transformation into cellular oncogenes is proved:***

1) Depression of protooncogene. May occur either as a result of violations of the structure and, consequently, of the function of the corresponding anti-oncogene or due to mutations in the genes repressors, blocking the activity (expression) of proto-oncogene;

2) Increasing the expression of a proto-oncogene. Observed when the protein – a proto-oncogene product is formed and normal, but there is very little of it. Under the influence of certain genetic factors, the formation of such a product is sometimes considerably higher. This phenomenon may be happening due to the following specific arrangements:

a) gene amplification (increasing the number of copies);

b) chromosomal mutations – translocation;

c) impact of viral promoters and amplifiers (so there are retroviruses that do not have an oncogene in their structure);

d) influence of the cell migratory genes (transposons).

3) Qualitative changes in proto-oncogenes, causing the formation of a modified product. These changes are caused by point mutations in proto-oncogene. Anti-oncogenes – are cellular genes whose products cause the repression of proto-oncogenes. Anti-oncogenes loss (deletion) or mutations in them, leading to the formation of inactive products, may have an effect of depression of proto-oncogenes and cell transformation, i.e. formation of malignant tumors.

## Pathogenesis of tumors

*There are three stages*: the transformation of healthy cells into a tumor, promotion and progression of tumors.

**Transformation** (initiation) – Acquisition by normal cells of the ability to proliferate indefinitely and its transfer to the daughter cells. It could probably happen in two ways - mutation and epigenomic which are mechanisms of disturbances of cell division.

Mechanism to ensure cell division is the DNA replication of the cellular genome in the S phase of the cell cycle, starting with the appearance in the G1 phase of a specific initiator of cell division. Its appearance and the beginning of cell division are the results of the depression of the gene encoding this initiator.

According to this hypothesis of Hughes, the regulation of cell division occurs with the help of a system consisting of three regulatory genes. Repressor gene 1 and an encoded by it repressor-1, turn off the function of a gene initiator of cell division. In its turn, a gene-repressor 1 is under the control of gene-repressor 2, encoding the repressor 2, which turns off the function of gene-repressor 1. At the same time, the synthesis of repressor 1 is suspended and the gene initiator of cell division is activated. However, in normal circumstances, this does not happen, since the components of the initiator of cell division are able to repress gene-repressor 2. To make cells multiply, it's required to have in the genome a factor that prevents the repression of a gene-repressor 2 by the component of the initiator of cell division and repression of the gene initiator of cell division by the repressor 1.

**Mutation carcinogenesis**. It is assumed that the mitogenic factor causes a disturbance in gene repressor 1, and an active repressor 1 is not synthesized. This disinhibits the gene initiator of cell division which leads to uncontrolled cell division. A similar situation is observed in mutations of the gene encoding the initiator of cell division, resulting in it becoming unavailable to the inhibitory effect of the gene-repressor 1.

**Epigenomic carcinogenesis** is possible under the influence of factors (e.g., viruses) that do not belong to the genome of the cell, but create a dysregulation of the genome regulation, resulting in limitless growth. In the genome of the virus, there seems to be the gene of a type of cellular gene-repressor 2, and with the emergence of the virus, the cell begins the synthesis of viral repressor 2, inhibiting a gene-repressor 1 and synthesis of a repressor 1, which activates a gene initiator of the cell division and cell division begins. Initiator of the cell division turns off gene-repressor 2 of cells because of the peculiarities of its structure. Thus, while the virus is in the cell, the synthesis of repressor 2 is maintained on the basis of the viral gene. This leads to the repression of the gene-repressor 1 of the cell, and therefore the gene initiator of cell division is depressed and the cells

multiply. The resulting cells contain the viral genome, which supports a violation of the regulation of cell division in the subsequent generations of cells.

Under certain circumstances, such cellular genes can become acting oncogenes, that's why they are called proto-oncogenes. Such a transformation can occur:

1) Due to excessive activity, when the proto-oncogenes are attached to an exogenous controlling genetic element (from leukemia retrovirus, which does not contain its oncogene) or due to multiplication (amplification) of protooncogene to a few tens or even hundreds of copies The functions of proto-oncogene are getting out of normal cell control and the encoded by it protein product is produced at the wrong time and to spare;

2) In the appearance of mutations in proto-oncogene leading to protein synthesis with modified properties (protooncogene c-ras in human bladder cancer);

3) The translocation of chromosome region containing protooncogene, in part of the other chromosome, located in the active core of the chromatin, which rapidly synthesizes heavy polypeptide chains of immunoglobulins (human lymphoma Berkita)

The transformation of Protooncogene in an oncogene may be caused by physical and chemical factors. Within the transformation induced by a retrovirus, containing the reverse transcriptase enzyme, the cellular DNA has a DNA copy of RNA nucleotide sequence integrated into it, corresponding (complementary) to an oncogene, i.e. ready for action oncogene. Within the effect on the cell of the DNA-containing oncogenic virus, which has no analogs in the DNA of the cell, ready-oncogene is integrated into the cellular genome.

I. Necessary precondition for the transformation is the acquisition by a cell of the ability to divide indefinitely. A characteristic feature of the "immortal" cells – is to reduce dependence on the environment and especially on the concentration of factors that regulate reproduction as a result of the acquisition of hypersensitivity to them. Oncogenes of transformed cells are likely to produce the substances themselves, which control all the stages of cell division – growth factors, membrane receptors of these factors, which transmit signals from the outside or directly through the system, initiating DNA synthesis and proliferation.

**Promotion** (activation). Transformed cells may be a long time in an inactive state. Additional exposure to cocancirogen can lead to cell division and formation of the tumor site. Most carcinogens are complete. Molecular mechanism of promotion is the inclusion of transmembrane signaling system, terminating the activation of protein kinase C, which may be attached to the promoter action of growth factors, oncogenes products.

**Progression** – are the persistent qualitative changes in the properties of the tumor on the side of its malignancy within the growth. Expression of progression is the increasing anaplasia of tumor cells, acquisition by them of greater autonomy, infiltrative growth, the ability to metastasize, etc.

### The role of apoptosis in the pathogenesis of tumors

A large group of diseases, the genesis of which is related to the suppression of apoptosis, include cancers, especially those with hematogenous origin. In this case, the key event that promotes the development of pathology often serves as somatic mutations affecting the gene p-53. We have mentioned that the factor p-53 transforms the signal of unrepaired DNA strand breaks into a signal for the development of apoptosis. Because of this are eliminated the cells with damaged genetic apparatus, spontaneous, or induced (e.g., irradiation). In normal cells, the protein p-53 is not allocated, and in tumors, 70 % of the transformed cells synthesize its mutant form. However, the large spread of the mutation rate of p-53, in various malignant tumors can not let make universal conclusions about its role in the pathogenesis of malignant processes.

### Interaction of the tumor and body

Diverse and contradictory relationship of malignant tumors with the body. On the one hand, a tumor causes the body that serves as its external environment, to create the necessary conditions for its development, and on the other – the body is able to more or less successfully oppose this development. Finally, for a formed malignant neoplasm, the body becomes the object of his disastrous systemic effects, i.e. here to fully manifest their antagonistic relationship.

**The role of the body in malignancy.** Not every clone of tumor cells arising in the body transforms into a tumor. The organism has certain, albeit limited, means of protection. In the early stages works a system of so-called natural nonspecific resistance, is able to eliminate a small number of tumor cells. It includes natural killers – large granular lymphocytes. They lyse not only tumors but also normal damaged and embryonic cells are activated by interferon. The system of natural resistance also includes macrophages, their oxygen radicals formed by specific oxidases, and hydrogen peroxide.

The possibility of overcoming the tumor cells of the first barrier, natural resistance, is determined by their ability to produce factors (prostaglandin E), inhibiting this system, and resistance to hydrogen peroxide. Specific antitumor immunity develops too late and does not retain its activity for a long time. A significant impact on tumor growth has hormonal regulation. Hormones can act as endogenous carcinogens (gonadotrophic pituitary hormones, estrogens) or counteract tumor growth.

**Effect of tumor on the body.** There are two interrelated forms of systemic tumor effect on the body: a) successful competition with the tissues for the vital factors and metabolites, and b) changes in the biological characteristics of different tissues, leading to a weakening of their features and adjustability of the body. Malignant tumors hook from the body some vitamins (B1, C) and pyrimidine precursors of nucleic acids, glutamine, and other amino acids, i.e., organic nitrogen compounds.

Tumor growth causes a whole cascade of disorders of homeostasis, disrupting the normal operation of its physiological systems. These include the state of immunosuppression (increasing the susceptibility to infectious diseases), a tendency to increased blood clotting, cardiovascular disease, muscular dystrophy, some rare dermatoses (acanthosis nigricans), etc.

There is an intensification of the process of lipid peroxidation, the products of which have a toxic effect on cells by damaging their plasma and intracellular membranes. The catalytic reaction of hydrogen peroxide decomposition in the body is reduced, due to the influence of the so-called hormone. It reduces the amount of catalase in the liver and kidneys, and of iron in the blood, causing anemia through inhibition of erythropoiesis, the development of hypertrophy of the adrenal gland, and involution of the thymus gland, enlargement of the liver and spleen.

During the period of intensive growth of the tumor, break off the feedbacks governing the activity of central and peripheral endocrine glands. There is a low level of thyroxine in serum in combination with a high content of thyrotropin in it, which normally stimulates the secretion of thyroxine. The diversion of amino acids in the process of glucogenesis limits their participation in protein synthesis and is the basis of muscular dystrophy in a tumor body.

Low content of albumin in serum (hypoproteinemia), and high – of globulin and fibrinogen are characteristic.

Cancer cachexia (wasting) is characterized by loss of body weight, mainly by reducing the mass of skeletal muscles and parts of the myocardium as a result of increased protein breakdown in these tissues, as well as due to depletion of fat depots.

***In general, the development of malignant tumors can occur in three groups of common disorders in the body:***

1) ***Cancer cachexia*** – is the total exhaustion. Characterized by a sharp decrease in body weight, weakness, lack of appetite, and anemia. The emergence of cancer cachexia is explained by the following phenomena:

a) The tumor captures from the blood large amounts of glucose, "glucose trap", resulting in a hypoglycemia and energetic "theft" of the body;

b) The tumor captures from the blood large amounts of amino acids ("nitrogen trap "). There is a plastic "theft" of the body;

c) The toxic products of dead tumor cells enter blood – toxic hormones. They determine the effects of intoxication;

d) tumor cells let out a lot of unoxidized products – develop ungreased acidosis;

e) release of enzymes from dying tumor cells in the blood ;

f) when the tumor is located in the gut the functions of the digestive system are violated;

2) Common manifestations associated with local changes in tissue. This group includes ulceration, secondary infection, bleeding, pain;

3) Paraneoplastic syndromes. They often accompany the development of tumors, but their pathogenesis and relationship to malignant tumor growth remain unclear. This group includes:

*a) endocrinopathies;*

*b) hypercalcemia;*

*c) neuromuscular syndrome (myasthenia, CNS and peripheral nervous system disorders);*

*d) dermatological disorders;*

*e) damage of bones and joints;*

*f) cardiovascular and hematological disorders (thrombosis, anemia, leukemoid reaction).*

**Peculiarities in the behavior of tumor cells in culture**

1. Lack of contact inhibition. Normal cells in culture divide until a monolayer covering the bottom of the vessel forms. And the division does not cease (contact inhibition). Tumor cells multiply all the time, forming a multilayered structure (no contact inhibition).

2. Ability to divide without attachment to any surface. Tumor cells, unlike normal, may divide, floating in a fluid and maintaining a spherical shape.

3. For the growth of tumor cells it is not necessary to have the presence of serum in the environment. The division of normal cells in a culture solution requires not only nutrients and oxygen but also blood serum at a concentration of 10 to 30 %. It is believed that the latter contains proteins that are growth factors for normal cells.

4. Immortalization (immortality) – lack of the cell division limit. Normal cells in culture after a certain number of transfers from one vessel into the other one gradually lose their ability to divide, the culture gets older and cells eventually die. In cancer cells Hayflick limit – is a genetically programmed number of divisions, which a cell can carry out, is missing, their division during the creation of the appropriate conditions has got no limits.

**The mechanisms of natural antitumor defense, immune and non-immune mechanisms of resistance**

Mechanisms of natural nonspecific resistance of the body to tumors do not have immunological specificity and do not require prior immunization. They are carried out by the following cells:

a) By NK-cells (natural killers) are a kind of O-lymphocytes. They recognize the tumor cells and destroy them;

b) By LAK-cells (lymphokine-activated by killer cells). They, like the NK cells, carry out the cytolysis of tumor cells;

c) By macrophages. Destruction of tumor cells by macrophages is carried out by means of phagocytosis and extracellular mechanisms of cytotoxicity.

*Mechanisms of natural nonspecific anti-tumor protection are effective if the number of tumor cells in the body is less than $10^3$.*

Reactions of the **acquired (specific) anti-tumor immunity** are obtained due to specific tumor antigens and include both cells, associated with the function of T lymphocytes, and humoral, associated with the formation of antibodies, and the immune response. These reactions are effective if the number of cells in tumors is from $10^3$ to $10^6$. If their number exceeds $10^6$, then develops the state of immunological depression and tumor-defense mechanisms described above are suppressed. The mechanisms of antitumor protection (natural resistance) of the body are functioning at all stages of cancer.

Identified the activation of a number of microsomal enzymes and antioxidants that ingest the body of chemical compounds in order to prevent the formation of their active metabolites and/or acceleration of the clearance of the blastogenic factor. An important place among these anticarcinogenic substances occupies inhibitors of beta-glucuronidase, which prevent the decay of glucuronides and release of carcinogenic compounds. Biological carcinogenic agents, including oncogenic viruses, can be inhibited by specific antiviral antibodies and interferon. Natural Killer (NK-cells) can destroy the virus + cell complex by producing reactive oxygen species, hydrogen peroxide, lysosomal enzymes, and proteases.

**Pathophysiological basis for prevention and treatment of tumors**

The aim of tumor prevention is the prevention of carcinogenic cells' impact on the cellular genome, a significant reduction of their blastogenic actions and thereby preventing the occurrence of tumor cells. To achieve this, various activities are carried out: reduction or elimination of carcinogenic agents in the human environment; personal body protection, especially in manufacturing; enhancing common and antitumor resistance of the organism; early detection and elimination of the so-called precancerous conditions. These include pockets of excessive cell proliferation (e.g., breast, uterus, prostate).

Treatment of tumors can be radical and palliative. Radical treatment is aimed at eliminating tumors and suggests the possibility of full recovery or long-term remission. Palliative treatment can be used when radical therapy is impossible. Methods of treatment include surgical removal; radiation therapy (the use of radiation exposure); chemotherapy; immunotherapy; increased non-specific resistance (for example, the introduction of BCG). Treatment leads to a lengthening of life and reduction of suffering. The risk of recurrence is sufficiently large, although initially, the patient may feel completely healthy.

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**PRACTICAL LESSON № 11 (13 stomat.)**
**Topic: HYPOXIA**

**Relevance of the topic.** Hypoxia or oxygen starvation – is a typical pathological process that arises in different diseases and considerably influences their development and end. Human life from its birth to death is accompanied by the hypoxia phenomena therefore not incidentally studying hypoxemic states has long since drawn it self attention of many researchers.

Because oxygen starvation is observed in many diseases, and in a complex pathogenetic therapy it is necessary to use anti-hypoxemic actions, and it demands knowledge of the main external manifestations of oxygen starvation, the essence of processes that are a cornerstone of hypoxia, mechanisms of their development.

**General aim** – to be able to characterize a hypoxia is a typical pathological process, to estimate functional frustration in an organism, explain the main mechanisms of damage and compensation at oxygen starvation to develop an ability to apply the symptomatic and pathogenetic treatment of this pathology on chairs of a clinical profile.

**For this it is necessary to be able to (specific objectives):**

1. To interpret the definition "hypoxia", and "hypoxemia", to be able to classify oxygen starvation by an etiology and pathogenesis.
2. To find the main manifestations of hypoxia and to define, if the reactions are pathological or protective and adaptive, to explain mechanisms of their emergence for the purpose of justification of symptomatic and pathogenetic therapy of hypoxemic states.

**Required to achieve the learning basic knowledge – skills.**

**To be able to:**

1. To characterize pulmonary ventilation, to explain the mechanism of its change according to changes in the gas composition of blood.
2. To interpret the oxygen capacity of the blood.
3. To estimate data of results of research of frequency of breath and results of the spectrometer analysis of blood on the maintenance of methemoglobin

## THE QUESTIONS FOR THE LESSON

1. Definition "hypoxemia", "hypoxia".
2. Classification of oxygen starvation by etiology and pathogenesis.
3. Essence and mechanisms of development of functional frustration in an organism in oxygen starvation.
4. Main pathogenetic mechanisms of development of each form of oxygen starvation.
5. Compensatory mechanisms which interfere with the development of oxygen starvation

## EXPERIMENTAL PART OF LESSON

**Experiment:** studying of hypothermia influence on the organism's sensibility to oxygen starvation.

**The object of the experiment:** white mice.

**Apparatus:** 200 ml cans, thermometers, ring-stands, ice, water.

**The conduction of the experiment:** take two mice and put them into separate cups (a free inlet of air). The cup N 1 is placed into the mixture of water with ice and left it in a room temperature. In 5 min study of the initial state of both animals. Define the animal's behavior, sound reaction, the color of skin, and respiratory rate. Then hermetic both cups simultaneously. Observe till the death of animals. Write down the results every 2–3 min into the table.

| Time | Mouse N 1 | | | | Mouse N 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Hypoxia ( 3–4 °C ) | | | | Hypoxia ( 18–20 °C ) | | | |
| | Behaviour | Sound reaction | Skin colour | Respiratory rate | Behaviour | Sound reaction | Skin colour | Respiratory rate |
| | | | | | | | | |
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**Result:**

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THEORETICAL MATERIAL FOR PREPARATION TO LESSON "**HYPOXIA**"

The effectiveness of biological oxidation under normal conditions (the main source of phosphorus compounds – energy), which requires an adequate amount of oxygen, corresponds to the functional activity of organs and systems. A state of energy deficit appears in case of a defect of this correspondence. It leads to various functional and morphological disorders, up to death (necrosis) of a tissue.

**Hypoxia (oxygen deficiency, oxygen starvation) is a condition characterized by insufficient energy supply of vital processes and it occurs in case of**:

***a) an inadequate supply of body tissues with oxygen;***

***b) and/or disorders of its utilization in the process of biological oxidation.***

Founder of native physiology I. Sechenov laid the foundations of the theory of pulmonary gas exchange and transport of blood gases, he studied the breathing and gas exchange function of blood under normal, low, and high atmospheric pressure.

His disciple, the founder of pathophysiology V. Pashutin created the general theory of oxygen starvation as one of the major problems of general pathology, he studied hypoxic hypoxia and classified hypoxic states (1881).

V. V. Pashutin's disciple P. M. Albitsky studied the role of the time factor in the development of hypoxia and its compensatory reactions and he was the first to describe tissue hypoxia (the term was then reintroduced in 1932 by Peters and Van Slyke).

N. N. Serotinin investigated the role of reactivity, and hypoxia in the high mountains, and gave the modern classification of hypoxic states (1949).

I. P. Petrov studied the role of the nervous system in the development of hypoxia and suggested his classification of hypoxic states (1949).

Zuntz, Levy, and Van Lear explored high-altitude and other forms of hypoxia (1906, 1942).

Barcroft explored the importance of blood for oxygen transport (1919) and proposed a classification of hypoxic states (1925).

Warburg studied the role of tissue respiratory enzymes in the development of hypoxia (1948).

The term "hypoxia" was introduced by Diggers (1940; previously the term "anoxia" was used). With the term "hypoxia" he described all states of decrease of oxygen content in respirable air from 20,9 to 12 %, "anoxia" – below 12 %. Currently, the term "hypoxia" has fully supplanted the term "anoxia".

**Classification of hypoxia**

The main classification was approved in 1949 at the All-Union Meeting regarding hypoxia (N. Sirotinin):

1. **Hypoxic hypoxia**. It is caused by:
   a) lowering of the partial pressure of oxygen in respirable air;
   b) the difficulty of penetration of oxygen through the respiratory tract into the blood;
   c) respiratory disorders.
2. **Hemic hypoxia:**
   a) the anemic type (decrease of blood oxygen capacity);
   b) hypoxia due to inactivation of hemoglobin (decrease in oxygen-binding capacity of hemoglobin).
3. **Circulatory (slowing of blood transport):**
   a) congestive form;
   b) ischemic form.
4. **Tissue hypoxia** (disorders of oxidative processes in tissues), and mixed hypoxia.

Classification of I. Petrov (1949, 1967):

I. Hypoxia as a result of lowering of partial pressure of oxygen in the inhaled air (exogenous);

II. Hypoxia in the pathological processes that disturb:

a) the oxygen supply of tissues at its normal content in the environment (1–3),

b) the utilization of oxygen from blood at normal oxygen saturation (4):

1. respiratory (pulmonary) type;
2. cardiovascular (circulatory)type;
3. blood (hemic) type;

4. tissue (histotoxic) type;
5. mixed type.

He has also proposed to differentiate between general and local hypoxia.

Hypoxia can also be divided into acute and chronic hypoxia, sometimes acute and subacute forms.

Hypoxia is possible even without the presence of any pathological processes in an organism - when functional reserves of transport and oxygen uptake systems are incapable to satisfy sharply increased requirements for energy in connection with an extreme intensity of function.

**Objective criteria of hypoxia (allow us to define any type of hypoxia):**

1. The pressure of oxygen: in the environment, alveolar air, arterial, venous blood, and tissues.
2. The rate of mass transfer of oxygen in the body and its consumption (the amount of oxygen received by the lungs, and alveoli, transported with arterial and venous blood, consumed by the tissues per 1 minute).
3. Modes of mass transport of carbon dioxide.
4. Changing the pH of arterial and venous blood.
5. Blood levels of lactic and pyruvic acids, buffer bases, and other indicators of acid-base status of blood.

These modes are set by controlling the ventilation, circulation, and oxygen-binding characteristics of blood.

***There are different changes in oxygen modes of the body for various types and degrees of hypoxia:***

1. ***Hypoxic (exogenous) hypoxia***: a) decrease of the oxygen pressure in respirable air, b)decrease of the oxygen pressure in alveolar air, c) decrease of the oxygen pressure in arterial blood, i) reduction of the total air-venous pressure gradient of oxygen.
2. ***Respiratory hypoxia***: reduction of the oxygen pressure in arterial blood, arterial hypoxemia as a result of disorders of pulmonary gas exchange and mass transfer of oxygen through the alveolar-capillary membrane without change in the partial pressure of oxygen in respirable air, and air-venous gradient of partial pressure of oxygen.
3. ***Hemic hypoxia:*** the oxygen content in arterial and mixed venous blood decreases because of reduced blood oxygen capacity or oxygen-binding capacity of hemoglobin; a common air-venous gradient of partial pressure of oxygen, partial pressure of oxygen in alveolar air and arterial blood are without abnormalities.
4. ***Circulatory hypoxia***: reduction of the rate of arterial and capillary oxygen transport due to dysfunctions of the cardiovascular system under normal or reduced oxygen content in arterial blood; decrease of the oxygen pressure in venous blood, and as a result –increase of venous-alveolar and total air-venous gradient of partial pressure of oxygen.

**Etiology and pathogenesis of the main types of hypoxia**

The reason for breathing (respiratory) hypoxia is a lack of pulmonary gas exchange – respiratory failure.

Respiratory failure occurs due to alveolar hypoventilation, decreased perfusion of blood in the lungs, disorders of diffusion of oxygen through aerogematic barrier, and dissociation of ventilation-perfusion ratio. Regardless of the origin of respiratory hypoxia, an initial pathogenetic link is arterial hypoxemia, usually combined with hypercapnia and acidosis.

Alveolar hypoventilation is characterized by the fact that the volume of ventilation per unit of time is below the body's need for gas exchange at the same time. This state is the result of a disorder of biomechanical characteristics of the respiratory apparatus and disorders of the regulation of ventilation. The disorders of the biomechanics of breathing can be obstructive and restrictive.

Causes of obstructive respiratory disorders are: swelling of the bronchial tubes' walls, tumors, and extraneous bodies in the lumen of airways.

Causes of restrictive respiratory disorders are extensive pneumonia, atelectasis, pulmonary edema and pnevmosclerosis, pneumo- or hemothorax, the rigidity of the osteochondral apparatus of the chest, significant amount of fluid in the pleural cavity.

Reasons for the disorders of breathing regulation are a direct effect of damaging factors on neurons of the respiratory center (hemorrhage, tumor, swelling, inflammation in the medulla or in the pons) and reflex effects in the form of deficit of afference which activates neurons in the respiratory center (drug poisoning), excess of excitatory impulses that leads to frequent superficial breathing (during stress, neurosis, encephalitis), excess of inhibitory afference (irritation of nasal passages and trachea with chemicals or mechanically, acute tracheitis and bronchitis).

***Causes of disorders of pulmonary blood perfusion are:*** reduction of blood volume, a failure of the contractile heart function, increased resistance to the bloodstream in the pulmonary vessels and air

pressure in alveoli and airways; the opening of arteriovenous anastomoses and shunting of blood to intra-extrapulmonary shunts from the right to the left bypassing the capillaries of alveoli.

***Causes of disorders of the oxygen diffusion through aerogematic barrier are***: thickening or compaction of the alveolar-capillary membrane components. This leads to more or less significant alveolar-capillary disintegration of the gas environment of alveoli and blood capillaries.

***Causes of dissociation of ventilation-perfusion ratio are:*** defect of the bronchial tubes patency, decrease of distensibility of alveoli; local decrease of bloodstream in lungs.

***Pathogenetic chain for this type of hypoxia***: reduction of the minute volume of breath → decrease of the partial pressure of $O_2$ in the alveolar air → decrease of $O_2$ pressure in the blood that flows through the lungs → reduction of saturation of Hb by oxygen → reduction of $O_2$ in arterial blood (hypoxemia).

***The reason for the cardiovascular (circulatory, hemodynamic) hypoxia***: insufficient blood supply to tissues and organs. Lack of blood supply is formed on the basis of hypovolemia, heart failure, reducing the tone of vascular walls, microcirculatory disorders, and disorders of oxygen diffusion from capillary blood to the cells.

Hypovolemia is the reduction of the total volume of blood in the bloodstream and heart cavities. This is one of the most important mechanisms for the development of circulatory failure and ccirculatoryhypoxia. Causes of hypovolemia are large blood loss; loss of water by an organism (chronic diarrhea, burns, massive and prolonged sweating).

Heart failure is manifested by reduced blood ejection from the ventricles of the heart and as a consequence - a decrease in blood volume. Causes: direct damage to the myocardium, overload of the myocardium, disorders of diastolic relaxation of the heart.

Reduction of the tonus of vascular walls (arterial and venous) occurs due to a decrease of adrenergic influences on vascular walls, as well as the dominance of cholinergic effects, and deficiency of mineralocorticoids in the body. Hypotonia of vascular walls of any origin causes decreased arterial and perfusional blood pressure, as well as the volume of blood flow in vessels of tissues and organs.

Defect of oxygen diffusion through a wall of microvessels into intercellular liquid through plasmalemma and cytosol to mitochondria finally leads to a deficiency of oxygen in the matrix of mitochondria and, consequently, to the reduction of the intensity of tissue respiration. The reasons are sealing of the walls of microvessels, and cellular membranopathies. An important feature of circulatory hypoxia is the possibility of the development of its local and systemic forms. Causes of local hypoxia are local circulatory disorders, regional disturbances of diffusion of oxygen from the blood to cells and their mitochondria Causes of systemic hypoxia are hypovolemia, heart failure, and generalized form of reduction of vascular tonus.

The pathogenetic basis of this hypoxia is a reduction in the minute volume of the heart. In this case, there is normal pressure and content of $O_2$ in arterial blood, and reduction of these indicators in venous blood, as well as a high arterio-venous difference in $O_2$.

The reason of the blood (hemic) hypoxia is the reduced effective oxygen capacity of blood and, consequently, its oxygen-transporting function.

Hemoglobin is the best transmitting agent of oxygen. The transport of oxygen from the lungs to the tissues is almost completely done with the participation of hemoglobin. Objectively the transport ability of hemoglobin is defined by the amount of oxygen connected with Hb, and the amount of oxygen given to tissues. At oxygen saturation of Hb by an average of 96 % oxygen capacity of arterial blood reaches approximately 20 % (by volume). In venous blood, this figure is approaching 14 % (by volume). Consequently, the arteriovenous oxygen difference is 6 %.

The main links in the mechanism of reduction of blood oxygen capacity are a decrease of Hb content per unit volume of blood and disorders of transport properties of Hb. In general, the type of hemic hypoxia is characterized by decreased ability of hemoglobin of red blood cells to bind oxygen (in the capillaries of lungs), transport, and give its optimal quantity in the tissues. Leading to hypoxia, a decrease of Hb content per unit volume of blood in the body as a whole is observed at a very substantial decrease in the number of red blood cells and/or reduction of Hb content (sometimes up to 40–60 g/l), i.e. in the case of expressed anemias.

Defects of the transport properties of Hb are due to changes in its ability to oxygen in blood capillaries of the alveoli and deoxygenation in capillaries of tissues. These changes (hemoglobinopathy) can be inherited or acquired. The reasons for the inherited decrease in the ability of Hb to transport oxygen to tissues are mutations of genes accompanied by the abnormal amino acid structure of globins. A lot of hereditary hemoglobinopathies are known nowadays.

Causes of acquired hemoglobinopathies are increased amount of methemoglobin forms in the blood, carbon monoxide, karbilamingemoglobin, nitroxigemoglobin.

The pathogenetic mechanism of blood (hemic) hypoxia is characterized by a combination of normal pressure of $O_2$ in arterial blood with its decreased content (up to 4–5 % vol.) (in severe cases). Causes of tissue hypoxia are factors that reduce the efficiency of oxygen utilization by cells of tissues and/or conjugation of oxidation and phosphorylation.

Reducing the effectiveness of oxygen uptake by cells is the result of inhibition of enzyme activity of biological oxidation, significant changes in Physico-chemical parameters in the tissues, inhibition of synthesis of enzymes of biological oxidation, and damage in cell membranes.

Suppression of enzyme activity of biological oxidation is observed in the case of specific inhibition of enzymes. Examples are cy anid. Competitive inhibition of enzymes of biological oxidation is the blocking of enzyme activity center by a substance that has a structural analogy with the natural substrate of the reaction. This effect of competitive inhibition of the enzyme can be eliminated or reduced by increasing the content of the true substrate in the cell. Oxalate and malonate can act as competitive inhibitors, which block the interaction of succinate with succinatedehydrogenase in the citric acid cycle; flourcitric acid competes with citrate for the active center of aconitase.

Changes in physicochemical parameters of tissues in a more or less pronounced extent reduce the effectiveness of biological oxidation.

Inhibition of enzyme synthesis of biological oxidation can be observed in total and partial (especially protein) starvation, and most hypo-and avitaminosis; disorders of metabolism of minerals which are necessary for the synthesis of enzymes.

Damage to membranes is observed in mitochondria. It is the result of over-intensification of free radical and lipoperoxide processes, lysosomal hydrolases activation, detergent action of excess amphiphilic compounds; overdistension, and rupture of swollen cells and their mitochondria.

The reduced degree of conjugation of oxidation and phosphorylation of macroergic compounds in the respiratory chain. In these conditions the use of oxygen by tissues and the intensity of functioning of components of the respiratory chain increases. The effectiveness of biological oxidation is reduced, and cells are not supplied with energy in a proper way. In connection with this functions and vitality of the whole organism suffer. Many endogenous agents (e.g., excess of $Ca_2^+$ , $H^+$, iodine-containing thyroid hormones) and exogenous substances (2,4-dinitrophenol, dicumarol, pentachlorophenol) have a pronounced ability to dissociate oxidation and phosphorylation.

The pathogenetic mechanism of this type of hypoxia is characterized by a decrease in the arterial-venous difference of $O_2$, like pressure, saturation and $O_2$ content in arterial blood are normal and in venous blood, it exceeds the normal level.

Mixed forms of hypoxia. A mixed type of hypoxia is a result of a combination of several types of hypoxia.

The reasons are factors that disturb two or more mechanisms of delivery and the use of oxygen and metabolic substrates in the process of biological oxidation. Examples are drugs that can depress heart function in high doses, neurons of the respiratory center, and the activity of enzymes of tissue respiration. As a result, mixed hypoxia of hemodynamic, respiratory, and tissue types develops. Acute massive blood loss leads to a decrease in blood oxygen capacity (due to a decrease in Hb content), and to a circulatory disorder: hemic and hemodynamic types of hypoxia develop. Sequential impact of the factors which lead to damage of different mechanisms of oxygen transport, metabolism of substrates, and processes of biological oxidation is observed in severe hypoxia of any origin.

For example, acute massive blood loss leads to hemodynamic and hemic hypoxia. Reduced blood flow to the heart leads to a decrease in the ejection of blood, and disorders of cerebral blood flow. Ischemia of brain tissue can cause disorder in the function of the respiratory center and respiratory type of hypoxia. Mutual potentiation of hemodynamic and respiratory disorders leads to significant deficiency of oxygen and metabolic substrates in tissues, grave damage to cell membranes and enzymes of biological oxidation and as a consequence – tissue hypoxia.

Pathogenesis of mixed hypoxia includes mechanisms linked to different types of hypoxia. Mixed hypoxia is often characterized by the development of severe, extreme, and even terminal conditions. Changes in gas composition and pH in blood in mixed hypoxia are determined by dominant disorders of mechanisms of transport and utilization of oxygen, substrates of metabolism, and disorders of processes of biological oxidation in different tissues. The nature of these changes may be different and very dynamic.

**Immediate and long-term mechanisms of habituation and adaptation to hypoxia**

The effect of a factor that causes hypoxia of any type is accompanied by an introduction of two categories of processes: those which are responsible for the development of hypoxia and those which provide adaptation to hypoxia and maintain homeostasis in these conditions.

**General characteristics of the processes of adaptation to hypoxia**. With the development of even moderate hypoxia a certain behavioral reaction forms immediately. This behavioral reaction is aimed at finding a living environment that can provide an optimal level of biological oxidation. A person can change the living conditions directionally in order to eliminate the state of hypoxia. Emerged hypoxia is a system factor: a dynamic functional system on an organism forms in order to achieve and maintain an optimal level of biological oxidation in cells.

This system works through the activation of the delivery of oxygen and metabolic substrates to the tissues and their inclusion in the reactions of biological oxidation. The structure of the system includes lungs, heart, vascular system, blood, systems of biological oxidation, and regulatory systems.

Adaptive responses are divided into two groups: emergency adaptation and long-term adaptation. Acute reactions occur during acute evolving hypoxia and are expressed primarily in changing respiratory and circulatory functions. An increase in cardiac minute output due to tachycardia and an increase in systolic volume increased blood pressure, blood velocity, and venous return of blood to the heart take place in order to accelerate the oxygen delivery to the tissues. In the case of severe hypoxia, the centralization of blood circulation occurs - a significant part of the blood rushes to vital organs. Blood vessels of the brain dilate. Hypoxia is a potent vasodilative factor for coronary arteries. The volume of coronary blood flow increases significantly with the decrease in blood oxygen content to 8–9 %. However, blood vessels of muscles and the abdominal cavity narrow. Bloodstream through the tissues is regulated by the presence of oxygen, and the lower its concentration is, the more tissues are replenished with blood. Breakdown products of ATP (ADP, AMP, inorganic phosphate) as well as **$CO_2$ , $H^+$- ions**, and lactic acid have vasorelaxant action. Under hypoxia, their amount increases. Under the conditions of acidosis the excitability of beta-adrenergic receptors in relation to catecholamines decreases, which also contributes to vasodilatation.

Emergent adaptive responses of the respiratory system are manifested by breath acceleration and deepening, which helps to improve ventilation of the alveoli. Reserve alveoli begin to take part in the act of breathing. Blood supply of the lungs increases. Alveolar hyperventilation causes the development of hypocapnia, which increases the affinity of hemoglobin for oxygen and accelerates the oxygenation of blood flowing to the lungs. Within two days of acute hypoxia the content of ATP in red cells increases, which accelerates the return of oxygen to tissues.

Among the responses to acute hypoxia, one can also observe the increase in mass of circulating blood through the emptying of the blood pool and rapid washout of red blood cells from bone marrow, thereby the oxygen capacity of blood increases.

Adaptive reactions at a level of tissues suffering from oxygen starvation are expressed in the rising conjugation of oxidation and phosphorylation and activation of glycolysis, through which the cellular energy needs can be satisfied for some time. Enhancement of glycolysis in the tissues causes accumulation of lactic acid, and acidosis develops, which accelerates the dissociation of oxyhemoglobin in the capillaries. In acute hypoxia, one can observe the decrease in functions and oxygen need of tissues and organs which don't take part in oxygen provided by the body directly.

**Long-term compensatory-adaptive reactions** occur in chronic hypoxia on the basis of various diseases, prolonged stay in the mountains, in case of special training in hyperbaric chambers. Under these conditions, an increase in the number of red blood cells and hemoglobin is observed due to the activation of erythropoiesis under the influence of erythropoietin which is excreted hard by the kidneys when they are hypoxic. As a result oxygen capacity of blood and blood volume increase. The content of 2,3-DPG in red blood cells increases, which lowers the affinity of hemoglobin for oxygen and accelerates its return to tissues. The respiratory surface and vital capacity of the lungs increases due to the formation of new alveoli. In people who are in a state of chronic hypoxia, enhanced vascularization of the peripheral tissues is observed. One of its signs is increased size of terminal phalanges with loss of a normal angle of nail-bed ("drumsticks").

Changes in the function of the respiratory and circulatory system, resulting in acute hypoxia, are largely reflectory. They are caused by irritation of the respiratory center and chemoreceptors of the aortic arch and the coronary band by low oxygen tension in arterial blood. These receptors are sensitive to changes in the content of **$CO_2$** and **$H^+$ -** ions**,** but to a less degree than the respiratory

center. Tachycardia may be a result of a direct action of hypoxia on the cardiac conducting system. ATP breakdown products and the number of other tissue factors mentioned previously have vasodilative activity, and their number increases during hypoxia.

Hypoxia is a strong stress factor, under which the activation of the hypothalamic-pituitary-adrenal system occurs, and the release of glucocorticoids in the blood increases, which activate the respiratory chain enzymes and increase the stability of cell membranes, including lysosomal membrane.

In chronic hypoxia, not only functional but also structural changes occur that have large compensatory and adaptive significance. It was established that the deficit of macroergic phosphorus compounds due to hypoxia causes the activation of synthesis of nucleic acids and proteins. The result of these biochemical changes is the enhancement of plastic processes in tissues underlying the hypertrophy of myocardiocytes and respiratory muscles and the growth of new alveoli and blood vessels. As a result, the efficiency of the apparatus of external respiration and blood circulation increases. However, the functioning of these organs becomes more economical due to the higher power of the energy supply system in the cells (increase in the number of mitochondria and activity of respiratory enzymes).

It was established that during prolonged adaptation to hypoxia production of thyroid-stimulating hormones and thyroid hormones decreases; it is accompanied by reduced basal metabolic rate and reduced oxygen consumption by various organs, particularly the heart, at constant external work. Activation of the synthesis of nucleic acids and proteins in adaptation to chronic hypoxia was found in the brain and improves its function.

The state of sustainable adaptation to hypoxia is characterized by a decrease in lung hyperinflation, normalization of heart function, reduced degree of hypoxia, and removal of the stress syndrome. The activation of stress-limiting systems of the body occurs, particularly in the repeated elevation of the content of opioid peptides in the adrenal glands, as well as in the brain of animals exposed to acute and subacute hypoxia. Along with the antistress action, opioid peptides reduce the intensity of energy metabolism and tissue oxygen demand. The activity of enzymes that eliminate the damaging effect of products of lipid peroxidation (superoxide dismutase, catalase) increases. It was established that adaptation may persist for many years.

## Mechanisms of hypoxic cell damage. Stability to hypoxia of individual organs and tissues

In pronounced hypoxia adaptation mechanisms may be insufficient, and decompensation occurs which is characterized by marked biochemical, functional, and structural disorders. The sensitivity of various tissues and organs to the damaging effect of hypoxia varies greatly. With the complete cessation of oxygen delivery tendons, cartilages and bones retain their vitality for many hours, striated muscle – about 2 hours, the myocardium, kidneys, and liver – 20–40 min, whereas necrotic focuses in the cerebral cortex and cerebellum in these conditions appear after 2,5–3 min, and after 6–8 minutes all cells of the cerebral cortex die. Neurons of the medulla oblongata are slightly more resistant – their activities can be restored after 30 minutes after the cessation of oxygen delivery.

The basis of all metabolic disorders during hypoxia is the lowering or complete cessation of the formation of macroergic phosphorus compounds, which limits the ability of cells to perform normal functions and maintain a state of intracellular homeostasis. With the insufficient flow of oxygen to the cells process of anaerobic glycolysis enhances, but it can only lowly compensate for the weakening of oxidative processes. Especially this concerns cells of the CNS whose need for the synthesis of macroergic compounds is the highest. Normally, oxygen consumption by the brain is about 20 % of the total demand by an organism. Under the influence of hypoxia the permeability of the brain capillaries increases which leads to swelling of the brain. The myocardium is also characterized by a weak capacity to energy supply by anaerobic processes. Glycolysis can provide myocardiocytes with energy only for a few minutes. Glycogen reserve in the myocardium is being rapidly depleted. The content of glycolytic enzymes in myocardiocytes is low.

Glycolysis is not only an inadequate way to release energy, it also has a negative effect on other metabolic processes in the cell, so far as the accumulation of lactic and pyruvic acid causes metabolic acidosis, which reduces the activity of tissue enzymes; the activity of monoamine oxidase reduces significantly. The function of energy-dependent membranous pumps is broken as a result of serious deficit of high-energy substances. Increased output of potashium from cells and increased sodium intake occurs. This leads to a decrease in membrane potential and changes in neuromuscular excitability, which is initially enhanced and then attenuated and lost. The water follows sodium ions and enters cells, it causes their swelling. In addition to sodium, excess calcium in cells takes place in

relation to the dysfunction of the energy-dependent calcium pump. Increased intake of calcium into neurons is due to the opening of additional calcium channels under the action of glutamate; the formation of glutamate increases during hypoxia. The calcium ions activate phospholipase A2 which destroys the lipid complexes of a cellular membrane pump and mitochondrial functions.

The stress syndrome developing in acute hypoxia, along with the previously mentioned positive effect of glucocorticoids, has a pronounced catabolic effect on protein metabolism, it causes negative nitrogen balance and increases the consumption of fat reserves of the organism. The damaging effect on cells is provided by lipid peroxidation products, which are enhanced in hypoxic conditions. Reactive oxygen species and other free radicals formed in this process damage the outer and inner cell membranes, including the lysosomal membrane. The development of acidosis contributes to this process. As a result, lysosomes release their hydrolytic enzymes which have an injurious effect on the cells up to the development of autolysis.

**Modern principles of oxygen therapy. Iso-and hyperbaric oxygenation**

Oxygen therapy is not effective enough in histotoxic (tissue) hypoxia, in hypoxia caused by venous-arterial shunting of blood at embolism of a. pulmonalis and some congenital defects of heart and blood vessels, when a significant portion of venous blood enters the arterial blood stream, bypassing the lungs. Inhalation of oxygen under normal or high *(hyperbaric oxygenation*) pressure is an effective kind of treatment for some severe forms of hypoxia.

**Normobaric (isobaric) oxygen-therapy** must be performed in those cases when the partial pressure of oxygen in arterial blood is below 60 mm Hg, and the percentage of hemoglobin oxygenation is less than 90. In the case of alveolar hypoventilation and disorders of the diffusion of oxygen through the alveolar membrane oxygen therapy eliminates.

**Hyperbaric oxygen therapy** is particularly indicated for the treatment of patients with acute post-hemorrhagic anemia and in severe poisonings with carbon monoxide or substances causing metgemoglobin formation, with decompression sickness, arterial gas embolism, acute injury with the development of tissue ischemia and in some other severe conditions.

**The toxic action of oxygen. Hyperoxia and free radical reactions.**
**Hyperoxia as a cause of hypoxia**

Long-term oxygen therapy may have a toxic effect, which manifests itself in loss of consciousness, the development of convulsions and brain edema, in the depression of cardiac activity; in the lungs, the disorders similar to those with respiratory distress syndrome in adults may occur. The factors which play a role in the mechanism of the damaging effect of oxygen: lowering of the activity of many enzymes involved in cellular metabolism, the formation of large quantities of oxygen free radicals, and increased lipid peroxidation, which leads to damage of cell membranes. In this regard, hyperoxia may act as a cause of tissue hypoxia. The use of oxygen therapy is dangerous to some extent in case of reducing of sensitivity of the respiratory center to increased $CO_2$ content in the blood, which occurs in elderly and senile patients with the presence of cerebral atherosclerosis and organic disorders of CNS. In these patients, the regulation of respiration occurs with the participation of carotid chemoreceptors which are sensitive to hypoxemia. Its removal can lead to respiratory arrest.

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## PRACTICAL LESSON № 12 (14 stom.)
## The final control of students' knowledge on topics «TYPICAL PATHOLOGICAL PROCESSES»

**On the Moodle platform, in the section corresponding to the lesson number, control questions and tasks of the KROK-1 database are presented.**
**https://distance.knmu.edu.ua/mod/folder/view.php?id=92477**

## PRACTICAL LESSON № № 13 (15 stom.)
## Topic: DISORDERS OF CARBOHYDRATE METABOLISM

**The topicality.** Disturbances of carbohydrate metabolism (hyper- and hypoglycemia) are manifestations of a number of diseases. Of particular importance is attached to the study of the etiology and pathogenesis of diabetes, which occurs in 1–4 % of the population, especially among the elderly (2–30 %), diabetes mellitus, depending on the cause and degree of insulin deficiency can be primary and secondary (symptomatic). Primary may be insulin-dependent and insulin-independent. Other types of diabetes are secondary and are associated with certain diseases, such as acromegaly, pituitary Cushing's, diseases of the pancreas, the influence of drugs and chemicals, genetic syndromes, and others. At the same time, the hypoglycemic state is a severe complication of a number of diseases that are caused, first of all, by the high sensitivity of the central nervous system to a shortage of glucose, which is the sole source of energy for the nerve cells without glycogen. This causes disruption of the functioning of vital organs and body systems.

**Overall Objective** – be able to carry out analysis of pathophysiological situations associated with disorders of carbohydrate metabolism, characterized by the etiology and pathogenesis of diabetes mellitus. known experimental models of diabetes.

**To do this we should be able to (specific objectives):**

1. Describe the syndrome of hypoglycemia: types, causes, mechanisms, and pathogenesis of hypoglycemic coma.
2. To characterize the syndrome of hyperglycemia: types, causes, the mechanism of development.
3. Define the diabetes classification.
4. Describe the etiology, pathogenesis of type 1 diabetes, and pathogenesis of absolute insulin deficiency.
5. Describe the etiology, pathogenesis of type 2 diabetes, and the options relative to insulin deficiency in diabetes type 2 (secretory disorders β-cell resistance of target tissues to insulin).
6. Show the importance in clinical practice of different forms of disorders of carbohydrate metabolism.

**The necessary basic knowledge and skills to achieve the goals of studying.**

**To be able to:**

1. Determine the main mechanisms of regulation of blood glucose levels.
2. Taking the blood of the animal for biochemical investigations.
3. To have an intramuscular injection technique.
4. Owning facilities Laboratory chemical works.

**Questions to the lesson**

1 Disorders during carbohydrate absorption.
2. An understanding of the terms glycogenesis, glycogenolysis, and gluconeogenesis. Their disorders.
3. Hyperglycemia. Types. Glucosuria. Mechanisms of glucosuria. Experimental hyperglycemia and glucosuria.
4. Insulin insufficiencies (pancreatic and non-pancreatic).
5. Understanding of the term diabetes. Etiology and pathogenesis.
6. Types of diabetes. Different types of metabolic disorders during diabetes.
7. Experimental models of diabetes.
8. Pathogenesis of diabetic coma.
9. Hypoglycemia. Types. Hypoglycemic coma.
10. Hereditary disorders of carbohydrate metabolism.

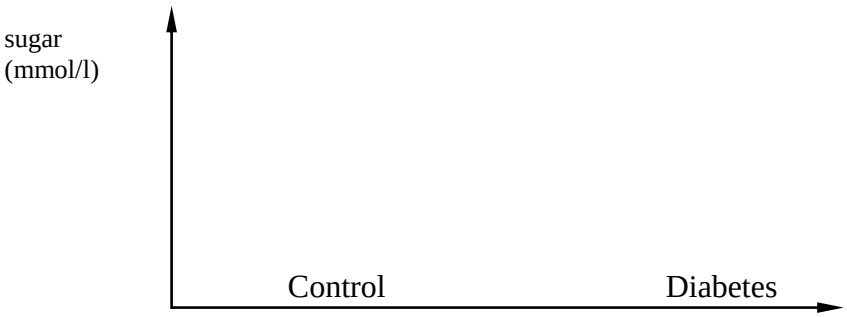
**EXPERIMENTAL PART OF LESSON**

**Experiment 1:** Find the sugar content in blood during experimental diabetes.

**The object of the experiment:** Rabbits

**Apparatus and reactives:** chemical tubes and reactives necessary for determining sugar in blood by ortotholuidine method.

**The conduction of the experiment:** Take two rabbits, one of which was injected with alloxan (160–170 mg/kg body mass) to receive alloxan diabetes. In your class take blood from the control rabbit and from the rabbit with diabetes and determine the amount of sugar in the blood. Method: Pour 1.8 % of a 3 ml solution of trichloride acid into a test tube and add 0.2 ml of blood, taken from the marginal vein of the rabbit's ear. Mix and leave for 10 minutes at room temperature. Then filter. To 0.5 ml of the filtrate, add 4.5 ml of ortotholuidine reactive. Place the test tube in a beaker of boiling water for 8 minutes. The water has to boil continuously. Take out the test tube and immediately cool it under tap water to room temperature. With the help of a photocolorimeter and the length of waves, 590–650 nm (red light-filter) carry out colorimetry against the control test.




**Result:**

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## THEORETICAL MATERIAL FOR PREPARATION TO LESSON

### Hormonal Control of Blood Glucose

The body uses glucose, fatty acids, and other substrates as fuel to satisfy its energy needs. Although the respiratory and circulatory systems combine efforts to furnish the body with the oxygen needed for metabolic purposes, it is the liver, in concert with the endocrine pancreas, that controls the body's fuel supply (*Fig. 1*).

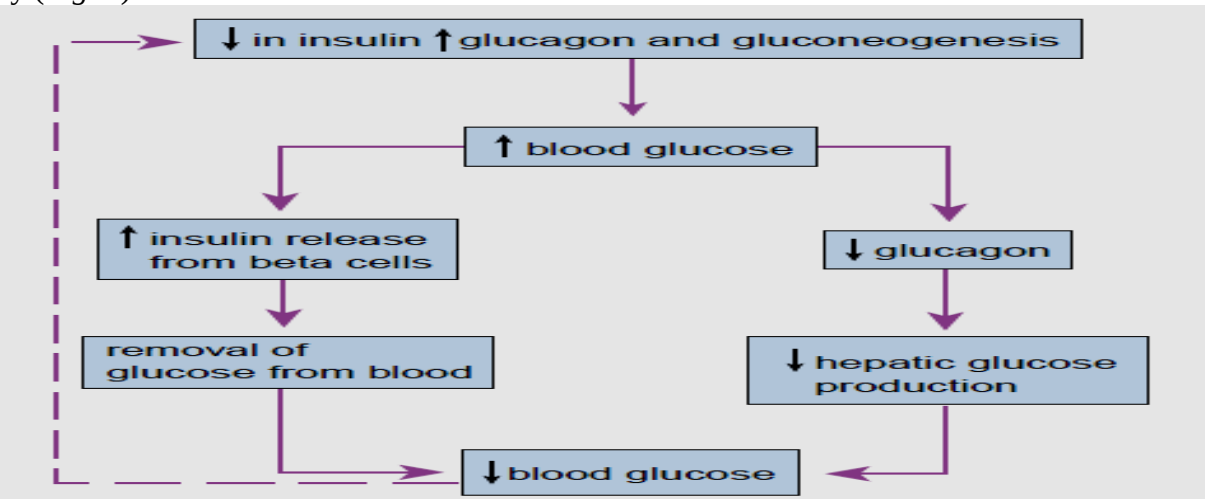


**Figure 1.** Hormonal and hepatic regulation of blood glucose

The pancreas is made up of two major tissue types: the acini and the islets of Langerhans. The acini secrete digestive juices into the duodenum, and the islets of Langerhans secrete hormones into the blood. Each islet is composed of beta cells that secrete insulin and amylin, alpha cells that secrete glucagon, and delta cells that secrete somatostatin. Insulin lowers the blood glucose concentration by facilitating the movement of glucose into body tissues. Glucagon maintains blood glucose by increasing the release of glucose from the liver into the blood. Somatostatin inhibits the release of insulin and glucagon. Somatostatin also decreases gastrointestinal activity after ingestion of food. By decreasing gastrointestinal activity, somatostatin is thought to extend the time during which food is absorbed into the blood, and by inhibiting insulin and glucagon, it is thought to extend the use of absorbed nutrients by the tissues.

**Blood glucose.** Body tissues obtain glucose from the blood. In nondiabetic individuals, fasting blood glucose levels are tightly regulated between 80 and 90 mg/dL. After a meal, blood glucose levels rise, and insulin is secreted in response to this rise in glucose. Approximately two - thirds of the glucose that is ingested with a meal are removed from the blood and stored in the liver as glycogen. Between meals, the liver releases glucose as a means of maintaining blood glucose within its normal range. Glucose is an optional fuel for tissues such as muscle, adipose tissue, and the liver, which largely use fatty acids and other fuel substrates for energy. Glucose that is not needed for energy is stored as glycogen or converted to fat. When tissues such as those in the liver and skeletal muscle become saturated with glycogen, the additional glucose is converted into fatty acids and then stored as triglycerides in fat cells. When blood glucose levels fall below normal, as they do between meals, glycogen is broken down by a process called ***glycogenolysis,*** and glucose is released. Glycogen stored in the liver can be released into the bloodstream. Although skeletal muscle has glycogen stores, it lacks the enzyme glucose-6-phosphatase that allows glucose to be broken down sufficiently to pass through the cell membrane and enter the bloodstream, limiting its usefulness to the muscle cell. In addition to mobilizing its glycogen stores, the liver synthesizes glucose from amino acids, glycerol, and lactic acid in a process called ***gluconeogenesis.*** In contrast to other body tissues such as the liver and skeletal muscle, which use fatty acids and other substrates for fuel, the brain and nervous system rely almost exclusively on glucose for their energy needs. Because the brain can neither synthesize nor store more than a few minutes' supply of glucose, normal cerebral function requires a continuous supply from the circulation. Severe and prolonged hypoglycemia can cause brain death, and even moderate hypoglycemia can result in substantial brain dysfunction. The body maintains a system of counterregulatory mechanisms to counteract hypoglycemia-producing situations and ensure brain function and survival. The physiologic mechanisms that prevent or correct hypoglycemia include the actions of the counterregulatory hormones: glucagon, the catecholamines, growth hormone, and the glucocorticoids.

**Glucose-regulating hormones**

**Insulin**

Although several hormones are known to increase blood glucose levels, insulin is the only hormone known to have a direct effect in lowering blood glucose levels.

The actions of insulin are threefold:

*(1) promotes glucose uptake by target cells and provides for glucose storage as glycogen*

*(2) prevents fat and glycogen breakdown*

*(3) inhibits gluconeogenesis and increases protein synthesis and increases protein synthesis*. Insulin acts to promote fat storage by increasing the transport of glucose into fat cells. It also facilitates triglyceride synthesis from glucose in fat cells and inhibits the intracellular breakdown of stored triglycerides. Insulin also inhibits protein breakdown and increases protein synthesis by increasing the active transport of amino acids into body cells; and it inhibits gluconeogenesis, or the building of glucose from new sources, mainly amino acids.

Body tissues obtain glucose from the blood. In nondiabetic individuals, fasting blood glucose levels are tightly regulated between 80 and 90 mg/dL. After a meal, blood glucose levels rise, and insulin is secreted in response to this rise in glucose. Approximately two thirds of the glucose that is ingested with a meal is removed from the blood and stored in the liver as glycogen. Between meals, the liver releases glucose as a means of maintaining blood glucose within its normal range. Glucose is an optional fuel for tissues such as muscle, adipose tissue, and the liver, which largely use fatty acids and other fuel substrates for energy. Glucose that is not needed for energy is stored as glycogen or converted to fat. When tissues such as those in the liver and skeletal muscle become saturated with glycogen, the additional glucose is converted into fatty acids and then stored as triglycerides in fat cells. When blood glucose levels fall below normal, as they do between meals, glycogen is broken down by a process called ***glycogenolysis,*** and glucose is released. Glycogen stored in the liver can be released into the bloodstream. Although skeletal muscle has glycogen stores, it lacks the enzyme glucose-6-phosphatase that allows glucose to be broken down sufficiently to pass through the cell membrane and enter the bloodstream, limiting its usefulness to the muscle cell. In addition to mobilizing its glycogen stores, the liver synthesizes glucose from amino acids, glycerol, and lactic acid in a process called ***gluconeogenesis.*** Insulin is produced by the pancreatic beta cells in the islets of Langerhans. The active form of the hormone is composed of two polypeptide chains—an A chain and a B chain. Active insulin is formed in the beta cells from a larger molecule called proinsulin. In

converting proinsulin to insulin, enzymes in the beta cell cleave proinsulin at specific sites to form two separate substances: active insulin and a biologically inactive C-peptide (connecting peptide) chain that joined the A and B chains before they were separated. Active insulin and the inactive C-peptide chain are released simultaneously from the beta cell. The C-peptide chains can be measured clinically, and this measurement can be used to study beta cell activity. Amylin is an 37-amino acid peptide that is cosecreted with insulin from the pancreatic beta cells in response to glucose and other beta-cell stimulators. The amylin acts as a hormone, with several effects that complement the actions of insulin in regulating postprandial blood glucose levels. These include a suppression of glucagon secretion and a slowing of the rate at which glucose is delivered to the small intestine for absorption. The release of insulin from the pancreatic beta cells is regulated by blood glucose levels, increasing as blood glucose levels rise and decreasing when blood glucose levels decline.

Blood glucose enters the beta cell by means of the glucose transporter, is phosphorylated by an enzyme called glucokinase, and is metabolized to form the adenosine triphosphate (ATP) needed to close the potassium channels and depolarize the cell. Depolarization, in turn, results in the opening of the calcium channels and insulin secretion. Secretion of insulin occurs in an oscillatory or pulsatile fashion. After exposure to glucose, which is a nutrient secretagogue, the first-phase release of stored preformed insulin occurs, followed by a second-phase release of newly synthesized insulin. Diabetes may result from dysregulation or deficiency in any of the steps involved in this process (e.g., impaired function of the glucose transporters, intracellular metabolic defects, glucokinase deficiency). Serum insulin levels begin to rise within minutes after a meal, reach a peak in approximately 3 to 5 minutes, and then return to baseline levels within 2 to 3 hours. Insulin, which is rapidly bound to peripheral tissues or destroyed by the liver or kidneys, has a half-life of approximately 15 minutes once it is released into the general circulation. To initiate its effects on target tissues, insulin binds to a membrane receptor. The insulin receptor is involved in insulin binding. Activation of the kinase enzyme results in autophosphorylation of the β subunit itself. Phosphorylation of the β subunit in turn activates some enzymes and inactivates others, thereby directing the desired intracellular effect of insulin on glucose, fat, and protein metabolism. Because cell membranes are impermeable to glucose, they require a special carrier, called a glucose transporter, to move glucose from the blood into the cell. These transporters move glucose across the cell membrane at a faster rate than would occur by diffusion alone. Considerable research has revealed a family of glucose transporters termed GLUT-1, GLUT-2, and so forth.4 GLUT-4 is the insulindependent glucose transporter for skeletal muscle and adipose tissue. GLUT-2 is the major transporter of glucose into beta cells and liver cells. It has a low affinity for glucose and acts as a transporter only when plasma glucose levels are relatively high, such as after a meal. GLUT-1 is present in all tissues. It does not require the actions of insulin and is important in transport of glucose into the nervous system.

**Glucagon**, a polypeptide molecule produced by the alpha cells of the islets of Langerhans, maintains blood glucose between meals and during periods of fasting. Unlike insulin, glucagon produc-es an increase in blood glucose. The most dramatic effect of glucagon is its ability to initiate glyco-genolysis or the breakdown of liver glycogen as a means of raising blood glucose, usually within a matter of minutes. Glucagon also increases the transport of amino acids into the liver and stimulates their conversion into glucose, a process called gluconeogenesis. Because liver glycogen stores are limited, gluconeogenesis is important in maintaining blood glucose levels over time.

At high concentrations, glucagon activates adipose cell lipase, making fatty acids available for use as energy. At very high concentrations, glucagon can increase the strength of the heart, increase blood flow to some tissues, including the kidneys, enhance bile secretion, and inhibit gastric acid secretion. As with insulin, glucagon secretion is regulated by blood glucose. A decrease in blood glucose concentration to a hypoglycemic level produces an immediate increase in glucagon secretion, and an increase in blood glucose to hyperglycemic levels produces a decrease in glucagon secretion. High concentrations of amino acids, as occur after a protein meal, also can stimulate glu-cagon secretion.

**Other Hormones** that can affect blood glucose include the catecholamines, growth hormone, and glucocorticoids. These hormones, along with glucagon, are sometimes called counterregulatory hormones because they counteract the storage functions of insulin in regulating blood glucose levels during periods of fasting, exercise, and other situations that either limit glucose intake or deplete glucose stores.

***Catecholamines.*** The catecholamines, *epinephrine* and *norepinephrine,* help to maintain blood glucose levels during periods of stress. Epinephrine inhibits insulin release and promotes glyco-

genolysis by stimulating the conversion of muscle and liver glycogen to glucose. Muscle glycogen cannot be released into the blood; nevertheless, the mobilization of these stores for muscle use conserves blood glucose for use by other tissues such as the brain and the nervous system. During periods of exercise and other types of stress, epinephrine inhibits insulin release from the beta cells and thereby decreases the movement of glucose into muscle cells. The catecholamines also increase lipase activity and thereby increase mobilization of fatty acids; this process conserves glucose. The blood glucose–elevating effect of epinephrine is an important homeostatic mechanism during periods of hypoglycemia.

***Growth Hormone.*** Growth hormone has many metabolic effects. It increases protein synthesis in all cells of the body, mobilizes fatty acids from adipose tissue, and antagonizes the effects of insulin. Growth hormone decreases cellular uptake and use of glucose, thereby increasing the level of blood glucose. The increased blood glucose level stimulates further insulin secretion by the beta cells. The secretion of growth hormone normally is inhibited by insulin and increased levels of blood glucose. During periods of fasting, when both blood glucose levels and insulin secretion fall, growth hormone levels increase. Exercise, such as running and cycling, and various stresses, including anesthesia, fever, and trauma, increase growth hormone levels.

Chronic hypersecretion of growth hormone, as occurs in acromegaly, can lead to glucose intolerance and the development of diabetes mellitus.

***Glucocorticoid*** HormonesThe glucocorticoid hormones, which are synthesized in the adrenal cortex along with other corticosteroid hormones, are critical to survival during periods of fasting and starvation. They stimulate gluconeogenesis by the liver, sometimes producing a 6- to 10-fold increase in hepatic glucose production. These hormones also moderately decrease tissue use of glucose. In predisposed persons, the prolonged elevation of glucocorticoid hormones can lead to hyperglycemia and the development of diabetes mellitus.There are several steroid hormones with glucocorticoid activity; the most important of these is cortisol(95% of all glucocorticoid activity). Cortisol levels increase during periods of stress, such as that produced by infection, pain, trauma, surgery, prolonged and strenuous exercise, and acute anxiety. Hypoglycemia is a potent stimulus for cortisol secretion.

## DIABETES MELLITUS

The term diabetes is derived from a Greek word meaning “going through” and mellitus from the Latin word for “honey” or “sweet”.

***Diabetes is a disorder of carbohydrate, protein, and fat metabolism resulting from an imbalance between insulin availability and insulin need.***

It can represent an absolute insulin deficiency, impaired release of insulin by the pancreatic beta cells, inadequate or defective insulin receptors, or the production of inactive insulin or insulin that is destroyed before it can carry out its activities. A person with uncontrolled diabetes is unable to transport glucose into fat and muscle cells; as a result, the body cells are starved, and the breakdown of fat and protein is increased.

**Classification and etiology.** Although diabetes mellitus clearly is a disorder of insulin availability, it probably is not a single disease. A revised system for the classification of diabetes was developed in 1997 by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.

**The revised system continues to include type 1 and type 2 diabetes**, but uses Arabic rather than Roman numerals and eliminates the use of “insulindependent” and “non–insulin-dependent” diabetes mellitus.

Type 2 diabetes currently accounts for about 90 % to 95 % of the cases of diabetes. Included in the classification system are the categories of gestational diabetes mellitus (i.e., diabetes that develops during pregnancy) and other specific types of diabetes, many of which occur secondary to other conditions (e.g., Cushing’s syndrome, hemochromatosis, pancreatitis, acromegaly). The revised classification system also includes a system for diagnosing diabetes according to stages of glucose intolerance. The revised criteria have retained the former category of impaired glucose tolerance (IGT) and have added a new category of impaired fasting plasma glucose (IFG). The categories of IFG and IGT refer to metabolic stages intermediate between normal glucose homeostasis and diabetes and are labeled together as prediabetes. A fasting plasma glucose (FPG) of less than 100 mg/dL or a 2-hour oral glucose tolerance test (OGTT) result of less than 140 mg/dL is considered normal. IFG is defined as FPG of 100 mg/dL to 125 mg/dL. IGT reflects abnormal plasma glucose measurements (140 mg/dL but < 200 mg/dL) 2 hours after an oral glucose load. IFG and IGT (i.e., prediabetes) is associated with increased risk for atherosclerotic heart disease and increased risk for progression to type 2 diabetes.

**Type 1 Diabetes Mellitus** is characterized by destruction of the pancreatic beta cells. Type 1 diabetes is subdivided into two types: type 1A, immune-mediated diabetes, and type 1B, idiopathic diabetes. Type 1A diabetes is characterized by autoimmune destruction of beta cells. This type of diabetes, formerly called juvenile diabetes, occurs more commonly in young persons but can occur at any age. Type 1 diabetes is a catabolic disorder characterized by an absolute lack of insulin, an elevation in blood glucose, and a breakdown of body fats and proteins. The absolute lack of insulin in people with type 1 diabetes mellitus means that they are particularly prone to the development of ketoacidosis. One of the actions of insulin is the inhibition of lipolysis (i.e., fat breakdown) and release of free fatty acids (FFAs) from fat cells. In the absence of insulin, ketosis develops when these fatty acids are released from fat cells and converted to ketones in the liver. Because of the loss of the first-phase insulin (preformed insulin) response, all people with type 1A diabetes require exogenous insulin replacement to reverse the catabolic state, control blood glucose levels, and prevent ketosis. The rate of beta cell destruction is quite variable. The rapidly progressive form commonly is observed in children, but also may occur in adults. The slowly progressive form usually occurs in adults and is sometimes referred to as latent autoimmune diabetes in adults (LADA). LADA may constitute up to 10 % of adults. Much evidence has focused on the inherited major histocompatibility complex (MHC) genes that encode three human leukocyte antigens (HLA-DP, HLA-DQ, and HLA-DR) found on the surface of body cells. Susceptibility to type 1 diabetes also has been associated with HLADR3 and HLA-DR4.4

It appears that what is inherited as part of the HLA genotype in people with type 1 diabetes is a susceptibility to an abnormal immune response that affects the beta cells. Type 1 diabetes–associated autoantibodies may exist for years before the onset of hyperglycemia. There are two major types of autoantibodies: insulin autoantibodies (IAAs), and islet cell autoantibodies and antibodies directed at other islet autoantigens, including glutamic acid decarboxylase (GAD) and the protein tyrosine phosphatase IA-2.

Strategies for full evaluation of the risk for developing future type 1 diabetes should include determination of at least three of the four bestestablished markers, IAAs, islet cell autoantibodies, and antibodies to GAD and IA-2, as well as a test of the firstphase insulin response. These people also may have other autoimmune disorders such as Graves' disease, rheumatoid arthritis, and Addison's disease. After the diagnosis of type 1 diabetes, there often is a short period of beta cell regeneration, during which symptoms of diabetes disappear and insulin injections are not needed. This is sometimes called the *honeymoon period.*

Immune interventions (immunomodulation) designed to interrupt the destruction of beta cells before the development of type 1 diabetes are being investigated in various trials, including the Immune interventions (immunomodulation) designed to interrupt the destruction of beta cells development of type 1 diabetes are being investigated in various trials. The term idiopathic type 1B diabetes is used to describe those cases of beta-cell destruction in which no evidence of autoimmunity is present. Only a small number of people with type 1 diabetes fall into this category; most are of African or Asian descent. Type 1B diabetes is strongly inherited. People with the disorder have episodic ketoacidosis due to varying degrees of insulin deficiency with periods of absolute insulin deficiency that may come and go.

**Type 2 Diabetes Mellitus and the Metabolic Syndrome**

**Type 2** diabetes mellitus is a heterogeneous condition that describes the presence of hyper-glycemia in association with relative insulin deficiency. In contrast to type 1 diabetes in which ab-solute insulin deficiency is present, type 2 diabetes can be associated with high, normal, or low in-sulin levels. However, in the presence of insulin resistance, the insulin cannot function effectively, and hyperglycemia can result. Type 2 diabetes is therefore a disorder of both insulin levels (beta cell dysfunction) and insulin function (insulin resistance).

**The metabolic abnormalities that contribute to hyperglycemia in people with type 2 diabetes include**

***(1) impaired beta cell function and insulin secretion***

***(2) peripheral insulin resistance***

***(3) increased hepatic glucose production.***

Insulin resistance initially produces an increase in beta cell secretion of insulin (resulting in hyperinsulinemia) as the body attempts to maintain a normoglycemic state. In time, however, the insulin response declines because of increasing beta cell dysfunction. During the evolutionary phase, an individual with type 2 diabetes may eventually develop absolute insulin deficiency because of progressive beta cell failure. As with persons with type 1 diabetes, these persons require insulin

therapy to survive. Because most persons with type 2 diabetes do not have an absolute insulin deficiency, they are less prone to develop ketoacidosis as compared with people with type 1 diabetes (the presence of circulating insulin in most type 2 diabetics suppresses ketone body formation).

***Beta Cell Dysfunction.*** Specific causes of beta cell dysfunction in patients with prediabetes and type 2 diabetes may include:

***(1) an initial decrease in the beta cell mass (this may be related to genetic factors responsible for beta cell differentiation and function, and environmental factors such as the presence of maternal diabetes during pregnancy),***

***(2) increased beta cell apoptosis/decreased regeneration,***

***(3) long-standing insulin resistance leading to beta cell exhaustion,***

***(4) chronic hyperglycemia can induce beta cell desensitization termed glucotoxicity,***

***(5) chronic elevation of free fatty acids can cause toxicity to beta cells termed lipotoxicity,***

***(6) amyloid deposition in the beta cell can cause dysfunction.***

***Insulin Resistance and the Metabolic Syndrome.*** There is increasing evidence to suggest that insulin resistance not only contributes to the hypergly-cemia in persons with type 2 diabetes, but may also play a role in other metabolic abnormalities. These include high levels of plasma triglycerides and low levels of high-density lipoproteins (HDLs), hypertension, systemic inflammation (as detected by C-reactive protein [CRP] and other mediators), abnormal fibrinolysis, abnormal function of the vascular endothelium, and macrovascular disease (coronary artery, cerebrovascular, and peripheral arterial disease). This constellation of abnormalities often is referred to as the insulin resistance syndrome, syndrome X, or the preferred term, metabolic syndrome. A major factor in persons with the metabolic syndrome that leads to type 2 diabetes is central obesity. Approximately 80% of persons with type 2 diabetes are overweight. Obese people have increased resistance to the action of insulin and impaired suppression of glucose production by the liver, resulting in both hyperglycemia and hyperinsulinemia. The type of obesity is an important consideration in the development of type 2 diabetes. It has been found that people with upper body obesity (central obesity) are at greater risk for developing type 2 diabetes and metabolic disturbances than persons with lower body obesity.

It has been theorized that the insulin resistance and increased glucose production in obese people with type 2 diabetes may stem from an increased concentration of free fatty acids (FFAs). Visceral obesity is especially important because it is accompanied by increases in fasting and postprandial FFA con-centrations.

**This has several consequences:**

(1) acutely, FFAs act at the level of the beta cell to stimulate insulin secretion, which, with excessive and chronic stimulation, causes beta cell failure (lipotoxicity);

(2) they act at the level of the peripheral tissues to cause insulin resistance and glucose underutilization by inhibiting glucose uptake and glycogen storage through a reduction in muscle glycogen synthetase activity;

(3) the accumulation of FFAs and triglycerides reduce hepatic insulin sensitivity, leading to increased hepatic glucose production and hyperglycemia, especially fasting plasma glucose levels.

A proposed link to the insulin resistance associated with obesity is an adipose cell secretion (adipocytokine) called adiponectin. Adiponectin is secreted by adipose tissue and circulates in the blood. It has been shown that decreased levels of adiponectin coincide with insulin resistance patients with obesity and type 2 diabetes.

**Other Specific Types**. The category of other specific types of diabetes, formerly known as secondary diabetes, describes diabetes that is associated with certain other conditions and syndromes. Such diabetes can occur with pancreatic disease or the removal of pancreatic tissue and with endocrine diseases, such as acromegaly, Cushing's syndrome, or pheochromocytoma. Environmental agents that have been associated with altered pancreatic beta-cell function include viruses (e.g., mumps, congenital rubella, coxsackievirus) and chemical toxins. Among the suspected chemical toxins (nitrosamines, streptozocin). Several diuretics – thiazides and loop diuretics elevate blood glucose. These diuretics in-crease potassium loss, which is thought to impair insulin release. Other drugs known to cause hyperglycemia are diazoxide, glucocorticoids, levodopa, oral contraceptives, sympathomimetics, phenothiazines, phenytoin, and total parenteral nutrition (i.e., hyperalimentation).

However, these patients are now developing metabolic derangements similar to the features seen in the metabolic syndrome (insulin resistance, high levels of plasma triglycerides, low levels of high-density lipoproteins, hypertension, obesity, systemic inflammation [as detected by C-reactive protein (CRP) and other mediators], abnormal fibrinolysis, endothelial dysfunction, and macrovascular disease).

**CLINICAL MANIFESTATIONS.** Diabetes mellitus may have a rapid or an insidious onset. In type 1 diabetes, signs and symptoms often arise suddenly. Type 2 diabetes usually develops insidiously; its presence may be detected during a routine medical examination or when a patient seeks medical care for other reasons.

**The most commonly identified signs and symptoms of diabetes are referred to as the *three polys:***

(1) polyuria (*i.e.,* excessive urination),

(2) polydipsia (*i.e.,* excessive thirst),

(3) polyphagia (*i.e.,* excessive hunger).

**These three symptoms are closely related to the hyperglycemia and glycosuria of diabetes.** lucose is a small, osmotically active molecule. When blood glucose levels are sufficiently elevated, the amount of glucose filtered by the glomeruli of the kidney exceeds the amount that can be reabsorbed by the renal tubules; this results in glycosuria accompanied by large losses of water in the urine. Thirst results from the intracellular dehydration that occurs as blood glucose levels rise and water is pulled out of body cells, including those in the thirst center. Cellular dehydration also causes dryness of the mouth. Polyphagia usually is not present in people with type 2 diabetes. Type 1 diabetes, probably results from cellular starvation and the depletion of cellular stores of carbohydrates, fats, and proteins. Weight loss despite normal or increased appetite is a common occurrence in people with uncontrolled type 1 diabetes. The cause of weight loss is twofold. First, loss of body fluids results from osmotic diuresis.

**Vomiting** may exaggerate the fluid loss in ketoacidosis. Second, body tissue is lost because the lack of insulin forces the body to use its fat stores and cellular proteins as sources of energy. In terms of weight loss, there often is a marked difference between type 2 diabetes and type 1 diabetes.

**Weight loss** is a frequent phenomenon in people with uncontrolled type 1 diabetes, whereas many people with uncomplicated type 2 diabetes have problems with obesity. Other signs and symptoms of hyperglycemia include recurrent blurred vision, fatigue, paresthesias, and skin infections. **Blurred vision** develops as the lens and retina are exposed to hyperosmolar fluids. Lowered plasma volume produces weakness and fatigue.

**Paresthesias reflect** a temporary dysfunction of the peripheral sensory nerves. Chronic skin infections are common in people with type 2 diabetes.

**Pruritus and vulvovaginitis** resulting from candidal infections (hyperglycemia and glycosuria favor the growth of yeast organisms) are common initial complaints in women with diabetes. Balanitis secondary to candidal infections can occur in men.

**Diagnostic tests.** The diagnosis of diabetes mellitus in nonpregnant adults is based on fasting plasma glucose levels, casual plasma glucose tests, or the results of a glucose challenge test (Table 1). Testing for diabetes should be considered in all individuals 45 years of age and older. Testing should be considered at a younger age in people who are obese, have a first-degree relative with diabetes, are members of a high-risk group, or have delivered an infant weighing more than

***Blood Tests*** Blood glucose measurements are used in both the diagnosis and management of diabetes. Diagnostic tests include the fasting plasma glucose, casual plasma glucose, and glucose tolerance test. Laboratory and capillary or "finger stick" glucose tests are used for glucose management in people with diagnosed diabetes. Glycosylated hemoglobin (A1C, previously termed HbA1c) provides a measure of glucose control over time Table 4.

***Fasting Blood Glucose Test.*** The fasting plasma glucose has been suggested as the preferred diagnostic test because of ease of administration, convenience, patient acceptability, and cost. Glucose levels are measured after food has been withheld for at least 8 hours. An FPG level below 100 mg/dL is considered normal. A level between 100 mg/dL and 126 mg/dL is significant and is defined as impaired fasting glucose. If the FPG level is 126 mg/dL or higher on two occasions, diabetes is diagnosed.

***Casual Blood Glucose Test.*** A casual plasma glucose is one that is done without regard to the time of the last meal. A casual plasma glucose concentration that is unequivocally elevated (≥200 mg/dL) in the presence of classic symptoms of diabetes such as polydipsia, polyphagia, polyuria, and blurred vision is diagnostic of diabetes mellitus at any age.

***Glucose Tolerance Test.*** The oral glucose tolerance test is an important screening test for diabetes. The test measures the body's ability to store glucose by removing it from the blood. In men and

women, the test measures the plasma glucose response to 75 g of concentrated glucose solution at selected intervals, usually 1 hour and 2 hours. In pregnant women, a glucose load of 100 g is given with an additional 3-hour plasma glucose determination. In people with normal glucose tolerance, blood glucose levels return to normal within 2 to 3 hours after ingestion of a glucose load, in which case, it can be assumed that sufficient insulin is present to allow glucose to leave the blood and enter body cells. Because a person with diabetes lacks the ability to respond to an increase in blood glucose by releasing adequate insulin to facilitate storage, blood glucose levels rise above those observed in normal people (*Table 1*).

Table 1

**Expert Committee on the Diagnosis and Classification of Diabetes Mellitus Using Fasting Plasma Glucose (FPG) and Oral Glucose Tolerance Test (OGTT)**

| Test | Normoglycemic | Impaired FPG (IFG)* | Impaired GT (IGT)* | Diabetes Mellitus† |
|---|---|---|---|---|
| FPG‡ | <100 mg/dL (5.6 mmol/L) | 100–125 mg/dL (5.6–6.9 mmol/L) | | ≥126 mg/dL (7.0 mmol/L) |
| 2-h OGTT§ | <140 mg/dL (7.8 mmol/L) | | 140–199 mg/dL (7.8–11.1 mmol/L) | ≥200 mg/dL (11.1 mmol/L) |
| Other | | | | Symptoms of diabetes mellitus and casual plasma glucose ≥200 mg/dL |

***Capillary Blood Tests and Self-Monitoring of CapillaryBlood Glucose Levels.*** These methods use a drop of capillary blood obtained by pricking the finger or forearm with a special needle or small lancet.The drop of capillary blood is placed on or absorbed by a reagent strip, and glucose levels are determined electronically using a glucose meter. Laboratory tests that use plasma for measurement of blood glucose give results that are 10 % to 15 % higher than the finger stick method, which uses whole blood.

***Glycated Hemoglobin Testing.*** Glycated hemoglobin, also referred to as glycohemoglobin, glycosylated hemoglobin, HbA1c, or A1C (the preferred term), is a term used to describe hemoglobin into which glucose has been incorporated. Hemoglobin normally does not contain glucose when it is released from the bone marrow. During its 120-day life span in the red blood cell, hemoglobin normally becomes glycated to form hemoglobins A1a and A1b (2 % to 4 %) and A1c (termed A1C, 4 % to 6 %). In uncontrolled diabetes or diabetes with hyperglycemia, there is an increase in the level of A1c. Because glucose entry into the red blood cell is not insulin dependent, the rate at which glucose becomes attached to the hemoglobin molecule depends on blood glucose. Glycosylation is irreversible, and the level of A1c present in the blood provides an index of blood glucose levels over the previous 6 to 12 weeks.

**Urine Tests**. The ease, accuracy, and convenience of self-administered blood glucose monitoring techniques have made urine testing for glucose obsolete for most people with diabetes. These tests only reflect urine glucose levels and are influenced by such factors as the renal threshold for glucose, fluid intake and urine concentration, urine testing methodologies, and some drugs. Unlike glucose tests, urine ketone determinations remain an important part of monitoring diabetic control, particularly in people with type 1 diabetes who are at risk for devel-oping ketoacidosis and in pregnant diabetic women to check the adequacy of nutrition and glucose control

**ACUTE COMPLICATIONS**

**The three major acute complications of diabetes are**

- *diabetic ketoacidosis*
- *hyperosmolar hyperglycemic state*
- *hypoglycemia*.

**Diabetic Ketoacidosis.** Diabetic ketoacidosis (DKA) occurs when ketone production by the liver exceeds cellular use and renal excretion. DKA most commonly occurs in a person with type 1 diabetes, in whom the lack of insulin leads to mobilization of fatty acids from adipose tissue because of the unsuppressed adipose cell lipase activity that breaks down triglycerides into fatty acids and glycerol. The increase in fatty acid levels leads to ketone production by the liver. It can occur at the onset of the disease, often before the disease has been diagnosed. For example, a mother may bring a child into the clinic or emergency department with reports of lethargy, vomiting, and abdominal pain, unaware that the child has diabetes. Stress increases the release of gluconeogenic hormones and predisposes the person to the development of ketoacidosis. DKA often is preceded by physical or emotional stress, such as infection, pregnancy, or extreme anxiety. In clinical practice, ketoacidosis also occurs with the omission or inadequate use of insulin.

***The three major metabolic derangements in DKA are:***

- *hyperglycemia*
- *ketosis*
- *metabolic acidosis*.

Hyperglycemia leads to osmotic diuresis, dehydration, and a critical loss of electrolytes. Hyperosmolality of extracellular fluids from hyperglycemia leads to a shift of water and potassium from the intracellular to the extracellular compartment. Extracellular sodium concentration frequently is low or normal despite enteric water losses because of the intra-cellular–extracellular fluid shift. This dilutional effect is referred to as pseudohyponatremia. Serum potassium levels may be normal or elevated, despite total potassium depletion resulting from protracted polyuria and vomiting. Metabolic acidosis is caused by the excess ketoacids that require buffering by bicarbonate ions; this leads to a marked decrease in serum bicarbonate levels. Compared with an insulin reaction, DKA usually is slower in onset, and recovery is more prolonged. The person typically has a history of 1 or 2 days of polyuria, polydipsia, nausea, vomiting, and marked fatigue, with eventual stupor that can progress to coma. Abdominal pain and tenderness may be experienced without abdominal disease. The breath has a characteristic fruity smell because of the presence of the volatile ketoacids. Hypotension and tachycardia may be present because of a decrease in blood volume. A number of the signs and symptoms that occur in DKA are related to compensatory mechanisms. The heart rate increases as the body compensates for a decrease in blood volume, and the rate and depth of respiration increase (i.e., Kussmaul's respiration) as the body attempts to prevent further decreases in pH. volume and tissue perfusion, decrease serum glucose, correct the acidosis, and correct electrolyte imbalances.

*It is important to replace fluid and electrolytes and correct pH while bringing the blood glucose concentration to a normal level. Too rapid a drop in blood glucose may cause hypoglycemic symptoms and cerebral edema.*

**Hyperosmolar Hyperglycemic State.** The hyperosmolar hyperglycemic state (HHS) is characterized by hyperglycemia (blood glucose > 600 mg/dL), hyperosmolarity (plasma osmolarity > 310 mOsm/L) and dehydration, the absence of ketoacidosis, and depression of the sensorium. HHS may occur in various conditions, including type 2 diabetes, acute pancreatitis, severe infection, myocardial infarction, and treatment with oral or parenteral nutrition solutions. Two factors appear to contribute to the hyperglycemia that precipitates the condition: an increased resistance to the effects of insulin and an excessive carbohydrate intake. In hyperosmolar states, the increased serum osmolarity has the effect of pulling water out of body cells, including brain cells. The condition may be complicated by thromboembolic events arising because of the high serum osmolality. The most prominent manifestations are dehydration, neurologic signs and symptoms, and excessive thirst. The neurologic signs include grand mal seizures, hemiparesis, Babinski's reflexes, aphasia, muscle fasciculations, hyperthermia, hemianopia, nystagmus, and visual hallucinations.

**Hypoglycemia**

***Hypoglycemia, or an insulin reaction, occurs from a relative excess of insulin in the blood and is characterized by below normal blood glucose levels.*** It occurs most commonly in people treated with insulin injections, but also can result from some oral hypoglycemic agents. Hypoglycemia usually has a rapid onset and progression of symptoms.

**The signs and symptoms of hypoglycemia can be divided into two categories:**

- those caused by altered cerebral function (headache, difficulty in problem solving, disturbed or altered behavior, coma)
- those related to activation of the autonomic nervous system.

Because the brain relies on blood glucose as its main energy source, hypoglycemia produces behaviors related to altered cerebral function. At the onset of the hypoglycemic episode, activation of the parasympathetic nervous system often causes hunger. The initial parasympathetic response is followed by activation of the sympathetic nervous system; this causes anxiety, tachycardia, sweating, and constriction of the skin vessels (i.e., the skin is cool and clammy).

The signs and symptoms of hypoglycemia are more variable in children and in elderly people. Elderly people may not display the typical autonomic responses associated with hypoglycemia but frequently develop signs of impaired function of the central nervous system, including mental confusion. Some medications, such as β-adrenergic–blocking drugs, interfere with the sympathetic response normally seen in hypoglycemia. Many factors precipitate an insulin reaction in a person with

type 1 diabetes, including error in insulin dose, failure to eat, increased exercise, decreased insulin need after removal of a stress situation, medication changes, and a change in insulin site.

The most effective treatment of an insulin reaction is the immediate administration of 15 to 20 g of glucose in concentrated carbo-hydrate source, which can be repeated as necessary. Monosaccharides such as glucose, which can be absorbed directly into the bloodstream, work best for this purpose. Complex carbohydrates can be administered after the acute reaction has been controlled to sustain blood glucose levels. Alternative methods for increasing blood glucose: a small amount of glucose gel (available in most pharmacies) may be inserted into the buccal pouch when glucagon is unavailable. Glucagon may be given intramuscularly or subcutaneously. Glucagon acts by hepatic glycogenolysis to raise blood sugar. The liver contains only a limited amount of glycogen (approximately 75 g); glucagon is ineffective in people whose glycogen stores have been depleted.

## COUNTERREGULATORY MECHANISMS AND THE SOMOGYI EFFECT AND DAWN PHENOMENON

The Somogyi effect describes a cycle of insulin-induced posthypoglycemic episodes. In people with diabetes, insulininduced hypoglycemia produces a compensatory increase in blood levels of catecholamines, glucagon, cortisol, and growth hormone. These counterregulatory hormones cause blood glucose to become elevated and produce some degree of insulin resistance.

The cycle begins when the increase in blood glucose and insulin resistance is treated with larger insulin doses. The hypoglycemic episode often occurs during the night or at a time when it is not recognized, rendering the diagnosis of the phenomenon more difficult. Research suggests that even rather mild insuli-nassociated hypoglycemia, which may be asymptomatic, can cause hyperglycemia in those with type 1 diabetes through the recruitment of counterregulatory mechanisms, although the insulin action does not wane.

**Chronic complications.** The chronic complications of diabetes include disorders of the microvasculature (*i.e.,* neuropathies, nephropathies, and retinopathies), macrovascular complications, and foot ulcers. The microvascular complications occur in the insulinindependent tissues of the body—tissues that do not require insulin for glucose entry into the cell. This probably means that intracellular glucose concentrations in many of these tissues approach or equal those in the blood. The level of chronic glycemia is the best-established concomitant factor associated with diabetic complications. The Diabetes Control and Complications Trial (DCCT), which was conducted with 1441 people with type 1 diabetes, has demonstrated that the incidence of retinopathy, nephropathy, and neuropathy can be reduced by intensive diabetic treatment. Similar results have been demonstrated by the UKPDS in people with type 2 diabetes.

**Theories of Pathogenesis**. The interest among researchers in explaining the causes and development of chronic lesions in a person with diabetes has led to a number of theories. Several of these theories have been summarized to prepare the reader for understanding specific chronic complications.

***Polyol Pathway.*** A polyol is an organic compound that contains three or more hydroxyl (OH) groups. The polyol pathway refers to the intracellular mechanisms responsible for changing the number of hydroxyl units on a glucose molecule. In the sorbitol pathway, glucose is transformed first to sorbitol and then to fructose. This process is activated by the enzyme aldose reductase. Although glucose is converted readily to sorbitol, the rate at which sorbitol can be converted to fructose and then metabolized is limited. Sorbitol is osmotically active, and it has been hypothesized that the presence of excess intracellular amounts may alter cell function in those tissues that use this pathway (e.g., lens, kidneys, nerves, blood vessels). In the lens, for example, the osmotic effects of sorbitol cause swelling and opacity. Increased sorbitol also is associated with a decrease in myoinositol and reduced adenosine triphosphatase activity.

The reduction of these compounds may be responsible for the peripheral neuropathies caused by Schwann cell damage. Aldose reductase inhibitors are in development to try to reduce complications resulting from this pathway.

***Formation of Advanced Glycation End Products.*** Glycoproteins, or what could be called *glucose proteins,* are normal components of the basement membrane in smaller blood vessels and capillaries. These glycoproteins are also termed *advanced glycation end products* (AGEs). It has been suggested that the increased intracellular concentration of glucose associated with uncontrolled blood glucose levels in diabetes favors the formation of AGEs. These abnormal glycoproteins are thought to produce structural defects in the basement membrane of the microcirculation and to contribute to eye, kidney,

and vascular complications. Some of the altered cellular functions resulting from AGEs are due to binding to specific receptors for AGEs (RAGEs).

***Problems With Tissue Oxygenation*** Proponents of the tissue oxygenation theories suggest that many of the chronic complications of diabetes arise because of a decrease in oxygen delivery in the small vessels of the microcirculation. Among the factors believed to contribute to this inadequate oxygen delivery is a defect in red blood cell function that interferes with the release of oxygen from the hemoglobin molecule. In support of this theory is the finding of a two- to threefold increase in A1C in some people with diabetes.

***Protein Kinase C.*** Diacylglycerol (DAG) and protein kinase C (PKC) are critical intracellular signaling molecules that can regulate many vascular functions, including permeability, vasodilator release, endothelial activation, and growth factor signaling. Levels of DAG and PKC are elevated in diabetes. Activation of PKC in blood vessels of the retina, kidney, and nerves can produce vascular damage.

**Neuropathies.** The incidence of peripheral neuropathies is high among people with diabetes. **Two types of pathologic changes have been observed in connection with diabetic peripheral neuropathies.**

- ***The first*** *is a thickening of the walls of the nutrient vessels that supply the nerve, leading to the assumption that vessel ischemia plays a major role in the development of these neural changes.*
- ***The second*** *finding is a segmental demyelinization process that affects the Schwann cell. This demyelinization process is accompanied by a slowing of nerve conduction.*

***Somatic Neuropathy.*** A distal symmetric polyneuropathy, in which loss of function occurs in a stocking-glove pattern, is the most common form of peripheral neuropathy. Somatic sensory involvement usually occurs first and usually is bilateral, symmetric, and associated with diminished perception of vibration, pain, and temperature, particularly to the lower extremities. The loss of feeling, touch, and position sense increases the risk for falling. Impairment of temperature and pain sensation increases the risk for serious burns and injuries to the feet. Painful diabetic neuropathy involves the somatosensory neurons that carry pain impulse. This disorder, which causes hypersensitivity to light touch and occasionally severe "burning pain," particularly at night, can become physically and emotionally disabling.

***Autonomic Neuropathy.*** The autonomic neuropathies involve disorders of sympathetic and parasympathetic nervous system function, There may be disorders of vasomotor function, decreased cardiac responses, impaired motility of the gastrointestinal tract, inability to empty the bladder, and sexual dysfunction. Defects in vasomotor reflexes can lead to dizziness and syncope when the person moves from the supine to the standing position. Incomplete emptying of the bladder predisposes to urinary stasis and bladder infection and increases the risk for renal complications.

***Disorders of Gastrointestinal Motility.*** Gastrointestinal motility disorders are common in persons with longstanding diabetes. The symptoms vary in severity and include constipation, diarrhea and fecal incontinence, nausea and vomiting, and upper abdominal discomfort referred as dyspepsia. Gastroparesis (delayed emptying of stomach) is commonly seen in persons with diabetes. The disorder is characterized by complaints of epigastric discomfort, nausea, postprandial vomiting, bloating, and early satiety. Abnormal gastric emptying also jeopardizes the regulation of the blood glucose level. Strict control of blood glucose is important because hyperglycemia may slow gastric emptying, even in the absence of diabetic neuropathy. Diarrhea is another common symptom is typically intermittent, watery, painless, and nocturnal and may be associated with fecal incontinence.

**Nephropathies.** Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD), accounting for 40% of new cases. The complication affects people with both type 1 and type 2 diabetes.The most common kidney lesions in people with diabetes are those that affect the glomeruli, including capillary basement membrane thickening, diffuse glomerular sclerosis, and nodular glomerulosclerosis. Changes in the capillary basement membrane take the form of thickening of basement membranes along the length of the glomeruli. Diffuse glomerulosclerosis consists of thickening of the basement membrane and the mesangial matrix. Nodular glomerulosclerosis, also called intercapillary glomerulosclerosis or Kimmelstiel-Wilson disease, is a form of glomerulosclerosis that involves the development of nodular lesions in the glomerular capillaries of the kidneys, causing impaired blood flow with progressive loss of kidney function and, eventually, renal failure. It is thought to occur only in people with diabetes. Changes in the basement membrane in diffuse glomerulosclerosis, causing proteinuria and the development of hypoproteinemia, edema, and others signs of impaired kidney function (risk factors: genetic, familial predisposition, elevated BP, smoking, hyperlipidemia, and microalbumuria.

Kidney enlargement, nephron hypertrophy, and hyperfiltration occur early in the disease, suggesting increased work of the kidneys in reabsorbing excessive amounts of glucose. One of the first manifestations of diabetic nephropathy is an increase in urinary albumin excretion (i.e., micro-albuminuria). Microalbuminuria is defined as a urine protein loss between 30 and 300 mg/day; or between and 300 μg/mg creatinine on albumin-to-creatinine ratio (A/C ratio) from a spot urine collection. Both systolic and diastolic hypertension accelerates the progression of diabetic nephropathy.

**Retinopathies.** Diabetes is the leading cause of acquired blindness. Although people with diabetes are at increased risk for development of cataracts and glaucoma, retinopathy is the most common pattern of eye disease. ***Diabetic retinopathy is characterized by abnormal retinal vascular permeability, microaneurysm formation, neovascularization and associated hemorrhage, scarring, and retinal detachment.*** Twenty years after the onset of diabetes, nearly all people with type 1 diabetes and more than 60 % of people with type 2 diabetes have some degree of retinopathy. Pregnancy, puberty, and cataract surgery can accelerate these changes.

People with persistently elevated glucose levels or proteinuria should be examined yearly. Women who are planning a pregnancy should be counseled on the risk for development or progression of diabetic retinopathy. People with macular edema, moderate to severe non proliferative retinopathy, or any proliferative retinopathy should receive the care of an ophthalmologist.

**Macrovascular Complications.** Diabetes mellitus is a major risk factor for ***coronary artery disease, cerebrovascular disease, and peripheral vascular disease.*** Multiple risk factors for macrovascular disease, including obesity, hypertension, hyperglycemia, hyperinsulinemia, hyperlipidemia, altered platelet function, endothelial dysfunction, systemic inflammation (as evidenced by increased CRP), and elevated fibrinogen levels, frequently are found in people with diabetes. There appear to be differences between type 1 and type 2 diabetes in terms of duration of disease and the development of macrovascular disease. In people with type 2 diabetes, macrovascular disease may be present at the time of diagnosis. In type 1 diabetes, the attained age and the duration of diabetes appear to correlate with the degree of macrovascular disease.

**Diabetic Foot Ulcers.** Foot problems are common among people with diabetes and may become severe enough to cause ulceration, infection, and, eventually, a need for amputation. Foot problems have been re-ported as the most common complication leading to hospitalization among people with diabetes. In people with diabetes, lesions of the feet represent the effects of neuropathy and vascular insufficiency. Approximately 60 % to 70 % of people with diabetic foot ulcers have neuropathy without vascular disease, 15 % to 20 % have vascular disease. Distal symmetric neuropathy is a major risk factor for foot ulcers. People with sensory neuropathies have impaired pain sensation and often are unaware of the constant trauma to the feet caused by poorly fitting shoes, improper weight bearing, hard objects or pebbles in the shoes. When the abnormal focus of pressure is coupled with loss of sensation, a foot ulcer can occur. Common sites of trauma are the back of the heel, the plantar metatarsal area, or the great toe, where weight is borne during walking. All persons with diabetes should receive a full foot examination. This examination should include assessment of protective sensation, foot structure and biomechanics, vascular status, and skin integrity. Evaluation of neurologic function should include a somatosensory test.

The monofilament is held in the hand or attached to a handle at one end. When the unattached or unsupported end of the monofilament is pressed against the skin until it buckles or bends slightly, it delivers 10 g of pressure at the point of contact. The test consists of having the person being tested report at which of two moments he or sheis being touched by the monofilament

For example, the examiner will call out “one” and then “two” and briefly touch the monofilament to the site at one of the two test times. Between 4 and 10 sites per foot are touched. An in-correct response at even one site indicates increased risk for neuropathy and foot complications. Smoking should be avoided because it causes vasoconstriction and contributes to vascular disease. Because cold produces vasoconstriction, appropriate foot coverings should be used to keep the feet warm and dry. Toenails should be cut straight across to prevent ingrown toenails.

Persons with diabetes mellitus develop more extensive and rapidly progressive peripheral vascular disease than do nondiabetic individuals. Cardiovascular risk factors should be addressed in patients with diabetic ulcers and peripheral vascular disease. Ulcers, which are resistant to standard therapy, may respond to the application of growth factors. Growth factors provide a means by which cells communicate with each other and can have profound effects on cell proliferation, mi-gration, and extracellular matrix synthesis.

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## PRACTICAL LESSON № 14 (16 stom.)
## Topic: DISORDERS OF WATER-ELECTROLYTE METABOLISM

**The topicality.** Disorders of water metabolism are typical metabolic disorders in the body, accompanied by a lot of serious diseases, as well as appear in healthy people who are in emergencies related to a limited or complete cessation of water flow. Variations in water content are one of the most dangerous disorders of homeostasis, which adversely affect the functions of all systems and is often the cause of complications and death of various diseases. Knowledge and systematic study of water balance should enter into an obligatory scheme of clinical research for many diseases, which will properly diagnose and implement a rational therapy to correct these violations.There are two forms of water metabolism disorders: dehydration and fluid retention (hyper-hydration). A variation of an excessive accumulation of extracellular fluid is swelling. The study of swelling can reveal the basic mechanisms of its development, and show the pathogenic nature of the localization of edema in vital organs (lungs, larynx, brain).

**Overall Objective –** be able to characterize a violation of water exchange as a typical metabolic disorders, swelling like a typical pathological process, to classify and explain the basic pathogenetic mechanisms of edema.

**To do this we should be able to (specific objectives):**

Classify forms of violation of water metabolism (dehydration, hyperhydration).

2. Formulate a definition of "swelling".

3. Give etiologic and pathogenetic classification of edema. Analyze the pathogenetic mechanisms that underlie the different types of edema.

4. Modeled pulmonary edema by intraperitoneal injection of adrenaline, select physiological indicators to assess the degree of its development, and analyze the mechanism.

5. Determine the amount of pulmonary factor. Show by neural mechanisms anesthesia's role in the pathogenesis of pulmonary edema.

6. To substantiate on the basis of the data obtained pathogenetic therapy in edema of various etiologies.

**The necessary basic knowledge and skills to achieve the goals of studying.**

**To be able to:**

1. Determine the concept of "water balance", its size, and components.

2. The mechanism of regulation of the water balance, to explain the role of hydrostatic, osmotic, and oncotic pressure in the mechanisms of transcapillary water exchange.

3. To show the role of neuroendocrine regulation in maintaining water balance.

**Questions to the lesson**

1. Positive and negative water balance. Hyperhydria and hypohydria. Their types.
2. What is edema. Etiology and pathogenesis.
3. The role of neuro-humoral mechanisms in the pathogenesis of oedemas.
4. Types of oedemas. The specific role of pathogenic factors in the mechanism of different types of oedemas.
5. The mechanism of adrenaline edema of the lungs.
6. Anasarca. Types.

### EXPERIMENTAL PART OF LESSON

**Experiment 1:** Experimental oedema of lungs and the study of the influence of CNS in its development.

**The object of the experiment:** white mice.

**Apparatus and reactives:** injections, scissors, pincers, hemostatic clamp, weigh balance, 0.1 % solution of adrenaline, 10 % solution of urethane.

**The conduction of the experiment:** Weigh the animal. Observe the condition of the animal, depth, rate of respiration, and the color of the skin. Inject intraperitoneally into one of the mice 0.3 ml solution of urethane. Within 15 minutes watch for the development of narcosis. Simultaneously inject intraperitoneally into mouse 1 (in a state of narcosis) and mouse 2 (control mouse) 0.3 ml 1 % solution of adrenaline. Compare the state of both animals. Watch for changes in behavior, respiration, skin color, and foaming in the mouth. After the death of one mouse, watch the second in a period of ten minutes. Cut open the animals, take the lungs out, describe the external appearance, weigh and calculate the lung coefficient.

**Method of calculating lung's coefficient:** Cut the skin of the neck along linea mediana, find the trachea and place a hemostatic clamp on it. Cut open the thoracic cavity, take out the lungs and the heart. Separate the heart and large vessels from the lungs, take off the clamp from the trachea and remove the trachea. Weigh the lungs and calculate the relative percentage of the weight of the lungs to the body weight (*Table 1*).

Table 1

| Mouse № 1 | | | | | Mouse № 2 | | | |
|---|---|---|---|---|---|---|---|---|
| Without of narcosis | | | | | With narcosis | | | |
| **Time** | **Behavior** | **Sound react** | **Colour skin** | **Respiratory rate** | **Behavior** | **Sound react** | **Colour skin** | **Respiratory rate** |
| | | | | | | | | |
| | **Injection of 0,5 ml 0,1 % solution of adrenalin** | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

**Result:**

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THEORETICAL MATERIAL FOR PREPARATION TO LESSON

**DISORDERS OF FLUID AND ELECTROLYTE BALANCE**

Fluids and electrolytes are present in body cells, in the tissue spaces between the cells, and in the blood that fills the vascular compartment. Body fluids transport gases, nutrients, and wastes, help generate the electrical activity needed to power body functions. Although fluid volume and composition remain relatively constant in the presence of a wide range of changes in intake and output, conditions such as environmental stresses and disease can increase fluid, impair its intake, and otherwise interfere with mechanisms that regulate fluid volume, composition, and distribution.

**The ICF (intracellular)** compartment consists of fluid contained within all of the billions of cells in the body. It is the larger of the two compartments, with approximately two thirds of the body water in healthy adults. The remaining one third of body water is in the **ECF (extracellular)** compartment, which contains all the fluids outside the cells, including those in the interstitial or tissue spaces and blood vessels. The ECF, including the plasma and interstitial fluids, contains large amounts of sodium and chloride, moderate amounts of bicarbonate, but only small quantities of potassium, magnesium, calcium, and phosphate. In contrast to the ECF, the ICF contains almost no calcium; small amounts of sodium, chloride, bicarbonate, and phosphate; moderate amounts of magnesium; and large amounts of potassium (*Table 2*). Particularly with potassium, which is approximately 28 times more concentrated inside the cell than outside.

Table 2

## Concentration extracellular intracellular electrolyte

| Electrolyte | Extracellular Concentration* | Intracellular Concentration* |
|---|---|---|
| Sodium | 135–145 mEq/L | 10–14 mEq/L |
| Potassium | 3.5–5.0 mEq/L | 140–150 mEq/L |
| Chloride | 98–106 mEq/L | 3–4 mEq/L |
| Bicarbonate | 24–31 mEq/L | 7–10 mEq/L |
| Calcium | 8.5–10.5 mg/dL | <1 mEq/L |
| Phosphate/ phosphorus | 2.5–4.5 mg/dL | 4 mEq/kg† |
| Magnesium | 1.8–3.0 mg/dL | 40 mEq/kg† |

The cell membrane serves as the primary barrier to the movement of substances between the ECF and ICF compartments. Lipid-soluble substances such as gases (*i.e.,* oxygen and carbon dioxide), which dissolve in the lipid bilayer of the cell membrane, pass directly through the membrane. Many ions, such as sodium ($Na^+$) and potassium ($K^+$) rely on transport mechanisms such as the $Na^+/K^+$ pump that is located in the cell membrane for movement across the membrane. Because the $Na^+/K^+$ pump relies on adenosine triphosphate (ATP) and the enzyme ATPase for energy, it is often referred to as the $Na^+/K^+$-ATPase membrane pump. Water rosses the cell membrane by osmosis using special protein channels called ***aquaporins.***

## INTRODUCTORY CONCEPTS

### Dissociation of Electrolytes

Body fluids contain water and electrolytes. Electrolytes are substances that dissociate in solution to form charged particles, or *ions.* For example, a sodium chloride (NaCl) molecule dissociates to form a positively charged $Na^+$ and a negatively charged $Cl^-$ion. Particles that do not dissociate into ions such as glucose and urea are called *nonelectrolytes.* The distribution of electrolytes between body compartments is influenced by their electrical charge. However, one cation may be exchanged for another, provided it carries the same charge. For example, a positively charged $H^+$ ion may be exchanged for a positively charged $K^+$ ion, and a negatively charged bicarbonate ($HCO_3^-$) ion may be exchanged for another negatively charged $Cl^-$anion.

### Diffusion and Osmosis

***Diffusion.*** *Diffusion* is the movement of charged or uncharged particles along a concentration gradient. It is the motion of these particles, each colliding with one another, that supplies the energy for diffusion. Because there are more molecules in constant motion in a concentrated solution, particles move from an area of higher concentration to one of lower concentration.

***Osmosis.*** *Osmosis* is the movement of water across a semipermeable membrane (*i.e.,* one that is permeable to water but impermeable to most solutes). As with particles, water diffuses down its concentration gradient, moving from the side of the membrane with the lesser number of particles and greater concentration of water to the side with the greater number of particles and lesser concentration of water. As water moves across the semipermeable membrane, it generates a pressure called the *osmotic pressure* (measured in millimeters of mercury [mm Hg]) needed to oppose the movement of water across the membrane. The osmotic activity that nondiffusible particles exert in pulling water from one side of the semipermeable membrane to the other is measured by a unit called an *osmole.* The osmole is derived from the gram molecular weight of a substance (*i.e.,* 1 gram molecular weight of a nondiffusible and nonionizable substance is equal to 1 osmole).

***Osmolarity*** refers to the osmolar concentration in 1 L of solution (mOsm/L) and *osmolality* to the osmolar concentration in 1 kg of water (mOsm/kg of $H_2O$). Osmolarity is usually used when referring to fluids outside the body and osmolality for describing fluids inside the body. Because 1 L of water weighs 1 kg, the terms *osmolarity* and *osmolality* are often used interchangeably.

The predominant osmotically active particles in the ECF are $Na^{2+}$ and its attendant anions **($Cl^-$and $HCO_3^-$)**, which together account for 90 % to 95 % of the osmotic pressure. Blood urea nitrogen (BUN) and glucose, which also are osmotically active, account for less than 5 % of the total osmotic pressure in the extracellular compartment. This can change, however, as when blood glucose levels are elevated in persons with diabetes mellitus or when BUN levels change rapidly in persons with renal failure. Serum osmolality, which normally ranges between 275 and 295 mOsm/kg.

***Tonicity***. A change in water content causes cells to swell or shrink. The term *tonicity* refers to the tension or effect that the effective osmotic pressure of a solution with impermeable solutes exerts on cell size because of water movement across the cell membrane. An effective osmole is one that exerts an osmotic force and cannot permeate the cell membrane, whereas an ineffective osmole is one that exerts an osmotic force but crosses the cell membrane. Tonicity is determined solely by effective solutes such as glucose that cannot penetrate the cell membrane, thereby producing an **n**osmotic force that pulls water into or out of the cell, causing it to change size. In contrast, urea, which is osmotically active but lipid soluble, tends to distribute equally across the cell membrane. Therefore, when ECF levels of urea are elevated, ICF levels also are elevated. Urea is therefore considered to be an ineffective osmole (*Fig.1*).

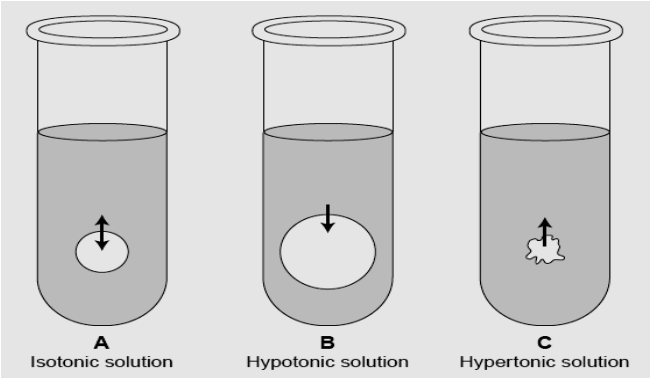


**Figure 1.** Osmosis. Red cells undergo no change in size in isotonic solutions (**A**). They increase in size in hypotonic solutions (**B**) and decrease**c**in size in hypertonic solutions (**C**).

Cells placed in an isotonic solution, which has the same effective osmolality as the ICF (*i.e.*, 280 mOsm/L), neither shrink nor swell. An example of an isotonic solution is a 0.9 % sodium chloride. When cells are placed in a hypotonic solution, which has a lower effective osmolality than the ICF, they swell as water moves into the cell, and when they are placed in a hypertonic solution, which has a greater effective osmolality than the ICF, they shrink as water is pulled out of the cell. However, an isoosmotic solution is not necessarily isotonic.

$$\text{Osmolality (mOsm/kg)} = 2[Na^+(\text{mmol/L})] + \frac{\text{glucose (mg/dl)*}}{18} + \frac{\text{BUN (mg/dl)*}}{2.8}$$

**1 mOsm of glucose equal 180 mg / L, and 1 mOsm of urea equals 28 mg / L*

Ordinarily, the calculated and measured osmolality are within 10 mOsm of one another. The difference between the calculated and measured osmolality is called the *osmolar gap.* An osmolar gap larger than 10 mOsm suggests the presence of an unmeasured, osmotically active substance such as alcohol, acetone, or mannitol.

## COMPARTMENTAL DISTRIBUTION OF BODY FLUIDS

Body water is distributed between the ICF and ECF compartments. In the adult, the fluid in the ICF compartment constitutes approximately 40 % of body weight. The fluid in the ECF compartment is further divided into two major subdivisions: the plasma compartment, which constitutes approximately 4% of body weight, and the interstitial fluid compartment, which constitutes approximately 15% of body weight (*Fig. 2*).

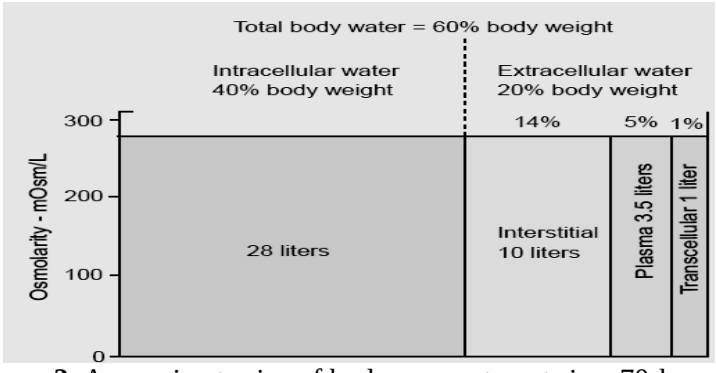


**Figure 2.** Approximate size of body compartments in a 70-kg adult

## CLINICAL APPLICATION

### Urine Osmolality

Urine osmolality reflects the kidneys' ability to produce a concentrated or diluted urine based on serum osmolality and the need for water conservation or excretion.

The ratio of urine osmolality to serum osmolality in a 24-hour urine sample normally exceeds 1 : 1, and after a period of overnight water deprivation, it should be greater than 3 : 1.

A dehydrated person (one who has a loss of water) may have a urine–serum ratio that approaches 4 :1 . In these persons, urine osmolality may exceed 1000 mOsm/kg $H_2O$.

In those who have difficulty concentrating their urine (*e.g.*, those with diabetes insipidus or chronic renal failure), the urine–serum ratio often is less than or equal to 1 : 1. Urine specific gravity compares the weight of urine with that of water, providing an index for solute concentration. Water is considered to be 1.000. In the sodium-depleted state, the kidneys usually try to conserve sodium, urine specific gravity is normal, and urine sodium and chloride concentrations are low.

A third, usually minor, subdivision of the ECF compartment is the transcellular compartment, which is defined as being separated by a layer of epithelium. It includes the cerebrospinal fluid and fluid contained in the various body spaces, such as the peritoneal, pleural, and pericardial cavities; the joint spaces; and the gastrointestinal tract. Normally, only approximately 1 % of ECF is in the transcellular space. This amount can increase considerably in conditions such as ascites.

**Intracellular Fluid Volume.** The ICF volume is regulated by proteins and organic compounds in the ICF and by solutes that move between the ECF and ICF. The membrane in most cells is freely permeable to water; therefore, water moves between the ECF and ICF fluid as a result of osmosis. In contrast, osmotically active proteins and other organic compounds cannot pass through the membrane. Water entry into the cell is regulated by these osmotically active substances as well as by solutes such as sodium and potassium that pass through the cell membrane. Many of the ntracellular proteins are negatively charged and attract positively charged ions such as the $K^+$ion, accounting for its higher concentration in the ICF. The $Na^+$ion, which has a greater concentration in the ECF, tends to enter the cell by diffusion. The $Na^+$ ion is osmotically active, and its entry would, if left unchecked, pull water into the cell until it ruptured. The reason this does not occur is because the $Na^+/K^+$-ATPase membrane pump continuously removes three $Na^+$ ions from the cell for every two $K^+$ ions that are moved back into the cell. Situations that impair the function of the $Na^+/K^+$-ATPase pump, such as hypoxia, cause cells to swell because of an accumulation of $Na^+$ ions. Other ions, such as $Ca^{2+}$and $H^+$, are exchanged by similar transport systems. Intracellular volume is also affected by the concentration of osmotically active substances in the ECF that cannot cross the cell membrane. In diabetes mellitus, for example, glucose cannot enter the cell, and its increased concentration in the ECF pulls water out of the cell.

**Extracellular Fluid Volume.** The ECF volume is divided between the vascular and interstitial fluid compartments. The vascular compartment contains blood, which is essential to the transport of substances such as electrolytes, gases, nutrients, and waste products throughout the body. Interstitial fluid acts as a transport vehicle for gases, nutrients, wastes, and other materials that move between the vascular compartment and bodycells. Interstitial fluid also provides a reservoir from which vascular volume can be maintained during periods of hemorrhage or loss of vascular volume. A tissue gel, which is a spongelike material composed of large quantities of mucopolysaccharides, fills the tissue spaces. Normally, most of the fluid in the interstitium is in gel form. The tissue gel is supported by collagen fibers that hold the gel in place. The tissue gel, which has a firmer consistency than water, opposes the outflow of water from the capillaries and prevents the accumulation of free water in the interstitial spaces.

## CAPILLARY–INTERSTITIAL FLUID EXCHANGE

***The transfer of water between the vascular and interstitial compartments occurs at the capillary level and is governed by the Starling forces.***

**Four forces control the movement of water between the capillary and interstitial spaces:**

(1) *the capillary filtration pressure, which pushes water out of the capillary into therinterstitium;*

*(2) the capillary colloidal osmotic pressure, which pulls water back into the capillary;*

*(3) the interstitial fluid pressure, which opposes the movement of water out of the capillary;*

*(4) the tissue colloidal osmotic pressure, which pulls water out of the capillary into the interstitium.*

Excess fluid is removed from the interstitium by the lymphatic system and returned to the systemic circulation. Capillary filtration refers to the move-ment of water through capillary pores because of a mechanical rather than an osmotic force. The capillary filtration pressure, sometimes called the capillary hydrostatic pressure, is the pressure pushing water out of the capillary into the interstitial spaces. It reflects the arterial and venous pressures, the precapillary (arterioles) and postcapillary (venules) resistances, and the force of gravity. A rise in arterial or venous pressure increases capillary pressure. The force of gravity increases capillary pressure in the dependent parts of the body. This pressure results from the weight of water and is therefore called hydrostatic pressure.

The hydrostatic pressure in the veins of an adult is pressure is then transmitted to the capillaries. The capillary colloidal osmotic pressure is the osmotic pressure generated by the plasma proteins that are too large to pass through the pores of the capillary wall. Because plasma proteins do not normally

penetrate the capillary pores and because their concentration is greater in the plasma than in the interstitial fluids, it is capillary colloidal osmotic pressure that pulls fluids back into the capillary. The interstitial fluid pressure and the tissue colloidal osmotic pressure contribute to movement of water into and out of the interstitial spaces. The interstitial fluid pressure opposes the outward movement of water from the capillary into the interstitial spaces. The tissue colloidal osmotic pressure pulls water out of the capillary into the tissue spaces. It reflects the small amount of plasma proteins that normally escape from the capillary to enter the interstitial spaces..

**Edema** can be defined as palpable swelling produced by expansion of the interstitial fluid volume. Edema does not become evident until the interstitial volume has been increased by 2.5–3L.

***Causes.*** The physiologic mechanisms that contribute to edema formation include factors that

(1) increase the capillary filtration pressure,

(2) decrease the capillary colloidal osmotic pressure,

(3) increase capillary permeability,

(4) produce obstruction to lymph flow.

*Increased Capillary Filtration Pressure.* As the capillary filtration pressure rises, the movement of vascular fluid into the interstitial spaces increases. Among the factors that increase capillary pressure are:

*(1) increased arterial pressure or decreased resistance to flow through the precapillary sphincters,*

*(2) an increase in venous pressure or increased resistance to outflow at the postcapillary sphincter,*

*(3) capillary distention due to increased vascular volume.*

**Edema can be either localized or generalized**. The localized edema that occurs with urticaria (*i.e.*, hives) or other allergic or inflammatory conditions results from the release of histamine and other inflammatory mediators that cause dilation of the precapillary sphincters and arterioles that supply the swollen lesions. Thrombophlebitis obstructs venous flow, producing an elevation of venous pressure and edema of the affected part, usually one of the lower extremities. Generalized edema is common in conditions such as congestive heart failure that produce fluid retention and venous congestion. Decreased sodium and water excretion by the kidneys leads to an increase in extracellular volume, with an increase in capillary volume and pressure and subsequent movement of fluid into the tissue spaces.

***Decreased Capillary Colloidal Osmotic Pressure.*** Plasma proteins exert the osmotic force needed to pull fluid back into the capillary from the tissue spaces. The plasma proteins constitute a mixture of proteins, including albumin, globulins, and fibrinogen. Albumin, the smallest of the plasma proteins, the concentration of albumin (approximately 4.5 g/dL) is greater than that of the globulins (2.5 g/dL) and fibrinogen (0.3 g/dL).

Edema due to decreased capillary colloidal osmotic pressure usually is the result of inadequate production or abnormal loss of plasma proteins, mainly albumin. The plasma proteins are synthesized in the liver. In starvation and malnutrition, edema develops because there is a lack of amino acids needed in plasma protein synthesis.

The most common site of plasma protein loss is the kidney. In kidney diseases such as nephrosis, the glomerular capillaries become permeable to the plasma proteins, particularly albumin, which is the smallest of the proteins. When this happens, large amounts of albumin are filtered out of the blood and lost in the urine. An excessive loss of plasma proteins also occurs when large areas of skin are injured or destroyed. Edema is a common problem during the early stages of a burn, re-sulting from capillary injury and loss of plasma proteins (of the face as well as the legs and feet).

***Increased Capillary Permeability***. When the capillary pores become enlarged or the integrity of the capillary wall is damaged, capillary permeability is increased. When this happens, plasma proteins and other osmotically active particles leak into the interstitial spaces, increasing the tissue colloidal osmotic pressure and thereby contributing to the accumulation of interstitial fluid (conditions- burn injury, capillary congestion, inflammation)Obstruction of Lymph Flow.

Osmotically active plasma proteins and other large particles that cannot be reabsorbed through the pores in the capillary membrane rely on the lymphatic system for movement back into the circulatory system. Edema due to impaired lymph flow is commonly referred to as lymphedema.

***Manifestations.*** The effects of edema are determined largely by its location. Edema of the brain, larynx, or lungs is an acute, life-threatening condition. Although not life threatening, edema may interfere with movement, limiting joint motion. Swelling of the ankles and feet often is insidious in onset and may or may not be associated with disease. At the tissue level, edema increases the distance for diffusion of oxygen, nutrients, and wastes. Edematous tissues usually are more susceptible to injury and development of ischemic tissue damage, including pressure ulcers. Edema can also compress blood vessels. The skin of a severely swollen finger can act as a tourniquet, shutting off the blood flow to the finger.

***Assessment and Treatment.*** Methods for assessing edema include daily weight, visual assessment, measurement of the affected part, and application of finger pressure to assess for pitting edema. Daily weight performed at the same time each day with the same amount of clothing provides a useful index of water gain (1 L of water weighs 2.2 pounds) due to edema. Visual inspection and measurement of the circumference of an extremity can also be used to assess the degree of swelling. This is particularly useful when swelling is due to thrombophlebitis.

Treatment of edema usually is directed toward maintaining life when the swelling involves vital structures, correcting or controlling the cause, and preventing tissue injury. Diuretic therapy commonly is used to treat edema. Edema of the lower extremities may respond to simple measures such as elevating the feet. Elastic support stockings and sleeves increase interstitial fluid pressure and resistance to outward movement of fluid from the capillary into the tissue spaces. Serum albumin levels can be measured, as can the colloidal osmotic pressure of the plasma (normally approximately 25.4 mm Hg). Albumin can be administered intravenously to raise the plasma colloidal osmotic pressure when edema is caused by hypoalbuminemia.

**Third-Space Accumulation.** Third spacing represents the loss or trapping of ECF into the transcellular space. The serous cavities are part of the transcellular compartment (i.e., third-space) located in strategic body areas where there is continual movement of body structures-the pericardial sac, the peritoneal cavity, and the pleural cavity. The exchange of ECF between the capillaries, the interstitial spaces, and the tran-scellular space of the serous cavity uses the same mechanisms as capillaries elsewhere in the body. The serous cavities are closely linked with lymphatic drainage systems. The milking action of the moving structures, such as the lungs, continually forces fluid and plasma proteins back into the cir-culation, keeping these cavities empty. Any obstruction to lymph flow causes fluid accumulation in the serous cavities. The transudation of fluid into the serous cavities is also referred to as effusion. Effusion can contain blood, plasma proteins, inflammatory cells (i.e., pus), and ECF.

**Sodium and Water Balance.** The movement of body fluids between the ICF and ECF compartments occurs at the cell membrane and depends on regulation of ECF water and sodium. Water provides approximately 90 % to 93 % of the volume of body fluids and sodium salts approximately 90 % to 95 % of extracel-lular solutes. Normally, equivalent changes in sodium and water are such that the volume and os-molality of ECF are maintained within a normal range. Because it is the concentration of sodium (in milligrams per liter) that controls ECF osmolality, changes in sodium are usually accompanied by proportionate changes in water volume. Protection of the circulatory volume can be viewed as the single most important characteristic of body fluid homeostasis.

**Two mechanisms protect the ECF (and vascular fluid) volume:**

(1*) alterations in hemodynamic variables such as vasoconstriction and an ↑ in heart rate,*

*(2) alterations in sodium and water balance.*

Both mechanisms serve to maintain filling of the vascular compartment. Tachycardia, peripheral arterial vasoconstriction occur within minutes of external fluid losses, whereas salt and water retention take hours to become effective.

**Alterations of sodium and water balance can be divided into two main categories**:

(1) isotonic contraction or expansion of ECF volume,

(2) hypotonic dilution (dilutional hyponatremia) or hypertonic concentration (hypernatremia) of extracellular sodium brought about by changes in extracellular water. Isotonic disorders usually are confined to the ECF compartment producing a contraction (fluid volume deficit) or expansion (fluid volume excess) of the interstitial and vascular fluids. Disorders of sodium concentration produce a change in the osmolality of the ECF with movement of water from the ECF compartment into the ICF compartment (hyponatremia) or from the ICF compartment into the ECF fluid compartment (hypernatremia).

**Regulation of sodium balance.** Sodium is the most abundant cation in the body, averaging approximately 60 Eq/kg of body weight. The resting cell membrane is relatively impermeable to sodium. Sodium that enters the cell is transported out of the cell against an electrochemical gradient by the energy-dependent $Na^+/K^+$-ATPase membrane pump. Sodium funcions mainly in regulating extracellular and vascular volume. As the major cation in the ECF compartment, $Na^+$ and its attendant anions ($Cl^-$and $HCO3^-$) account for approximately 90% to 95% of the osmotic activity in the ECF. Because sodium is part of the sodium bicarbonate molecule, it is important in regulating acid-base balance (*Fig. 3*).

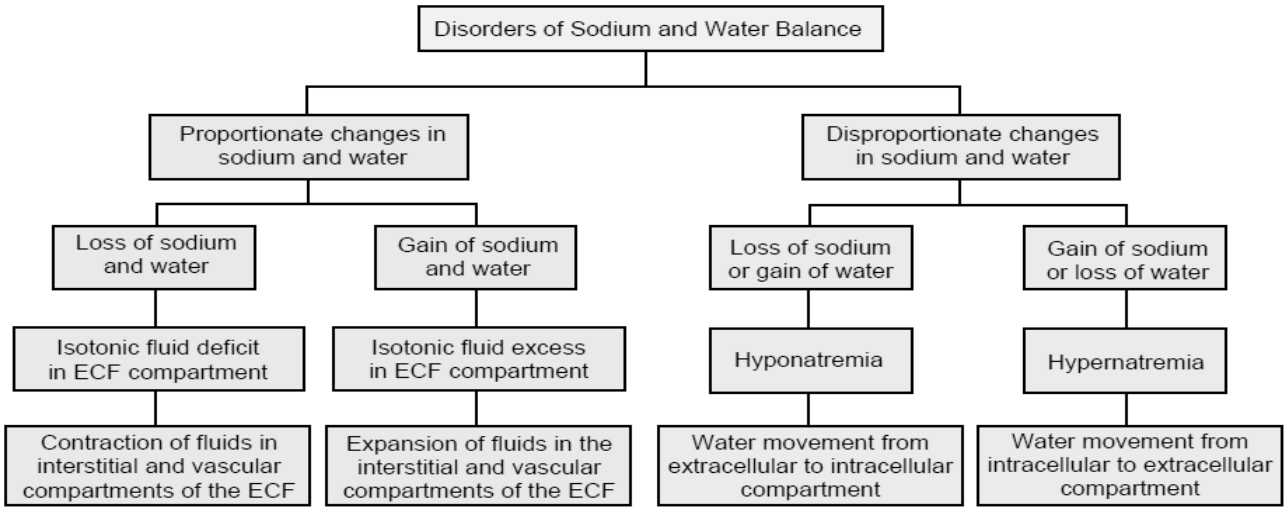


**Figure 3.** The effect of proportionate and disproportionate changes in sodium and water balance on extracellular sodium concentration

**Gains and Losses.** Sodium normally enters the body through the gastrointestinal tract and is eliminated by the kidneys or lost from the gastrointestinal tract or skin. Sodium intake normally is derived from dietary sources. Other sources of sodium are intravenous saline infusions and medications that contain sodium. Most sodium losses occur through the kidney. The kidneys are extremely efficient in regulating sodium output, and when sodium intake is limited or conservation of sodium is needed, the kidneys are able to reabsorb almost al the sodium that has been filtered by the glomerulus. This results in an essentially sodium-free urine. Conversely, urinary losses of sodium increase as intake increases.

Usually, less than 10 % of sodium intake is lost through the gastrointestinal tract and skin. Although the sodium concentration of fluids in the upper part of the gastrointestinal tract approaches that of the ECF, sodium is reabsorbed as the luids move through the lower part of the bowel. Sodium losses increase with conditions such as vomiting, diarrhea, fistula drainage, and gastrointestinal suction that remove sodium from the upper gastrointestinal tract. Excessive amounts of sodium can also be lost through the skin. Sweat losses, which usually are negligible, can in- crease greatly during exercise and periods of exposure to a hot environment. A person who sweats profusely can lose as much as 15 to 30 g of sodium per day. Fortunately, this amount de-creases to as little as 3 to 5 g/day with acclimatization to the heat.

**Mechanisms of Regulation.** The kidney is the main regulator of sodium. The kidney monitors arterial pressure and retains sodium when arterial pressure is decreased and eliminates it when arterial pressure is increased. The rate at which the kidney excretes or conserves sodium is coordinated by the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). Another possible regulator of sodium excretion by the kidney is atrial natriuretic peptide (ANP), which is released from cells in the atria of the heart. ANP, which is released in response to atrial stretch and overfilling, increases sodium excretion by the kidney.

***The Sympathetic Nervous System.*** The sympathetic nervous system responds to changes in arterial pressure and blood volume by adjusting the glomerular filtration rate and thus the rate at which sodium is filtered from the blood. Sympathetic activity also regulates tubular reabsorption of sodium and renin release.

***The Renin-Angiotensin-Aldosterone System.*** The RAAS exerts its action through angiotensin II and aldosterone. Renin is a small protein enzyme that is released by the kidney in response to changes in arterial pressure, the glomerular filtration rate, and the amount of sodium in the tubular fluid. Most of the renin that is released leaves the kidney and enters the bloodstream, where it interacts enzymatically to convert a circulating plasma protein called angiotensinogen to angiotensin I. Angiotensin I is rapidly converted to angiotensin II by the angiotensin-converting enzyme in the small blood vessels of the lung. Angiotensin II acts directly on the renal tubules to increase sodium reabsorption. It also acts to constrict renal blood vessels, thereby decreasing the glomerular filtration rate and slowing renal blood flow so that less sodium is filtered and more is reabsorbed. Angiotensin II is also a powerful regulator of aldosterone, a hormone secreted by the adrenal cortex. Aldosterone acts at the level of the cortical collecting tubules of the kidneys to increase sodium reabsorption while increasing potassium elimination.

**Regulation of water balance.** Total body water (TBW) varies with gender and weight. In men, body water approximates 60 % of body weight during young adulthood and decreases to approximately 50 % in old age; in young women, it is approximately 50 %, and in elderly women, approximately 40 %. Obesity produces further decreases in body water, sometimes reducing these levels to values as low as 30 % to 40 % of body weight in adults. Infants and young children have a greater water content than adults. TBW constitutes approximately 75 % to80 % of body weight in full-term infants and is even greater in premature infants. Infants have more than half of their TBW in the ECF compartment, whereas adults have only approximately one third. The greater ECF water content and water turnover of an infant can be explained in terms of its higher metabolic rate, larger surface area in relation to body mass, and its inability to concentrate its urine because of immature kidney structures. As an infant grows older, TBW decreases, and by the second year of life, the percentages and dis-tribution of body water approach those of an adult.

**Gains and Losses.** Regardless of age, all healthy persons require approximately 100 mL of water per 100 calories metabolized for dissolving and eliminating metabolic wastes. This means that a person who expends 1800 calories for energy requires approximately 1 800 mL of water for metabolic purposes. The me-tabolic rate increases with fever; it rises approximately 12 % for every 10 °C in-crease in body temperature. Fever also increases the respiratory rate, resulting in additional loss of water vapor through the lungs. The main source of water gain is through oral intake and metabolism of nutrients. Metabolic processes also generate a small amount of water. The amount of water gained from these processes varies from 150 to 300 mL/day, depending on metabolic rate.

Normally, the largest loss of water occurs through the kidneys, with lesser amounts being lost through the skin, lungs, and gastrointestinal tract. Even when oral or parenteral fluids are with-held, the kidneys continue to produce urine as a means of ridding the body of metabolic wastes. The urine output that is required to eliminate these wastes is called the obligatory urine output (300 to 500 mL/day). Water losses that occur through the skin and lungs are referred to as insensible water losses.

**Thirst** is controlled by the thirst center in the hypothalamus. There are two stimuli for true thirst based on water need:

(1) *cellular dehydration caused by an increase in extracellular osmolality*

*(2) a decrease in blood volume, which may or may not be associated with a decrease in serum osmolality.*

Sensory neurons, called osmoreceptors, which are located in or near the thirst center in the hypothalamus, respond to changes in extracellular osmolality by swelling or shrinking. Thirst normally develops when there is as little as a 1 % to 2 % change in serum osmolality.10 Stretch receptors in the vascular system that are sensitive to changes in arterial blood pressure (high-pressure baroreceptors located in the carotid sinus and aorta) and central blood volume (low-pressure baroreceptors located in the left atrium and major thoracic veins) also aid in the regulation of thirst.

Thirst is one of the earliest symptoms of hemorrhage and is often present before other signs of blood loss appear. Dryness of the mouth, such as the thirst a lecturer experiences during speaking, produces a sensation of thirst that is not necessarily associated with the body's hydration status.

**A third important stimulus** for thirst is angiotensin II, which becomes increased in response to low blood volume and low blood pressure. The renin-angiotensin mechanism contributes to nonosmotic thirst. Elevated levels of angiotensin II may lead to thirst in conditions, such as chronic renal failure and congestive heart failure, in which renin levels may be elevated. Thirst and elevated renin levels are also found in persons with primary hyperaldosteronism and in those with secondary hyperaldosteronism accompanying anorexia nervosa, hemorrhage, and sodium depletion.

***Adipsia and Hypodipsia.*** Adipsia represents an absence, and hypodipsia a decrease, in the ability to sense thirst. There is evidence that thirst is decreased and water intake reduced in elderly persons, despite higher plasma sodium and osmolality levels. The inability to perceive and respond to thirst is compounded in elderly persons who have had a stroke and may be further influenced by confusion and sensory disturbances.

***Polydipsia.*** Polydipsia, or excessive thirst, is normal when it accompanies conditions of water deficit. Increased thirst and drinking behavior can be classified into three categories: symptomatic or true thirst, inappropriate or false thirst that occurs despite normal levels of body water and serum osmolality, and compulsive water drinking. Symptomatic thirst develops when there is a loss of body water and resolves after the loss has been replaced. Among the most common causes of symptomatic thirst are water losses associated with diarrhea, vomiting, diabetes mellitus, and diabetes insipidus. Inappropriate or excessive thirst may persist despite adequate hydration. It is a common complaint in

persons with renal failure and congestive heart failure. Although the cause of thirst in these persons is unclear, it may result from increased angiotensin levels. Thirst is also a common complaint in persons with dry mouth caused by decreased salivary function or treatment with drugs with an anticholinergic action (*e.g.*, antihistamines, atropine) that lead to decreased salivary flow. Psychogenic polydipsia involves compulsive water drinking and is usually seen in persons with psychiatric disorders, most commonly schizophrenia. Persons with the disorder drink large amounts of water and excrete large amounts of urine. The cause of excessive water drinking in these persons is uncertain. It has been suggested that the compulsive water drinking may share the same pathology as the psychosis because persons with the disorder often increase their water drinking during periods of exacerbation of their psychotic symptoms. The condition may be compounded by antipsychotic medications that increase ADH levels and interfere with water excretion by the kidneys. Cigarette smoking, which is common among persons with psychiatric disorders, also stimulates ADH secretion. Excessive water ingestion coupled with impaired water excretion (or rapid ingestion at a rate that exceeds renal excretion) in persons with psychogenic polydipsia can lead to water intoxication (see Hyponatremia). Treatment usually consists of water restriction and behavioral measures aimed at decreasing water consumption.

***Antidiuretic Hormone.*** The reabsorption of water by the kidneys is regulated by ADH, also known as *vasopressin.* ADH is synthesized by cells in the supraoptic and paraventricular nuclei of the hypothalamus. ADH from neurons in the supraoptic and paraventricular nuclei is transported along a neural pathway (*i.e.*, hypothalamohypophysial tract) to the neurohypophysis (*i.e.*, posterior pituitary) and then stored for future release. ADH exerts its effects through two types of vasopressin (V) receptors-V1 and V2 receptors. V1 receptors, which are located in vascular smooth muscle, cause vasoconstriction-hence the name *vasopressin.* Although ADH can increase blood pressure through V1 receptors, this response occurs only when ADH levels are very high. The V2 receptors, which are located on the tubular cells of the cortical collecting duct, control water reabsorption by the kidney.

Binding of ADH to the V2 receptors increases water reabsorption by increasing the permeability of the collecting duct to water (i.e., the antidiuretic effect). In the absence of ADH, the permeability of the collecting duct to water is very low, and reabsorption of water decreases, leading to polyuria. The mechanism whereby ADH causes water reabsorption has recently been lucidated. ADH stimulates V2 receptors (and through cyclic AMP) results in the movement of water channels known as aquaporins. Aquaporin-2 water channels move from the cytoplasm of cells in the collect-ing duct to the luminal surface of these cells. The aquaporin-2 channels then allow free movement of water from the tubular lumen into the cell along a concentration gradient. Osmoreceptors in the hypothalamus sense changes in extracellular osmolality and stimulate the production and release of ADH.

Responsiveness to osmolality changes with age, with older persons being more responsive to changes in serum osmolality. Osmoregulation is also altered in normal pregnancy and the menstrual cycle. This change represents a resetting of the osmotic threshold for ADH and an increase in the ECF volume that accompanies pregnancy. Rapid catabolism of ADH (vasopressin) can also oc-cur during pregnancy due to the production of a vasopressinase. the abnormal synthesis and release of ADH occurs in a number of stress situations. Severe pain, nausea, trauma, surgery, certain anesthetic agents, and some analgesic drugs increase ADH levels. Nausea is a potent stimulus of ADH secretion; it can increase ADH levels 10 to 1000 times those required for maximal diuresis. Among the drugs that affect ADH are nicotine, which stimulates its release, and alco-hol, which inhibits it. Two important conditions alter ADH levels: diabetes insipidus and inappropriate secretion of ADH.

***Diabetes Insipidus.*** Diabetes insipidus, which means "tasteless diabetes," as opposed to diabetes mellitus, or "sweet diabetes," is caused by a deficiency of or a decreased response to ADH. Diabetes insipidus is characterized by excessive urination of a dilute urine (polyuria, usually greater than 2 L/day) and polydipsia.

There are two types of diabetes insipidus: central or neurogenic diabetes insipidus, which occurs because of a defect in the synthesis or release of ADH, and nephrogenic diabetes insipidus, which occurs because the kidneys do not respond to ADH. In neurogenic diabetes insipidus, loss of 75 % to 80 % of ADH-secretory neurons is necessary before polyuria becomes evident. Most persons with neurogenic diabetes insipidus have an incomplete form of the disorder and retain some ability to concentrate their urine. Temporary neurogenic diabetes insipidus may follow head injury or surgery near the hypothalamohypophysial tract. Nephrogenic diabetes insipidus is characterized by impairment of urine-concentrating ability and free-water conservation. It may occur as a genetic trait that affects the V2 receptor that binds ADH or in the aquaporin-2 protein that forms the water channels in the

collecting tubules. Other acquired causes of nephrogenic diabetes insipidus are drugs such as lithium and electrolyte disorders such as potassium depletion or chronic hypercalcemia. The danger arises when the condition develops in someone who is unable to communicate the need for water or is unable to secure the needed water. In such cases, inadequate fluid intake rapidly leads to hypertonic dehydration and increased serum osmolality. Evaluation is based on measurement of ADH levels along with plasma and urine osmolality before and after a period of fluid deprivation or hypertonic saline infusion. Persons with neurogenic di-abetes insipidus do not increase their ADH levels in response to increased plasma osmolality.

Another diagnostic approach is to conduct a carefully monitored trial of a pharmacologic form of ADH. Persons with nephrogenic diabetes insipidus do not respond to pharmacologic prepa-rations of the hormone. Both neurogenic and nephrogenic forms of the disorder respond partially to the thiazide diuretics (e.g., hydrochlorothiazide). These diuretics are thought to act by increasing sodium excretion by the kidneys, which lowers the glomerular filtration rate and increases reabsorp-tion of water in the proximal tubule.

***Syndrome of Inappropriate Antidiuretic Hormone.*** The syndrome of inappropriate antidiuretic hormone (SIADH) results from a failure of the negative feedback system that regulates the release and inhibition of ADH. In persons with this syndrome, ADH secretion continues even when serum osmolality is decreased; this causes marked retention of water in excess of sodium and dilutional hyponatremia. An increase in the glomerular filtration rate resulting from an increased plasma volume causes further increases in sodium loss by suppressing the renin-angiotensin mechanism. Urine osmolality is high, and serum osmolality is low. Urine output decreases despite adequate or increased fluid intake. Hematocrit and the plasma sodium and BUN levels are all decreased because of the expansion of the ECF volume.

The diagnosis of SIADH should only be considered if the five cardinal features are fulfilled***: (1) hypotonic hyponatremia, (2) natriuresis, (3) urine osmolality in excess of plasma osmolality, (4) absence of edema and volume depletion, and (5) normal renal and adrenal function. SIADH can be caused by a number of conditions;*** however, the major causes are neoplasia, neurologic diseases, lung diseases, and a variety of pharmacologic agents. Other intrathoracic conditions, such as dvanced tuberculosis, severe pneumonia, and positive-pressure breathing, also cause SIADH. The suggested mechanism for SIADH in positive-pressure ventilation is activation of baroreceptors (*e.g.,* aortic baroreceptors, cardiopulmonary receptors) that respond to marked changes in intrathoracic pressure. Disease and injury to the central nervous system (CNS) can cause direct pressure on or direct involvement of the hypothalamic–posterior pituitary structures(brain tumors, hydrocephalus, head injury, meningitis, and encephalitis). SIADH may occur as a transient condition, as in a stress situation, or as a chronic condition, resulting from disorders such as lung tumors. The manifestations of SIADH are those of dilutional hyponatremia. The severity of symptoms usually is proportional to the extent of sodium depletion and water intoxication.

## ALTERATIONS IN ISOTONIC FLUID VOLUME

Isotonic fluid volume disorders represent an expansion or contraction of the ECF brought about by proportionate changes in both sodium and water.

**Isotonic Fluid Volume Deficit** Fluid volume deficit is characterized by a decrease in the ECF, including the circulating blood volume. The term ***isotonic fluid volume deficit*** is used to differentiate the type of fluid deficit in which there are proportionate losses in sodium and water from water deficit and the hyperosmolar state associated with hypernatremia. Unless other fluid and electrolyte imbalances are present, the concentration of plasma electrolytes remains essentially unchanged. When the effective circulating blood volume is compromised, the condition is often referred to as ***hypovolemia.***

***Causes*** Isotonic fluid volume deficit results when water and electrolytes are lost in isotonic proportions. It is almost always caused by a loss of body fluids and is often accompanied by a decrease in fluid intake. It can occur because of a loss of gastrointestinal fluids, polyuria, or sweating due to fever and exercise. Fluid intake may be reduced because of a lack of access to flu-ids, impaired thirst, unconsciousness, oral trauma, impaired swallowing, or neuromuscular problems that prevent fluid access. In Asiatic cholera, death can occur within a matter of hours as the cholera organism causes excessive amounts of fluid to be secreted into the bowel. These fluids are then lost as vomitus or excreted as diarrheal fluid.

Certain forms of kidney disease are characterized by salt wasting due to impaired sodium reabsorption. In Addison disease, a condition of chronic adrenocortical insufficiency, there is unregulated loss of sodium in the urine with a resultant loss of ECF. This is accompanied by in-creased potassium

retention. The skin acts as an exchange surface for heat and as a vapor barrier to prevent water from leaving the body. Body surface losses of sodium and water increase when there is excessive sweating or when large areas of skin have been damaged. In hot weather, water losses through sweating may be increased by as much as 1 to 3 L/hour, depending on acclimatization. The respiratory rate and sweating usually are increased as body temperature rises. As much as 3 L of water may be lost in a single day as a result of fever.

***Manifestations.*** The manifestations of fluid volume deficit reflect a decrease in ECF volume. They include thirst, loss of body weight, signs of water conservation by the kidney, impaired temperature regulation, and signs of reduced interstitial and vascular volume. A loss in fluid volume is accompanied by a decrease in body weight. One liter of water weighs 1 kg. A mild ECF deficit exists when weight loss equals 2 % of body weight. A moderate deficit equates to a 5 % loss in weight and a severe deficit to an 8 % or greater loss in weight. Thirst is a common symptom of fluid deficit, although it is not always present in early stages of isotonic fluid deficit. It develops as the effective circulating volume decreases to a point sufficient to stimulate the thirst mechanism. Urine output decreases and urine osmolality and specific gravity increase as ADH levels rise because of a decrease in vascular volume. Although there is an isotonic loss of fluid from the vascular compartment, blood components such as red blood cells and BUN become more concentrated.

The fluid content of body tissues decreases as fluid is removed from the interstitial spaces. The eyes assume a sunken appearance and feel softer than normal as the fluid content in the anterior chamber of the eye is decreased. Fluids add resiliency to the skin and underlying tissues that is re-ferred to as skin or tissue turgor. A loss of 3 % to 5 % of body water in children causes the resiliency of the skin to be lost, and the tissue remains raised for several seconds. Decreased tissue turgor is less predic-tive of fluid deficit in older persons because of the loss of tissue elasticity. In in-fants, fluid deficit may be evidenced by depression of the anterior fontanel due to a decrease in ce-rebrospinal fluid. There may be a rise in body temperature that accompanies fluid volume deficit. Arterial and venous volumes decline during periods of fluid deficit, as does fill-ing of the capillary circulation. As the volume in the arterial system declines, the blood pressure decreases, heart rate increases, and the pulse becomes weak and thready. Postural hypotension is an early sign of fluid deficit, characterized by a blood pressure that is at least 10 mm Hg lower when the patient is sitting or standing than when the patient is lying down. When volume depletion be-comes severe, signs of hypovolemic shock and vascular collapse appear.

***Diagnosis and Treatment.*** Diagnosis of fluid volume deficit is based on a history of conditions that predispose to sodium and water losses, weight loss, and observations of altered physiologic function indicative of decreased fluid volume. Intake and output measurements afford a means for assessing fluid balance. Although these measurements provide insight into the causes of fluid imbalance, they often are inadequate in measuring actual losses and gains because accurate measurements of intake and output often are difficult to obtain, and insensible losses are difficult to estimate. Measurement of heart rate and blood pressure provides useful information about vascular volume. When venous volume is decreased, as occurs in fluid deficit, venous refill time increases. Capillary refill time is also increased. Acute hypovolemia and hypovolemic shock can cause renal damage; therefore, prompt assessment of the degree of fluid deficit and adequate measures to resolve the deficit and treat the underlying cause are essential.

**Isotonic Fluid Volume Excess** Fluid volume excess represents an isotonic expansion of the ECF compartment. It occurs secondary to an increase in total body sodium, which in turn leads to an increase in body water. Fluid volume excess involves an increase in interstitial and vascular volumes. Although increased fluid volume is usually the result of a disease condition, this is not always true. For example, a compensatory isotonic expansion of body fluids can occur in healthy persons during hot weather as a mechanism for increasing body heat loss.

CausesIsotonic fluid volume excess almost always results from an increase in total body sodium that is accompanied by a proportionate increase in body water. Although it can occur as the result of excessive sodium intake, it is most commonly caused by a decrease in sodium and water elimination by the kidney. Among the causes of decreased sodium and water elimination are disorders of renal function, heart failure, liver failure, and corticosteroid excess. Heart failure produces a decrease in renal blood flow and a compensatory increase in sodium and water retention. Persons with severe congestive heart failure maintain a precarious balance between sodium and water intake and output. Even small increases in sodium intake can precipitate a state of fluid volume excess and a worsening of heart failure.

***Cushing's syndrome*** is a condition of glucocorticoid excess. Because cortisol, the most active of the glucocorticoids, has weak mineralocorticoid activity, Cushing's syndrome predisposes to increased sodium retention. The fact that cortisol increases salt and water retention also helps to explain why edema and hypertension may develop in persons who are being treated with corticosteroid drugs.

***Manifestations.*** Isotonic fluid volume excess is manifested by an increase in interstitial and vascular fluids. It is characterized by weight gain over a short period of time. Mild fluid volume excess represents a 2 % gain in weight; moderate fluid volume excess, a 5 % gain in weight; and severe fluid volume excess, a gain of 8 % or more in weight. Edema is characteristic of isotonic fluid excess. When the fluid excess accumulates gradually, as often happens in debilitating diseases and starvation, edema fluid may mask the loss of tissue mass. The eyelids often are puffy when the person awakens. There may be a decrease in BUN and hematocrit as a result of dilution due to expansion of the plasma volume. An increase in vascular volume may be evidenced by distended neck veins, slow-emptying peripheral veins, a full and bounding pulse, and an increase in central venous pressure. When excess fluid accumulates in the lungs (i.e., pulmonary edema), there are complaints of shortness of breath and difficult breathing, respiratory crackles, and a productive cough.

## ALTERATIONS IN SODIUM CONCENTRATION

The normal plasma concentration of sodium ranges from 135 to 145 mEq/L (135 to 145 mmol/L). Plasma sodium values reflect the sodium concentration (or dilution of sodium by extracellular water) expressed in milliequivalents or millimoles per liter, rather than an absolute amount. Because sodium and its attendant anions account for 90 % to 95 % of the osmolality of ECF, serum osmolality (normal).

### Hyponatremia

Hyponatremia represents a decrease in plasma sodium concentration below 135 mEq/L (135 mmol/L). Unlike hypernatremia, which is always associated with hypertonicity, hyponatremia may be associated with high, normal, or low tonicity because of the effects of other osmotically active particles in the ECF such as glucose. **Hypertonic (translocational)** hyponatremia results from an osmotic shift of water from ICF to the ECF as occurs with hyperglycemia. In this case, the sodium in the ECF becomes diluted as water moves out of cells in response to the osmotic effects of the elevated blood glucose level. There is approximately a 1.7mEq/L decrease in plasma sodium for every 100 mg/dL rise in plasma glucose above the normal level (100 mg/dL). **A normotonic hyponatremia, termed *pseudohyponatremia,*** can be detected in plasma samples from persons with hyperlipidemia and hyperproteinemia because of laboratory methods. This disturbance is caused by laboratory methods that include excess lipids or proteins in the water volume of the sample, causing an artifactual dilution of sodium.

Hypotonic (dilutional) is by far the most common form of hyponatremia. It is caused by water retention and characterized by a decrease in serum osmolality. Dilutional hyponatremia can present as a **hypervolemic, euvolemic, or hypovolemic** condition.

**Hypervolemic hyponatremia** involves an increase in ECF volume and is seen when hyponatremic conditions are accompanied by edema-forming disorders such as congestive heart failure, cirrhosis, and advanced kidney disease.

**Euvolemic hyponatremia** represents a retention of water with dilution of sodium while maintaining the ECF volume within a normal range. It is usually the result of inappropriate thirst or SIADH.

**Hypovolemic hyponatremia** occurs when water is lost along with sodium, but to a lesser extent. It occurs with diuretic use, excessive sweating in hot weather, and vomiting and diarrhea.

***Causes.*** Hypotonic, or dilutional, hyponatremia represents a decreased sodium concentration and tonicity of the ECF. The most common causes of acute dilutional hyponatremia in adults are drug therapy (diuretics and drugs that increase ADH levels), inappropriate fluid replacement during heat exposure or following heavy exercise, SIADH, and polydipsia in persons with psychotic disorder.

Among the causes of hypovolemic hyponatremia is the loss of salt and water from excessive sweating in hot weather, particularly during heavy exercise; hyponatremia develops when water rather than electrolyte-containing liquids is used to replace the fluids lost in sweating. Another potential cause of hypovolemic hyponatremia is the loss of sodium from the gastrointestinal tract due to repeated tap-water enemas or frequent gastrointestinal irrigations with distilled water. Iso-osmotic fluid loss, as in vomiting or diarrhea, does not usually lower plasma sodium levels unless these losses are replaced with disproportionate amounts of orally ingested or parenterally administered water.

Hypovolemic hyponatremia is a common complication of adrenal insufficiency and is due to the effects of aldosterone and cortisol deficiency. A lack of aldosterone increases renal losses of sodium,

and a cortisol deficiency leads to increased release of ADH with water retention. The hyponatremia becomes exaggerated when electrolyte-free fluids (5 % glucose in water) are used for fluid replacement. Excessive water drinking during this period can also increase the risk for hyponatremia.

***Manifestations.*** The manifestations of hypotonic hyponatremia are largely related to sodium dilution. Serum osmolality is decreased, and cellular swelling occurs owing to the movement of water from the ECF to the ICF compartment. The manifestations of hyponatremia depend on the rapidity of onset and the severity of the sodium dilution. The signs and symptoms may be acute, as in severe water intoxication, or more insidious in onset and less severe, as in chronic hyponatremia. Because of water movement, hyponatremia causes ICF hypoosmolality, which is responsible for many of the clinical manifestations of the disorder. Muscle cramps, weakness, and fatigue reflect the hypoosmolality of skeletal muscle cells and are often early signs of hyponatremia.

These effects commonly are observed in persons with hyponatremia that occurs during heavy exercise in hot weather. Gastrointestinal manifestations such as nausea and vomiting, abdominal cramps, and diarrhea may develop. The brain and nervous system are the most seriously affected by increases in intracellular water. Symptoms include apathy, lethargy, and headache, which can progress to disorientation, confusion, gross motor weakness, and depression of deep tendon ref-lexes. Seizures and coma occur when plasma sodium levels reach extremely low levels.

***Diagnosis.*** Diagnosis of hyponatremia is based on laboratory reports of decreased sodium concentration, the presence of conditions that predispose to sodium loss or water retention, and signs and symptoms indicative of the disorder.

**Hypernatremia.** Hypernatremia implies a plasma sodium level above 145 mEq/L and a serum osmolality greater than 295 mOsm/kg. Because sodium is functionally an impermeable solute, it contributes to tonicity and induces movement of water across cell membranes. Hypernatremia is characterized by hypertonicity of ECF and almost always causes cellular dehydration.

***Causes.*** Hypernatremia represents a deficit of water in relation to the body's sodium stores. It can be caused by net loss of water or sodium gain. Net water loss can occur through the urine, gastrointestinal tract, lungs, or skin. A defect in thirst or inability to obtain or drink water can interfere with water replacement. Rapid ingestion or infusion of sodium with insufficient time or opportunity for water ingestion can produce a disproportionate gain in sodium. Hypernatremia almost always follows a loss of body fluids that have a lower than normal concentration of sodium, so that water is lost in excess of sodium. This can result from increased losses from the respiratory tract during fever or strenuous exercise, from watery diarrhea, or when osmotically active tube feedings are given with inadequate amounts of water. Hypodipsia is particularly prevalent among the elderly population. In persons with diabetes insipidus, hypernatremia can develop when thirst is impaired or access to water is impeded. The Rarely, salt intake occurs rapidly, as in taking excess salt tablets or during near-drowning in salt water.

***Manifestations.*** The clinical manifestations of hypernatremia caused by water loss are largely those of ECF loss and cellular dehydration. The severity of signs and symptoms is greatest when the increase in plasma sodium is large and occurs rapidly. Body weight is decreased in proportion to the amount of water that has been lost. Thirst is an early symptom of water deficit, occurring when water losses are equal to 0.5 % of body water. Urine output is decreased and urine osmolality increased because of renal water-conserving mechanisms. Body temperature frequently is elevated, and the skin becomes warm and flushed. The vascular volume decreases, the pulse becomes rapid and thready, and the blood pressure drops. Hypernatremia produces an increase in serum osmolality and results in water being pulled out of body cells. As a result, the skin and mucous membranes become dry, and salivation and lacrimation are decreased. The mouth becomes dry and sticky, and the tongue becomes rough and fissured. Swallowing is difficult.

***Diagnosis and Treatment.*** The diagnosis of hypernatremia is based on history, physical examination findings indicative of dehydration, and results of laboratory tests. The treatment of hypernatremia includes measures to treat the underlying cause of the disorder and fluid replacement therapy to treat the accompanying dehydration. Replacement fluids can be given orally or intravenously. The oral route is preferable. Oral glucose–electrolyte replacement solutions are available for the treatment of infants with diarrhea. Glucose is preferred to sucrose (i.e., table sugar), which is a disaccharide and must be broken down before it can be absorbed.

Sport drinks usually contain more sodium and sugar than the oral rehydration solutions. Intravenous re-placement solutions continue to be the treatment of choice for severe fluid deficit. One of the se-rious aspects of fluid volume deficit is dehydration of brain and nerve cells. Serum osmolality should

be corrected slowly in cases of chronic hypernatremia. This is because brain cells synthesize osmotically active organic solutes to protect against volume changes.

These organic solutes serve to produce a gradual increase in intracellular osmolality, allowing osmotic flow of water back into the cell and restoring cell volume. This response begins within 4 to 6 hours of increased serum osmolality and takes several days to become fully effective. Changes in brain water content are greatest during acute hypernatremia but only slightly reduced in chronic hypernatremia. If hypernatremia is corrected too rapidly before the organic osmoles have had a chance to dissipate, the plasma may become relatively hypotonic in relation to brain cell osmolality. When this occurs, water moves into the brain cells, causing cerebral edema and potentially severe neurologic impairment.

## POTASSIUM BALANCE

Potassium is the second most abundant cation in the body and the major cation in the ICF compartment. Approximately 98% of body potassium is contained within body cells, with an intracellular concentration of 140 to 150 mEq/L.30 The potassium content of the ECF (3.5 to 5.0 mEq/L) is considerably less. Because potassium is an intracellular ion. Approximately 65% to 75% of potassium is in muscle. Thus, potassium content declines with age, mainly as a result of a decrease in muscle mass.

**Gains and Losses.** In healthy persons, potassium balance usually can be maintained by a daily dietary intake of 50 to 100 mEq. Additional amounts of potassium are needed during periods of trauma and stress. The kidneys are the main source of potassium loss (80% to 90%) , with the re-mainder being lost in stools or sweat.

**Mechanisms of Regulation**

Normally, the ECF concentration of potassium is precisely regulated because many cell functions are sensitive to even small changes in ECF potassium levels. An increase in potassium of only 0.3 to 0.4 mEq/L can cause serious cardiac dysrhythmias and even death.

Plasma potassium is largely regulated through two mechanisms:

*(1) renal mechanisms that conserve or eliminate potassium*

*(2) a transcellular shift between the intracellular and extracellular compartments.*

***Renal Regulation.*** The major route for potassium elimination is the kidney. The regulation of potassium elimination is controlled by secretion from the blood into the tubular filtrate rather than through reabsorption from the tubular filtrate into the blood. Potassium is filtered in the glomerulus, reabsorbed along with sodium and water in the proximal tubule and with sodium and chloride in the thick ascending loop of Henle, and then secreted into the late distal and cortical collecting tubules for elimination in the urine. Aldosterone plays an essential role in regulating potassium elimination by the kidney. The effects of aldosterone on potassium elimination are mediated through a sodium–potassium exchange system located in the late distal and cortical collecting tubules. In the presence of aldosterone, sodium is transported back into the blood, and potassium is secreted in the tubular filtrate for elimination in the urine. The rate of aldosterone secretion by the adrenal gland is strongly controlled by plasma potassium levels. For example, an increase of less than 1 mEq/L of potassium causes aldosterone levels to triple. The effect of plasma potassium on aldosterone secretion is an example of the powerful feedback regulation of potassium elimination. In the absence of aldosterone( Addison disease), renal elimination of potassium is impaired, causing plasma potassium levels to rise to dangerously high levels. Aldosterone is often referred to as a mineralocorticoid hormone because of its effect on sodium and potassium. The term mineralocorticoid activity also is used to describe the aldosterone-like actions of other adrenocortical hormones(cortisol). There is also a potassium–hydrogen ion exchange mechanism in the cortical collecting tubules of the kidney. When plasma potassium levels are increased, potassium ions ($K^+$) are secreted into the urine, and hydrogen ions ($H^+$) are reabsorbed into the blood, producing a decrease in pH and metabolic acidosis. Conversely, when potassium levels are low, $K^+$ions are reabsorbed, and $H^+$ions are secreted in the urine, leading to metabolic alkalosis.

***Extracellular–Intracellular Shifts.*** The transcellular shift of potassium between the ECF and ICF compartments allows potassium to move into body cells when plasma levels are high and move out when the plasma levels are low. This movement is controlled by the function of the $Na^+/K^+$-ATPase membrane pump and the permeability of ion channels in the cell membrane. Both insulin and β-adrenergic catecholamines (*e.g.*, epinephrine) increase cellular uptake of potassium by increasing the activity of the $Na^+/K^+$-ATPase membrane pump (*Fig.* 4).

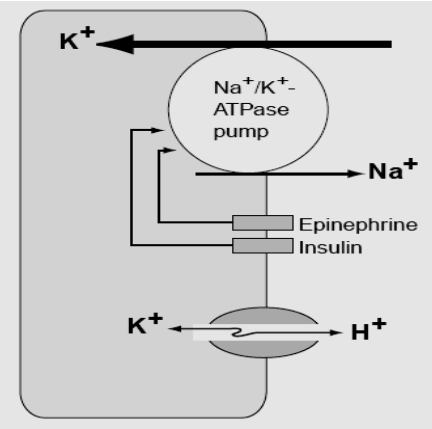


**Figure 4.** Mechanisms regulating transcellular shifts in potassium

Studies indicate that insulin deficiency impedes cellular uptake of potassium and that insulin excess increases uptake. The plasma potassium concentration directly affects insulin release from beta cells in the pancreas. An increase in potassium levels stimulates insulin release, and a decrease inhibits its release, suggesting a potassium – insulin regulatory feedback mechanism.

The catecholamines, particularly epinephrine, facilitate the movement of potassium into muscle tissue. The action of epinephrine on potassium transport is additive to that of insulin. The osmolality of the ECF also influences transcellular shifts in potassium. Acute increases in serum osmolality cause potassium to move out of cells. WThe loss of cell water produces an increase in ICF potassium concentration, causing potassium to diffuse out of the cell. There is usually a 1.0–1.5 mEq/L rise in plasma potassium that occurs in response to an acute 10 % increase in serum osmolality. A hyperosmolality-induced increase in plasma potassium is usually counteracted by the opposing actions of insulin and epi-nephrine.

The reverse condition, hypo-osmolality, usually occurs more slowly and does not affect plasma potassium levels. The exchange of $K^+$and $H^+$ions between the ICF and ECF plays a significant role in regulating the ECF concentration of both ions. In acidosis, $H^+$ions move into the cell as a means of preventing large changes in ECF pH. As $H^+$ ions move into the cell, other positively charged ions, such as $K^+$, must move out as a means of maintaining electrical neutrality.

The pH-related shifts in ICF to ECF potassium are more pronounced when changes in pH are caused by nonorganic acids (*i.e.*, hyperchloremic acidosis associated with diarrhea and renal failure), in which the companion anion, chloride, cannot permeate the cell membrane and remains outside the cell as a companion for the $K^+$ion. In contrast, acidosis due to accumulation of organic acids (*i.e.*, lactic acidosis and ketoacidosis) has little effect on potassium because the companion anion is able to enter the cell. Although there is increased movement of potassium out of the cell in diabetic ketoacidosis, it is more likely related to the effects of insulin deficiency and the hyperosmolality of the ECF. Respiratory acidosis and alkalosis cause little change in plasma potassium concentration. Metabolic alkalosis tends to have a smaller opposite effect: $H^+$ions move out of the cell as $K^+$ions move in. Exercise also produces compartmental shifts in potassium. Repeated muscle contraction releases potassium into the ECF.

**ALTERATIONS IN POTASSIUM BALANCE.** As the major intracellular cation, potassium is critical to many body functions. It is involved in a wide range of body functions, including the maintenance of the osmotic integrity of cells, acid-base balance, and the kidney's ability to concentrate urine. Potassium is necessary for growth, and it contributes to the intricate hemical reactions that ***transform carbohydrates into energy, change glucose into glycogen, and convert amino acids to proteins***. Potassium also plays a critical role in conducting **nerve impulses** and the ***excitability of skeletal, cardiac, and smooth muscle***. It does this by regulating the resting membrane potential the opening of the sodium channels that control the flow of current during the action potential, and the rate of membrane repolarization. Changes in ***nerve and muscle excitability*** are particularly important in the heart, where alterations in serum potassium can produce serious dysrhythmias and conduction defects. Changes in plasma potassium also affect skeletal muscles and the smooth muscle in blood vessels and the gastrointestinal tract. A decrease in serum potassium causes the resting membrane potential to become more negative (hyperpolarization), moving further from the threshold for excitation. An increase in serum potassium has the opposite effect; it causes the resting membrane potential to

become more positive (hypopolarized), moving closer to threshold. The activation and opening of the sodium channels, which control the flow of current during an action potential, are also affected by potassium levels. With severe hyperkalemia, the resting membrane approaches the threshold potential, causing sustained subthreshold depolarization. This inactivates the sodium channels and produces a net decrease in excitability. The *rate of repolarization* also varies with plasma potassium levels. It is more rapid in hyperkalemia and delayed in hypokalemia.

**Hypokalemia**

***Hypokalemia refers to a decrease in plasma potassium levels below 3.5 mEq/L (3.5 mmol/L).*** Because of transcellular shifts, temporary changes in plasma potassium may occur as the result of movement between the ICF and ECF compartments.

***Causes.*** The causes of potassium deficit can be grouped into three categories:

***(1) inadequate intake;***

***(2) excessive gastrointestinal, renal, and skin losses;***

***(3) redistribution between the ICF and ECF compartments.***

***Inadequate Intake*** is a frequent cause of hypokalemia. A potassium intake of at least 10 to 30 mEq/day is needed to compensate for obligatory urine losses. Insufficient dietary intake may result from the inability to obtain or ingest food or from a diet that is low in potassium-containing foods. Potassium intake is often inadequate in persons on fad diets and those who have eating disorders. Elderly persons are particularly likely to have potassium deficits. Many have poor eating habits as a consequence of living alone; they may have difficulty chewing many foods that have a high potassium content because of poorly fitting dentures; or they may have problems with swallowing. Many medical problems in elderly persons require treatment with drugs, such as diuretics, that in-crease potassium losses.

***Excessive Losses.*** The kidneys are the main source of potassium loss. Approximately 80% to 90% of potassium losses occur in the urine, with the remaining losses occurring in the stool and sweat. The kidneys do not have the homeostatic mechanisms needed to conserve potassium during periods of insufficient intake. After trauma and in stress situations, urinary losses of potassium are greatly increased, sometimes approaching levels of 150 to 200 mEq/L. This means that a potas-sium deficit can develop rather quickly if intake is inadequate. Renal losses also can be increased by medications, metabolic alkalosis, magnesium depletion, and increased levels of aldosterone. Some antibiotics, potassiumsparing diuretics, is the most common cause of hypokalemia. Both thiazide and loop diuretics increase the loss of potassium in the urine. Magnesium deficiency often coexists with potassium depletion due to diuretic therapy or disease processes such as diarrhea. Renal losses of potassium are accentuated by aldosterone and cortisol. Increased potassium losses occur in situations such as trauma and surgery that produce a stressrelated increase in these hormones. Primary aldosteronism is caused by a tumor in the cells of the adrenal cortex (in the zona glomerulosa) that secrete aldosterone. Excess secretion of aldosterone by the tumor cells causes severe potassium losses and a decrease in plasma potassium levels. Cortisol binds to aldosterone receptors and exerts aldosterone-like effects on potassium elimination. Potassium losses from the skin and the gastrointestinal tract usually are minimal. Gastrointestinal losses also can become excessive; this occurs with vomiting and diarrhea and when gastrointestinal suction is being used.

***Transcellular Shifts***. Because of the high ratio of intracellular to extracellular potassium, a redistribution of potassium from the ECF to the ICF compartment can produce a marked decrease in the plasma concentration. One cause of potassium redistribution is insulin. After insulin administration, there is increased movement of glucose and potassium into cells. This is one of the reasons that potassium deficit often develops during treatment of diabetic ketoacidosis. β-Adrenergic agonists, such as pseudoephedrine and albuterol, have a similar effect on potassium distribution. Theophylline and caffeine, although not catecholamines, may increase $Na^+/K^+$-ATPase membrane pump activity by inhibiting phosphodiesterase.

***Manifestations.*** The manifestations of hypokalemia include alterations in renal, gastrointestinal, cardiovascular, and skeletal muscle function. These manifestations reflect both the intracellular functions of potassium as well as the body's attempt to regulate ECF potassium levels within the very narrow range needed to maintain the normal electrical activity of excitable tissues such as nerve and muscle cells. The signs and symptoms of potassium deficit seldom develop until the plasma potassium level has fallen below 3.0 mEq/L. They are typically gradual in onset; therefore, the disorder may go undetected for some time. Urine output and plasma osmolality are increased, urine specific gravity is decreased, and complaints of polyuria, nocturia, and thirst are common. Metabolic alkalosis and renal

chloride wasting are signs of severe hypokalemia. There are numerous signs including anorexia, nausea, and vomiting. Atony of the gastrointestinal smooth muscle can cause constipation, and, in severe hypokalemia, paralytic ileus. The most serious effects of hypokalemia are those affecting cardiovascular function. Postural hypotension is common. Digitalis toxicity can be provoked in persons treated with this drug, and there is an increased risk for ventricular dysrhythmias, particularly in persons with underlying heart disease. Potassium and digitalis compounds compete for binding to sites on the $Na^+/K^+$-ATPase membrane pump. In hypokalemia, more sites are available for digitalis to bind to and exert its action. Most persons with plasma potassium levels below 3.0 mEq/L demonstrate electrocardiographic changes which include prolongation of the PR interval, depression of the ST segment, flattening of the T wave.

Normally, potassium leaves the cell during the repolarization phase of the action potential, returning the membrane potential to its normal resting value. Hypokalemia produces a decrease in potassium efflux that prolongs the rate of repolarization and lengthens the relative refractory period. The U wave normally may be present on the ECG but should be of lower amplitude than the T wave. With hypokalemia, the amplitude of the T wave decreases as the U-wave amplitude increases. Although these ECG changes usually are not serious, they may predispose to sinus bradycardia and ectopic ventricular dysrhythmias. Complaints of weakness, fatigue, and muscle cramps, particularly during exercise, are common in moderate hypokalemia (plasma potassium, 3.0 to 2.5 mEq/L). Muscle paralysis with life-threatening respiratory insufficiency can occur with severe hypokalemia (plasma potassium < 2.5 mEq/L). Leg muscles, particularly the quadriceps, are most prominently affected. Some persons complain of muscle tenderness and paresthesias rather than weakness. Three defects in skeletal muscle function occur with potassium deficiency: alterations in the resting membrane potential, alterations in glycogen synthesis and storage, and impaired ability to increase blood flow during strenuous exercise. Normal concentrations of intracellular potassium are necessary for glycogen synthesis in muscle cells. Therefore, hypokalemia can interfere with muscle metabolism, especially under exercise conditions that rely heavily on anaerobic pathways that use glycogen as fuel. Potassium released from muscle normally contributes to the autoregulation of blood flow during exercise. In a rare condition called hypokalemic familial periodic paralysis, episodes of hypokalemia cause attacks of flaccid paralysis.

**Hyperkalemia**

**Hyperkalemia refers to an increase in plasma levels of potassium in excess of 5.0 mEq/L (5.0 mmol/L).** It seldom occurs in healthy persons because the body is extremely effective in preventing excess potassium accumulation in the ECF.

***Causes.*** The three major causes of potassium excess are *decreased renal elimination, excessively rapid administration, and movement of potassium from the intracellular to extracellular compartment*.

A pseudohyperkalemia can occur secondary to release of potassium from intracellular stores after a blood sample has been collected, hemolysis of red blood cells, prolonged application of a tourniquet during venipuncture. The most common cause of hyperkalemia is decreased renal function associated with renal failure and decline glomerular filtration.

Persons with acute renal failure accompanied by lactic acidosis or ketoacidosis are at increased risk for development of hyperkalemia. Aldosterone acts at the level of the distal tubular sodium–potassium exchange system to increase potassium excretion while facilitating sodium reabsorption. A decrease in aldosterone-mediated potassium elimination can result from adrenal insufficiency (i.e., Addison's disease), depression of aldosterone release due to a decrease in renin or angiotensin II, or impaired ability of the kidneys to respond to aldosterone. Potassium-sparing diuretics (e.g., spironolactone, amiloride, triamterene, eplerenone) can produce hyperkalemia by means of the latter mechanism. Potassium excess can result from excessive oral ingestion or intravenous administration of potassium. In some cases, severe and fatal incidents of hyperkalemia have occurred when intravenous potassium solutions were infused too rapidly. Because the kidneys control potassium elimination, intravenous solutions that contain potassium should never be started until urine output has been assessed and renal function has been deemed to be adequate. The movement of potassium out of body cells into the ECF also can lead to elevated plasma potassium levels. Tissue injury causes release of intracellular potassium into the ECF compartment. For example, burns and crushing injuries cause cell death and release of potassium into the ECF. The same injuries often diminish renal function, which contributes to the development of hyperkalemia. Transient hyperkalemia may be induced during extreme exercise or sei-zures, when muscle cells are permeable to potassium

***Manifestations.***The signs and symptoms of potassium excess are closely related to the alterations in neuromuscular excitability. The effect that potassium has on membrane excitability is determined by the ratio of K-ions inside the cell membrane to those outside the cell membrane. As the ECF potassium concentration rises, there is a decrease in the potassium ratio. This change produces an initial increase in membrane excitability because it brings the resting membrane potential closer to the threshold potential, such that a lesser stimulus is needed for depolarization. The first symptom associated with hyperkalemia typically is paresthesia. There may be complaints of generalized muscle weakness or dyspnea secondary to respiratory muscle weakness. The most serious effect of hyperkalemia is on the heart. As potassium levels increase, disturbances in cardiac conduction occur. The earliest changes are peaked, narrow T waves and widening of the QRS complex. If plasma levels continue to rise, the PR interval becomes prolonged and is followed by disappearance of P waves . The heart rate may be slow.

## MECHANISMS REGULATING CALCIUM, PHOSPHATE, AND MAGNESIUM BALANCE

Calcium, phosphate, and magnesium are the major divalent cations in the body. They are ingested in the diet, absorbed from the intestine, filtered in the glomerulus of the kidney, reabsorbed in the renal tubules, and eliminated in the urine. Approximately 99 % of calcium, 85 % of phosphate, and 50 % to 60 % of magnesium is found in bone. Most of the remaining calcium (1%), phosphate (14%), and magnesium (40 % to 50 %) is located inside cells. Only a small amount of these three ions is present in ECF. This small, but vital, amount of ECF calcium, phosphate, and magnesium is directly or indirectly regulated by vitamin D and parathyroid hormone (PTH). Calcitonin, a hormone produced by C cells in the thyroid, is thought to act on the kidney and bone to remove calcium from the extracellular circulation.

**Vitamin D.** Although classified as a vitamin, vitamin D functions as a hormone. It acts to sustain normal plasma levels of calcium and phosphate by increasing their absorption from the intestine, and it also is necessary for normal bone formation. Vitamin D is synthesized by ultraviolet irradiation of 7-dehydrocholesterol, which is present in the skin or obtained from foods in the diet, many of which are fortified with vitamin D. The synthesized or ingested forms of vitamin D are essentially prohormones that lack biologic activity and must undergo metabolic transformation to achieve potency. Once vitamin D enters the circulation from the skin or intestine, it is concentrated in the liver. There, it is hydroxylated to form 25-hydroxyvitamin D [25-(OH)D3]. It is then transported to the kidney, where it is transformed into active 1,25-(OH)2D3. The major action of the activated form of vitamin D, also called *calcitriol*, is to increase the absorption of calcium from the intestine. Calcitriol also sensitizes bone to the resorptive actions of PTH. There is also recent evidence that vitamin D controls parathyroid gland growth and suppresses the synthesis and secretion of PTH. The formation of 1,25-(OH)2D3 in the kidneys is regulated in feedback fashion by plasma calcium and phosphate levels. Low calcium levels lead to an increase in PTH, which then increases vitamin D activation. A lowering of plasma phosphate levels also augment vitamin D activation. Additional control of renal activation of vitamin D is exerted by a negative feedback loop that monitors 1,25-(OH)2D3 levels.

**Parathyroid hormone (PTH)**, a major regulator of plasma calcium and phosphate, is secreted by the parathyroid glands. There are four parathyroid glands located on the dorsal surface of the thyroid gland. The dominant regulator of PTH is the plasma calcium concentration.When the plasma calcium level is high, PTH is inhibited, and the calcium is deposited in the bones. When the level is low, PTH secretion is increased, and calcium is mobilized from the bones. The response to a decrease in plasma calcium is prompt, occurring within seconds. Phosphate does not exert a direct effect on PTH secretion. Instead, it acts indirectly by complexing with calcium and decreasing plasma calcium concentration. The secretion, synthesis, and action of PTH are also influenced by magnesium. Magnesium serves as a cofactor in the generation of cellular energy and is important in the function of second messenger systems. Magnesium's effects on the synthesis and release of PTH are thought to be mediated through these mechanisms. Because of its function in regulating PTH release, severe and prolonged hypomagnesemia can markedly inhibit PTH levels. The main function of PTH is to maintain the calcium concentration of the ECF. It performs this function by promoting the release of calcium from bone, increasing the activation of vitamin D as a means of enhancing intestinal absorption of calcium, and stimulating calcium conservation by the kidney while increasing phosphate excretion.

The actions of PTH in terms of bone resorption require normal levels of both vitamin D and magnesium. The activation of vitamin D by the kidney is enhanced by the presence of PTH; it is through the activation of vitamin D that PTH increases intestinal absorption of calcium and phosphate.

PTH also acts directly on the kidney to increase tubular reabsorption of calcium and magnesium while increasing phosphate elimination. The accompanying increase in phosphate elimination ensures that calcium released from bone does not produce hyperphosphatemia and increase the risk for soft tissue deposition of calcium-phosphate crystals.

***Hypoparathyroidism.*** Hypoparathyroidism reflects deficient PTH secretion, resulting in hypocalcemia. PTH deficiency may be caused by a congenital absence of all of the parathyroid glands, as in DiGeorge syndrome. An acquired deficiency of PTH may occur after neck surgery, particularly if the surgery involves removal of a parathyroid adenoma, thyroidectomy. Hypoparathyroidism also may have an autoimmune origin. Functional impairment of parathyroid function occurs with magnesium deficiency. Correction of the hypomagnesemia results in rapid disappearance of the condition. Manifestations of acute hypoparathyroidism, which result from a decrease in plasma calcium, include tetany with muscle cramps, carpopedal spasm, and convulsions (see Hypocalcemia). Paresthesias, such as tingling of the circumoral area and in the hands and feet, are almost always present. Low calcium levels may cause prolongation of the QT interval, resistance to digitalis, hypotension, and refractory heart failure. Symptoms of chronic PTH deficiency include lethargy, anxiety state, and personality changes. Extrapyramidal signs, such as those seen with Parkinson disease, may occur because of calcification of the basal ganglia. Diagnosis of hypoparathyroidism is based on low plasma calcium levels, high plasma phosphate levels, and low plasma PTH levels. Plasma magnesium levels usually are measured to rule out hypomagnesemia as a cause of the disorder. Acute hypoparathyroid tetany is treated with intravenous calcium gluconate followed by oral administration of calcium salts and vitamin D. Magnesium supplementation is used when the disorder is caused by magnesium deficiency.

***Hyperparathyroidism.*** Hyperparathyroidism is caused by hypersecretion of PTH. Hyperparathyroidism can manifest as a primary disorder caused by hyperplasia (15 %), an adenoma (85 %), and rarely carcinoma of the parathyroid glands or as a secondary disorder seen in persons with renal failure or chronic malabsorption of calcium.

**Primary hyperparathyroidism** causes hypercalcemia and an increase in calcium in the urine filtrate, resulting in hypercalciuria and the potential for development of kidney stones. Chronic bone resorption may produce diffuse demineralization, pathologic fractures, and cystic bone lesions. At the present time, most patients with primary hyperparathyroidism manifest an asymptomatic disorder that is discovered in the course of routine biochemical testing. Diagnostic procedures, which include plasma calcium and intact PTH levels, are used to differentiate between the two most common causes of hypercalcemia: primary hyperparathyroidism and hypercalcemia of malignancy. In primary hyperparathyroidism, the intact PTH levels will be elevated in 75 % to 90 % of affected persons or will be inappropriately “normal” in the face of hypercalcemia when they should be suppressed.

**Secondary** hyperparathyroidism involves hyperplasia of the parathyroid glands and occurs primarily in persons with renal failure. In early renal failure, an increase in PTH results from decreased plasma calcium and activated vitamin D levels. As the disease progresses, there is a decrease in vitamin D and calcium receptors, making the parathyroid glands more resistant to vitamin D and calcium. At this point, elevated phosphate levels induce hyperplasia of the parathyroid glands independent of calcium and activated vitamin D. The bone disease seen in persons with secondary hyperparathyroidism due to renal failure is known as renal osteodystrophy. Treatment includes re-solving the hypercalcemia with large fluid intake.Calcium acetate or a newer calcium-free agent (sevelamer HCl [Renagel]) can be given with meals to bind phosphate. Calcitriol, the activated form of vitamin D, may be used to control parathyroid growth and suppress the synthesis and secretion of PTH. However, because of its potent effect on intestinal absorption and bone mobilization, calcitriol can cause hypercalcemia.

**ALTERATIONS IN CALCIUM BALANCE.** Calcium enters the body through the gastrointestinal tract, is absorbed from the intestine under the influence of vitamin D, is stored in bone, and is excreted by the kidney. Approximately 99 % of body calcium is found in bone, where it provides the strength and stability for the skeletal system and serves as an exchangeable source to maintain extracellular calcium levels. Most of the remaining calcium (approximately 1 %) is located inside cells, and only approximately 0.1 % to 0.2 % of the remaining calcium is present in the ECF. The extracellular concentrations of calcium and phosphate are reciprocally regulated such that calcium levels fall when phosphate levels are high, and vice versa. The ECF calcium exists in three forms: protein bound, complexed, and ionized. Approximately 40 % of ECF calcium is bound to plasma proteins, mostly albumin, and cannot diffuse or pass through the capillary wall to leave the vascular compartment. Another 10% is complexed (i.e., chelated) with substances such as citrate, phosphate, and sulfate. This form is not

ionized. The remaining 50 % of ECF calcium is present in the ionized form. It is the ionized form of calcium that is free to leave the vascular compartment and participate in cellular functions. The total plasma calcium level fluctuates with changes in plasma albumin and pH (the total plasma calcium level is decreased 0.75 to 1.0 mg/dL for every 1g/dL decrease from normal in the plasma albumin level). It participates in many enzyme reactions; exerts an important effect on membrane potentials and neuronal excitability; is necessary for contraction in skeletal, cardiac, and smooth muscle; participates in the release of hormones, neurotransmitters, and other chemical messengers; influences cardiac contractility and automaticity by way of slow calcium channels; and is essential for blood clotting.

**Gains and Losses.** The major sources of calcium are milk and milk products. Only 30 % to 50 % of dietary calcium is absorbed from the duodenum and upper jejunum; the remainder is eliminated in the stool. There is a calcium influx of approximately 150 mg/day into the intestine from the blood. Net absorption of calcium is equal to the amount that is absorbed from the intestine less the amount that moves into the intestine. Calcium balance can become negative when dietary intake (and calcium absorption) is less than intestinal secretion. 60% to 65% of filtered calcium is passively reabsorbed in the proximal tubule, driven by the reabsorption of sodium chloride; 15 % to 20 % is reabsorbed in the thick ascending loop of Henle, driven by the $Na^+/K^+$-$2Cl^-$ cotransport system; and 5 % to 10 % is reabsorbed in the distal convoluted tubule. PTH and possibly vitamin D stimulate calcium reabsorption in this segment of the nephron. Other factors that may influence calcium reabsorption in the distal convoluted tubule are phosphate levels and glucose and insulin levels.

**Hypocalcemia**

**Hypocalcemia represents a plasma calcium level of less than 8.5 mg/dL.** Hypocalcemia occurs in many forms of critical illness and has affected as many as 70 % to 90 % of patients in intensive care units.

***Causes.*** The causes of hypocalcemia can be divided into four categories:

***(1) impaired ability to mobilize calcium bone stores,***

***(2) abnormal losses of calcium from the kidney,***

***(3) increased protein binding or chelation such that greater proportions of calcium are in the nonionized form,***

***(4) soft tissue sequestration***.

Pseudohypocalcemia is caused by hypoalbuminemia. It results in a decrease in protein-bound, rather than ionized, calcium and usually is asymptomatic. Plasma calcium exists in a dynamic equilibrium with calcium in bone. The ability to mobilize calcium from bone depends on adequate levels of PTH. Decreased levels of PTH may result from primary or secondary forms of hypoparathyroidism. Suppression of PTH release may also occur when vitamin D levels are elevated. The activated form of vitamin D (calcitriol) can be used to failure suppress the secondary hyperpa-rathyroidism that occurs in persons with kidney.

Magnesium deficiency inhibits PTH release and impairs the action of PTH on bone resorption. This form of hypocalcemia is difficult to treat with calcium supplementation alone and requires correction of the magnesium deficiency. There is an inverse relation between calcium and phosphate excretion by the kidneys. Phosphate elimination is impaired in renal failure, causing plasma calcium levels to decrease.

Only the ionized form of calcium is able to leave the capillary and participate in body functions. change in pH alters the proportion of calcium that is in the bound and ionized forms. An acid pH decreases binding of calcium to protein, causing a proportionate increase in ionized calcium, whereas total plasma calcium remains unchanged. An alkaline pH has the opposite effect. As an example, hyperventilation sufficient to cause respiratory alkalosis can produce tetany because of increased protein binding of calcium. Elevations in free fatty acids sufficient to alter calcium binding may occur during stressful situations that cause elevations of epinephrine, glucagon, growth hor-mone, and adrenocorticotropic hormone levels. Hypocalcemia is a common finding in a patient with acute pancreatitis. Inflammation of the pancreas causes release of proteolytic and lipolytic enzymes. Inflammation of the pancreas causes release of proteolytic and lipolytic enzymes. It is thought that the $Ca^{2+}$ combines with free fatty acids released by lipolysis in the pancreas, forming soaps and removing calcium from the circulation. Calcium deficit due to dietary deficiency exerts its effects on bone stores rather than extracellular calcium levels. A dietary deficiency of vitamin D is seldom seen today because many foods are fortified with vitamin D. Vitamin D deficiency is more likely to occur in malabsorption states, such as biliary obstruction, pancreatic insufficiency, and celiac disease, in which the ability to absorb fat and fat-soluble vitamins is impaired.

***Manifestations.*** Hypocalcemia can manifest as an acute or chronic condition. The manifestations of acute hypocalcemia reflect the increased neuromuscular excitability and cardiovascular effects of a decrease in ionized calcium. Ionized calcium stabilizes neuromuscular excitability, thereby making nerve cells less sensitive to stimuli. Nerves exposed to low ionized calcium levels show decreased thresholds for excitation, repetitive responses to a single stimulus, and, in extreme cases, continuous activity. The manifestations depends on the underlying cause, rapidity of onset, accompanying electrolyte disorders, and extracellular pH. Increased neuromuscular excitability can manifest as paresthesias (i.e., tingling around the mouth and in the hands and feet) and tetany (i.e., muscle spasms of the muscles of the face, hands, and feet). Severe hypocalcemia can lead to laryngeal spasm, seizures, and even death. Cardiovascular effects include hypotension, cardiac insufficiency, cardiac dysrhythmias (block and ventricular fibrillation).

Chronic hypocalcemia is often accompanied by skeletal manifestations and skin changes. There may be bone pain, fragility, deformities, and fractures. The skin may be dry and scaling, the nails brittle, and the hair dry. Development of cataracts is common. Chvostek's and Trousseau's tests can be used to assess for an increase in neuromuscular excitability and tetany. Chvostek's sign is elicited by tapping the face just below the temple at the point where the facial nerve emerges. Tapping the face over the facial nerve causes spasm of the lip, nose, or face when the test result is positive. An inflated blood pressure cuff is used to test for Trousseau's sign. The cuff is inflated above systolic blood pressure for 3 minutes. Contraction of the fingers and hands (i.e., carpopedal spasm) indicates the presence of tetany.

**Hypercalcemia**

**Hypercalcemia represents a total plasma calcium concentration of greater than 10.5 mg/dL.** Falsely elevated levels of calcium can result from prolonged drawing of blood with an excessively tight tourniquet. Increased plasma proteins (*e.g.,* hyperalbuminemia, hyperglobulinemia) may elevate the total plasma calcium but not affect the ionized calcium concentration.

***Causes.*** A plasma calcium excess (*i.e.,* hypercalcemia) results when calcium movement into the circulation overwhelms the calcium regulatory hormones or the ability of the kidney to remove excess calcium ions. The two most common causes of hypercalcemia are increased bone resorption due to neoplasms and hyperparathyroidism. These two etiologies account for more than 90 % of all patients with hypercalcemia. Hypercalcemia is a common complication of malignancy, occurring in approximately 10 % to 20 % of persons with advanced disease. Less frequent causes of hypercalcemia are prolonged immobilization, increased intestinal absorption of calcium, excessive doses of vitamin D, and the effects of drugs such as lithium and thiazide diuretics. Prolonged immobilization and lack of weight bearing cause demineralization of bone and release of calcium into the bloodstream. Intestinal absorption of calcium can be increased by excessive doses of vitamin D or as a result of a condition called the milk-alkali syndrome. The milk-alkali syndrome is caused by excessive ingestion of calcium (often in the form of milk) and absorbable antacids. Because of the advent of nonabsorbable antacids, the condition is seen less frequently than in the past, but it may occur in women who are overzealous in taking calcium preparations for osteoporosis prevention. The condition is thought to be initiated by mild hypercalcemia leading to increased sodiumexcretion along with a decrease in ECF volume and glomerular filtration rate. The decreased glomerular filtrationrate leads to alkalosis and increased calcium reabsorption by the kidney. Discontinuance of the antacid repairs the alkalosis and increases calcium elimination. A variety of drugs elevate calcium levels. The thiazide diuretics seldom cause hypercalcemia, they can unmask hypercalcemia from other causes such as underlying bone disorders and conditions that increase bone resorption.

***Manifestations.*** The signs and symptoms associated with calcium excess originate from three sources: changes in neural excitability, alterations in smooth and cardiac muscle function, and exposure of the kidneys to high concentrations of calcium. Neural excitability is decreased in patients with hypercalcemia. There may be a dulling of consciousness, stupor, weakness, and muscle flaccidity. The heart responds to elevated levels of calcium with increased contractility and ventricular dysrhythmias. Gastrointestinal symptoms reflect a decrease in smooth muscle activity and include constipation, anorexia, nausea, and vomiting. Pancreatitis is another potential complication of hypercalcemia and is probably related to stones in the pancreatic ducts. High calcium concentrations in the urine impair the ability of the kidneys to concentrate urine by interfering with the action of ADH (an example of nephrogenic diabetes insipidus).

**ALTERATIONS IN PHOSPHATE BALANCE**

Phosphorus is mainly an intracellular anion. It is the fourth most abundant element in the body after carbon, nitrogen, and calcium. Phosphate is essential to many bodily functions. It plays a major role in bone formation; is essential to certain metabolic processes, including the formation of ATP and the enzymes needed for metabolism of glucose, fat, and protein; is a necessary component of several vital parts of the cell, being incorporated into the nucleic acids of DNA and RNA and the phospholipids of the cell membrane; and serves as an acid-base buffer in the ECF and in the renal excretion of hydrogen ions. Delivery of oxygen by the red blood cell depends on organic phosphates in ATP and 2,3-diphospho-glycerate. Phosphate is also needed for normal function of other blood cells, including the white blood cells and platelets. ECF phosphorus exists mainly as phosphate, although laboratory measurements are often reported as elemental phosphorus. Most of the intracellular phosphorus (90 %) is in the organic form (*e.g.*, nucleic acids, phosphoproteins, ATP). Entry of phosphate into cells is enhanced after glucose uptake because phosphorus is incorporated into the phosphorylated intermediates of glucose metabolism. Cell injury or atrophy leads to a loss of cell components that contain organic phosphate; regeneration of these cellular components results in withdrawal of inorganic phosphate from the extracellular compartment. In the adult, the normal plasma phosphate level ranges from 2.5 to 4.5 mg/dL.

**Gains and Losses.** Phosphate is ingested in the diet and eliminated in the urine. Phosphate is derived from many dietary sources, including milk and meats. Approximately 80 % of ingested phosphate is ab-sorbed in the intestine, primarily in the jejunum. Absorption is diminished by concurrent ingestion of substances that bind phosphate, including calcium, magnesium, and aluminum. Essentially all of the phosphate that is present in the plasma is filtered in the glomerulus. Renal elimination of phosphate is then regulated by an overflow mechanism in which the amount of phosphate lost in the urine is directly related to phosphate concentrations in the blood. Phosphate is reabsorbed from the filtrate into the proximal tubular epithelial cells through the action of a sodium phosphate cotransporter. PTH also plays a significant role in regulating phosphate concentration. Thus, whenever PTH is increased, tubular phosphate reabsorption is decreased, and more phosphate is lost in the urine (because PTH decreases the synthesis and expression of the NPT2a transporter on the luminal surface of the proximal tubular cell).

**Hypophosphatemia.** Hypophosphatemia is commonly defined by a plasma phosphorus level of less than 2.5 mg/dL in adults; it is considered severe at oncentration of less than 1.0 mEq/L.5 1 Hypophosphatemia may occur despite normal body phosphate stores as a result of movement from the ECF into the ICF compartment. Serious depletion of phosphate may exist with low, normal, or high plasma concentrations.

***Causes.*** The most common causes of hypophosphatemia are depletion of hosphate because of insufficient intestinal absorption, transcompartmental shifts, and increased renal losses. Often, more than one of these mechanisms is active. Unless food intake is severely restricted, dietary intake and intestinal absorption of phosphorus are usually adequate. Intestinal absorption may be inhibited by administration of glucocorticoids, high dietary levels of magnesium, and hypothyroidism. Prolonged ingestion of antacids may also interfere with intestinal absorption. Antacids that contain aluminum hydroxide, aluminum carbonate, and calcium carbonate bind with phosphate, causing increased posphate losses in the stool. Because of their ability to bind phosphate, calcium-based antacids are sometimes used therapeutically to decrease phosphate levels in persons with chronic renal failure. Malnutrition and diabetic ketoacidosis increase phosphate excretion and phosphate loss from the body. Refeeding of malnourished patients increases the incorporation of phosphate into nucleic acids and phosphorylated compounds in the cell. The same thing happens when diabetic ketoacidosis is reversed with insulin therapy.

Hypophosphatemia can occur during prolonged courses of glucose administration or hyperalimentation. Glucose administration causes insulin release, with transport of glucose and phosphorus into the cell. The catabolic events that occur with diabetic ketoacidosis also deplete phosphate stores. Because only a small amount of total body phosphorus is in the extracellular compartment, even a small redistribution between the extracellular and intracellular compartments can cause hypophos-phatemia, even though total phosphate levels have not changed. Respiratory alkalosis due to pro-longed hyperventilation can produce hypophosphatemia through decreased levels of ionized calcium from increased protein binding, increased PTH release, and increased phosphate excretion.Clinical conditions associated with hyperventilation include gram-negative septicemia, alcohol withdrawal, heat stroke, and primary hyperventilation.

***Manifestations.*** Many of the manifestations of phosphorus deficiency result from a decrease in cellular energy stores due to deficiency in ATP and impaired oxygen transportdue to a decrease in red blood cell 2,3-diphosphoglycerate. Hypophosphatemia results in altered neural function, disturbed usculoskeletal function, and hematologic disorders. Red blood cell metabolism is impaired by phosphate deficiency; the cells become rigid, undergo increased hemolysis, and have diminished ATP and 2,3-diphosphoglycerate levels. Chemotaxis and phagocytosis by white blood cells are impaired. Platelet function also is disturbed. Respiratory insufficiency resulting from impaired function of the respiratory muscles can develop in patients with severe hypophosphatemia. Neural manifestations include intention tremors, paresthesia, hyporeflexia, stupor, coma, and seizures. Anorexia and dysphagia can occur. Muscle weakness, which is common in hypophosphatemia, is related to a reduction in diphosphoglycerate. In growing children, this process causes abnormal endochondral growth and clinical manifestations of rickets.

**Hyperphosphatemia**

***Hyperphosphatemia represents a plasma phosphorus concentration in excess of 4.5 mg/dL in adults.*** Growing children normally have plasma phosphate levels higher than those of adults.

***Causes.*** Hyperphosphatemia results from failure of the kidneys to excrete excess phosphate, rapid redistribution of intracellular phosphate to the extracellular compartment, and excessive intake of phosphate. The most common cause of hyperphosphatemia is impaired renal function. Hyperphosphatemia is a common electrolyte disorder in persons with chronic renal failure. A reduction in glomerular filtration rate to less than 30 to 50 mL/minute results in a reduction of phosphate elimination. The increase in phosphate levels in persons with end-stage renal disease occurs despite compensatory increases in PTH.

The administration of excess phosphate-containing antacids, laxatives, or enemas can be another cause of hyperphosphatemia, especially when there is a decrease in vascular volume and a reduced glomerular filtration rate. Phosphate-containing laxatives and enemas predispose to hypovolemia and a decreased glomerular filtration rate by inducing diarrhea, thereby increasing the risk for hypophosphatemia. ***Manifestations.*** Hyperphosphatemia is accompanied by a decrease in plasma calcium. Many of the signs and symptoms of phosphate excess are related to a calcium deficit Ectopic calcifications may develop when the calcium ×phosphate concentration product exceeds.

**Alterations in magnesium balance.** Magnesium is the second most abundant intracellular cation. The average adult has approx-imately 24 g of magnesiumdistributed throughout the body. Of the total magnesium content, ap-proximately 50 % to 60 % is stored in bone, 39 % to 49 % is contained in the body cells, and the re-maining 1 % is dispersed in the ECF. Magnesium acts as a co-factor in many intracellular enzyme reactions, including those related to transfer of phosphate groups. It is essential to all reactions that require ATP, for every step related to replication and tran-scription of DNA, and for the translation of messenger RNA. It is required for cellular energy me-tabolism, functioning of the sodium–potassium membrane pump, membrane stabilization, nerve conduction, ion transport, and calcium channel activity. Magnesium binds to calcium receptors, and it has been suggested that alterations in magnesium levels may exert their effects through calcium-mediated mechanisms.

**Gains and Losses.** Magnesium is ingested in the diet, absorbed from the intestine, and excreted by the kidneys. Intestinal absorption is not closely regulated, and approximately 25 % to 65 % of dietary magnesium is absorbed. Magnesium is contained in all green vegetables, grains, nuts, meats, and seafood. The kidney is the principal organ of magnesium regulation. The greatest quantity, approximately 50 % to 70 %, is reabsorbed in the thick ascending loop of Henle. The distal tubule, which reabsorbs a small amount of magnesium, is the major site of magnesium regulation. Magnesium reabsorption is decreased in the presence of increased plasma levels, stimulated by PTH, and inhibited by increased calcium levels. The major driving force for magnesium absorption in the thick ascending loop of Henle is the $Na^+/K^+$-$2Cl^-$cotransport system. Inhibition of this transport system by loop diuretics lowers magnesium reabsorption.

**Hypomagnesemia.** Hypomagnesemia represents a plasma magnesium concentration of less than 1.8 mg/dL. It is seen in conditions that limit intake or increase intestinal or renal losses, and it is a common finding in emergency departments and critical care patients.

***Causes.*** Magnesium deficiency can result from insufficient intake, excessive losses, or movement between the ECF and ICF compartments. It can result from conditions that directly limit intake, such as malnutrition, starvation, or prolonged maintenance of magnesium-free parenteral nutrition. Other conditions, such as diarrhea, malabsorption syndromes, prolonged nasogastric suction, and laxative

abuse, decrease intestinal absorption. Excessive calcium intake impairs intestinal absorption of magnesium by competing for the same transport site. Another common cause of magnesium deficiency is chronic alcoholism. Many factors contribute to hypomagnesemia in alcoholism, including low intake and gastrointestinal losses from diarrhea. The effects of hypomagnesemia are exaggerated by other electrolyte disorders, such as hypokalemia, hypocalcemia, and metabolic acidosis. There also is evidence that alcohol inhibits reabsorption of magnesium by the kidney. Although the kidneys are able to defend against hypermagnesemia, they are less able to conserve magnesium and prevent hypo-magnesemia. Urine losses are increased in diabetic ketoacidosis, hyperparathyroidism, and hyperaldosteronism.

***Manifestations***

Magnesium deficiency usually occurs in conjunction with hypocalcemia and hypokalemia, producing a number of related neurologic and cardiovascular manifestations. Hypocalcemia is typical of severe hypomagnesemia. Most persons with hypomagnesemia-related hypocalcemia have decreased PTH levels, probably as a result of impaired magnesium dependent mechanisms that control PTH release and synthesis. There is also evidence that hypomagnesemia decreases both the PTH-dependent and PTH-independent release of calcium from bone. Hypokalemia also is a typical feature of hypomagnesemia. It leads to a reduction in intracellular potassium and impairs the ability of the kidney to conserve potassium. When hypomagnesemia is present, hypokalemia is unresponsive to potassium replacement therapy. Magnesium is vital to carbohydrate metabolism and the generation of both aerobic and anaerobic metabolisms. Many of the manifestations of magnesium deficit are due to related electrolyte disorders such as hypokalemia and hypocalcemia. Hypocalcemia may be evidenced by personality changes and neuromuscular irritability along with tremors, athetoid or choreiform movements, and positive Chvostek's or Trousseau's signs. Cardiovascular manifestations include tachycardia, hypertension, and ventricular dysrhythmias. There may be ECG changes such as widening of the QRS complex, appearance of peak T waves, prolongation of PR interval, T-wave inversion, and appearance of U waves.

***Treatment.*** Hypomagnesemia is treated with magnesium replacement. The route of administration depends on the severity of the condition. Symptomatic, moderate to severe magnesium deficiency is treated by parenteral administration. Treatment must be continued for several days to replace stored and plasma levels. In conditions of chronic intestinal or renal loss, maintenance support with oral magnesium may be required. Patients with any degree of renal failure must be carefully monitored to prevent magnesium excess. Magnesium often is used therapeutically to treat cardiac arrhythmia, myocardial infarct, angina, and pregnancy complicated by preeclampsia or eclampsia. Caution to prevent hypermagnesemia is essential.

**Hypermagnesemia.** Hypermagnesemia represents a plasma magnesium concentration in excess of 2.7 mg/dL. Because of the ability of the normal kidney to excrete magnesium, hypermagnesemia is rare.

***Causes.*** When hypermagnesemia does occur, it usually is related to renal insufficiency and the injudicious use of magnesium-containing medications such as antacids, mineral supplements, and laxatives. Elderly persons are particularly at risk because they have age-related reductions in renal function and tend to consume more magnesium-containing medications. Magnesium sulfate is used to treat toxemia of pregnancy and premature labor; in these cases, careful monitoring for signs of hypermagnesemia is essential.

***Manifestations.*** Hypermagnesemia affects neuromuscular and cardiovascular function (see Table). Because magnesium tends to suppress PTH secretion, hypocalcemia may accompany hypermagnesemia. The signs and symptoms occur only when plasma magnesium levels exceed 4.9 g/dL (2 mmol/L). Deep tendon reflexes begin to decrease as magnesium plasma levels exceed 4 mEq/L. Hypermagnesemia diminishes neuromuscular function, causing hyporeflexia, muscle weakness, and confusion. Magnesium decreases acetylcholine release at the myoneural junction and may cause neuromuscular blockade and respiratory paralysis. Cardiovascular effects are related to the calcium channel–blocking effects of magnesium. Blood pressure is decreased, and the ECG shows an increase in the PR interval, a shortening of the QT interval, T-wave abnormalities, and prolongation of the QRS and PR intervals. Hypotension due to vasodilation and cardiac dysrhythmias can occur with moderate hypermagnesemia (< 10 mg/dL), and confusion and coma can occur with severe hypermagnesemia (≥ 10 mg/dL). Very severe hypermagnesemia (> 15 mg/dL) may cause cardiac arrest.

***Treatment.*** The treatment of hypermagnesemia includes cessation of magnesium administration. Calcium is a direct antagonist of magnesium, and intravenous administration of calcium may be used. Peritoneal dialysis or hemodialysis may be required.

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## PRACTICAL LESSON № № 15 (17 stom.)
## Topic: DISORDERS OF ACID-BASE BALANCE

**The topicality.** Acid-base balance is one of the most important homeostasis signs. Due to its prevalence and lack of symptoms of acid-base state and balance deviations, are often skipped and revealed only by resuscitators in far-gone often critical cases. Knowing and systematic study of acid-base balance has to be necessary and added to the scheme of clinical study in different diseases. This will allow to diagnose correctly and to carry out rational therapy to correct those deviations.

**Overall Objective.** To be able to characterize acid-base balance disorders as typical changes of metabolism, to classify and define the main pathogenetic mechanisms of the main types of disorders.

**To do this we should be able to (specific objectives):**

1. Formulate the concept of "acid-base state", "acidosis" and "alkalosis".
2. Classify its forms.
3. Analyze the pathogenetic mechanisms forming different types of acid-base disorders.
4. Estimate acid-base indexes in different types of alkalosis and acidosis.
5. Substantiate using given data pathogenetic therapy of different types of acid-base disorders.

**The necessary basic knowledge and skills to achieve the goals of studying.**

**To be able to:**

1. Define the "acid-base state" concept, and indexes, and determine it.
2. Show mechanisms of the regulation (disorders compensation) of acid-base balance.

**Questions for the class**

1. Definition of acid-base state. Mechanisms of its regulation.
2. Acid-base balance indexes.
3. Classification of disorders.
4. Causes and mechanisms of disorders of acid-base system.
5. Respiratory (gas) acidosis and alkalosis.
6. Non-gas acidosis and alkalosis (metabolic, excretory and exogenous).
7. Principles of acid-base disorders correction.

THEORETICAL MATERIAL FOR PREPARATION TO LESSON

### DISORDERS OF ACID-BASE BALANCE

Metabolic activities of the body require the precise regulation of acid-base balance, which is reflected in the pH of extracellular fluids. Membrane excitability, enzyme systems, and chemical reactions depend on acid-base balance being regulated within a narrow physiologic range to function in an optimal way. Many conditions, pathologic or otherwise, can alter body pH. This chapterhas been organized into two sections: mechanisms of acid-base balance and disorders of acid-base balance.

**Mechanisms of Acid-Base Balance.** Normally, the concentration of body acids and bases is regulated so that the pH of extracellular body fluids is maintained within a very narrow range of 7.35 to 7.45. This balance is maintained through mechanisms that generate, buffer, and eliminate acids and bases. This section of the chapter focuses on acid-base chemistry, the production and regulation of metabolic acids and bicarbonate, calculation of pH, and laboratory tests of acid-base balance.

### METABOLIC ACID AND BICARBONATE PRODUCTION

Acids are continuously generated as byproducts of metabolic processes. Physiologically, these acids fall into two groups: the *volatile acid* $H_2CO_3$ and all other *nonvolatile* or *fixed acids.* The difference between the two types of acids arises because $H_2CO_3$ is in equilibrium with the volatile gas $CO_2$, which leaves the body by way of the lungs. The concentration of $H_2CO_3$ is therefore determined by the lungs and their respiratory capacity. The *fixed acids* (*e.g.*, sulfuric, hydrochloric, phosphoric) are *nonvolatile* and are not eliminated by the lungs. Instead, they are buffered by body proteins or extracellular buffers, such as $HCO_3^-$, and then excreted by the kidney.

**Carbon Dioxide and Bicarbonate Production**

Body metabolism results in the production of approximately 15,000 mmol of $CO_2$ each day. Carbon dioxide is transported in the circulation in three forms: attached to hemoglobin, as dissolved $CO_2$ in the plasma, and as $HCO_3^-$. Collectively, dissolved $CO_2$ and $HCO_3^-$constitute approximately 77 % of the $CO_2$ that is transported in the extracellular fluid; the remaining $CO_2$ travels attached to hemoglobin. Although $CO_2$ is not an acid, a small percentage of the gas combines with water in the bloodstream to form $H_2CO_3$. The reaction that generates $H_2CO_3$ from $CO_2$ and water is catalyzed by an enzyme called *carbonic anhydrase*, which is present in large quantities in red blood cells, renal tubular cells, and

other tissues in the body. The rate of the reaction between $CO_2$ and water is increased approximately 5000 times by the presence of carbonic anhydrase. Were it not for this enzyme, the reaction would occur too slowly to be of any significance. Because it is almost impossible to measure $H_2CO_3$, dissolved $CO_2$ measurements are commonly substituted when calculating pH. The $H_2CO_3$ content of the blood can be calculated by multiplying the partial pressure of $CO_2$ ($PCO_2$) by its solubility coefficient, which is 0.03. This means that the concentration of $H_2CO_3$ in arterial blood, which normally has a $PCO_2$ of approximately 40 mm Hg, is 1.2 mEq/L ($40 \times 0.03 \rightarrow 1.2$).

### Production of Noncarbonic Acids and Bases

The metabolism of dietary proteins and other substances results in the generation of noncarbonic acids and bases. Oxidation of the sulfur-containing amino acids (*e.g.,* methionine, cysteine, cystine) results in the production of sulfuric acid. Oxidation of arginine and lysine produces hydrochloric acid, and oxidation of phosphorus-containing nucleic acids yields phosphoric acid. Incomplete oxidation of glucose results in the formation of lactic acid, and incomplete oxidation of fats results in the production of ketoacids. The major source of base is the metabolism of amino acids such as aspartate and glutamate and the metabolism of certain organic anions (*e.g.,* citrate, lactate, acetate). Acid production normally exceeds base production, with the net effect being the addition of approximately 1 mmol/kg body weight of nonvolatile or fixed acid to the body each day. A vegetarian diet, which contains largeamounts of organic anions, results in the net production of base.

## CALCULATION OF pH

The plasma pH can be calculated using an equation called the *Henderson-Hasselbalch equation.* This equation uses the negative logarithm of the dissociation constant and the logarithm of the $HCO_3^-$ to $CO_2$ ($HCO_3$ / $CO_2$) ratio to calculate pH: $pH = pKa \times (6.1) + \log_{10} \times HCO_3 / (0.03 \times CO_2)$. It should be noted that it is the ratio rather than the absolute values for bicarbonate and dissolved $CO_2$ that determines pH (*e.g.,* when the ratio is 20 : 1, pH = 7.4). Plasma pH decreases when the ratio is less than 20 : 1, and it increases when the ratio is greater than 20:1. Because it is the ratio rather than the absolute values of $HCO_3^-$or $CO_2$ that determines pH, the pH can remain within relatively normal values as long as changes in $HCO_3^-$ are accompanied by similar changes in $CO_2$, or vice versa. For example, the pH will remain at 7.4 when plasma $HCO_3^-$ has increased from 24 to 48 mEq/L as long as $CO_2$ levels are also doubled. Likewise, the pH will remain at 7.4 when plasma $HCO3^-$ has decreased from 24 to 12 mEq/L as long as $CO_2$ levels are reduced by one half.

**REGULATION OF pH.** The pH of body fluids is regulated by intracellular and extracellular buffering systems that prevent large changes in the extracellular pH from occurring through respiratory mechanisms that eliminate $CO_2$ and by renal мechanisms that conserve $HCO_3^-$ ions and eliminate $H^+$ ions. The pH is further influenced by the electrolyte composition of the intracellular and extracellular compartments.

### Intracellular and Extracellular Buffer Systems

The moment-by-moment regulation of pH depends on intracellular and xtracellular buffer systems. A *buffer system* consists of a weak acid and the base salt of that cid or of a weak base and its acid salt. In the process of preventing large changes in pH, the system trades a strong acid for a weak acid or a strong base for a weak base. The two major buffer systems that protect the pH of body fluids are proteins and the bicarbonate buffer system. These buffer systems are immediately available to combine with excess acids or bases and prevent large changes in pH from occurring during the time it takes for respiratory and renal mechanisms to become effective. Bone also represents an important site for buffering of acids and bases. Although it is difficult to measure, it has been estimated that 40% of acute acid-base buffering occurs in bone. The role of bone buffers is even higher in chronic acid-base disorders. One consequence of bone buffering is the release of calcium from bone and increased renal excretion of calcium. In addition to causing demineralization of bone, it also predisposes to kidney stones.

***Protein Buffer Systems.*** Proteins are the largest buffer system in the body. Proteins are amphoteric, meaning that they can function as acids or bases. They contain many ionizable groups that can release or bind $H^+$. The protein buffers are largely located in cells, and $H^+$ ions and $CO_2$ diffuse across cell membranes for buffering by intracellular proteins. Albumin and plasma globulins are the major protein buffers in the vascular compartment.

***Bicarbonate Buffer System.*** The bicarbonate buffer system uses $H_2CO_3$ as its weak acid and a bicarbonate salt such as sodium bicarbonate ($NaHCO_3$) as its weak base. It substitutes the weak $H_2CO_3$ for a strong acid such as hydrochloric acid ($HCl + NaHCO_3 \leftrightarrow H_2CO_3 + NaCl$) or the weak bicarbonate base for a strong base such as sodium hydroxide ($NaOH + H_2CO_3 \leftrightarrow NaHCO_3 + H_2O$). The $HCO_3^-$ / $CO_2$ buffer system is a particularly efficient system because the buffer components can be

readily added or removed from the body. Metabolism provides an ample supply of $CO_2$, which can replace any $H_2CO_3$ that is lost when excess base is added, and $CO_2$ can be readily eliminated when excess acid is added. Likewise, the kidney can conserve or form new $HCO_3^-$ when excess acid is added, and it can excrete $HCO_3^-$ when excess base is added.

***Plasma Potassium–Hydrogen Exchange.*** Potassium ions ($K^+$) and $H^+$ions interact in important ways in the regulation of acid-base balance. Both ions are positively charged, and both ions move freely between the intracellular and extracellular compartments. In situations of acidosis, excess $H^+$ions move into the intracellular compartment for buffering. When this happens, another cation, in this case the $K^+$ion, must leave the cell and move into the extracellular fluid. When extracellular potassium levels fall, $K^+$ions move out of the cell and are replaced by $H^+$ions. Thus, alterations in extracellular potassium levels can affect acid base balance, and changes in acid-base balance can influence extracellular potassium levels. Potassium shifts tend to be more pronounced in metabolic acidosis than respiratory acidosis. Also, metabolic acidosis caused by an accumulation of nonorganic acids (*e.g.*, HCl that occurs in diarrhea, phosphoric acid that occurs in renal failure) produces a greater increase in extracellular potassium than does acidosis caused by an accumulation of organic acids (*e.g.*, lactic acid, ketoacids).

**Respiratory Control Mechanisms.** The second line of defense against acid-base disturbances is the control of $CO_2$ by the respiratory system. Excess $CO_2$ or excess $H^+$ ions in the blood mainly act directly on the respiratory center in the brain to control ventilation. Although $H^+$ ions do not easily cross the blood–brain barrier, $CO_2$ crosses with ease and in the process reacts with water to form carbonic acid, which dissociates into $H^+$ and $HCO_3^-$ ions. It is the $H^+$ ion that stimulates the respiratory center, causing an increase or decrease in ventilation. The respiratory control of pH is rapid, occurring within minutes, and is maximal within 12 to 24 hours. Although the respiratory response is rapid, it does not completely return the pH to normal. It is only about 50% to 75% effective as a buffer system. This means that if the pH falls from 7.4 to 7.0, the respiratory system can return the pH to a value of about 7.2 to 7.3. In acting rapidly, however, it prevents large changes in pH from occurring while waiting for the much more slowly reacting kidneys to respond. Although $CO_2$ readily crosses the blood–brain barrier, there is a lag for entry of the $HCO_3^-$ion. Thus, blood pH and $HCO_3^-$ levels drop more rapidly than cerebrospinal fluid (CSF) levels. In metabolic acidosis, for example, in which there is a primary decrease in $HCO_3^-$ions, there is often a 12- to 24-hour delay in maximal respiratory response. Likewise, when metabolic acid-base disorders are corrected rapidly, the respiratory response may persist because of a delay in CSF adjustments.

**Renal Control Mechanisms** The kidneys regulate acid-base balance by excreting either an acidic or an alkaline urine. Excreting an acidic urine reduces the amount of acid in the extracellular fluid, and excreting an alkaline urine removes base from the extracellular fluid. The renal mechanisms for regulating acid-base balance cannot adjust the pH within minutes, as respiratory mechanisms can, but they continue to function for days until the pH has returned to normal or near-normal range.

***Hydrogen Ion Elimination and Bicarbonate Conservation.*** The kidney regulates pH by excreting excess $H^+$ions and reabsorbing or regenerating $HCO_3^-$ ions. Bicarbonate is freely filtered in the glomerulus (approximately 4 500 mEq/day) and reabsorbed in the tubules. Loss of even small amounts of $HCO_3^-$impairs the body's ability to buffer its daily load of metabolic acids. Because $H^+$ions are not filtered in adequate amounts to maintain acid-base balance, they are secreted from blood in the peritubular capillaries into the urine filtrate in the renal tubules. Most of the $H^+$ ion secretion and reabsorption of $HCO_3^-$ ions takes place in the proximal tubule. The process begins with a coupled $Na^+/H^+$ transport system in which a $H^+$ ion is secreted into the tubular fluid and a $Na^+$ $H^+$ ion combines with a filtered $HCO_3^-$ ion to yield $CO_2$ and $H_2O$. The water is eliminated in the urine, and the $CO_2$ diffuses into the tubular cell, where it combines with water, in a carbonic anhydrase–mediated reaction to form a $HCO_3^-$ion and a $H^+$ ion. The $HCO_3^-$ion is then reabsorbed into the blood along with the $Na^+$ ion, and the newly generated $H^+$ ion is secreted into the tubular fluid to begin another cycle. Normally, only a few of the secreted $H^+$ ions remain in the tubular fluid because the secretion of $H^+$ ions is roughly equivalent to the number of $HCO_3^-$ ions that are filtered in the glomerulus.

***Tubular Buffer Systems.*** Because an extremely acidic urine would be damaging to structures in the urinary tract, the pH of the urine is maintained within a range from 4.5 to 8.0. This limits the number of unbuffered $H^+$ ions that can be excreted by the kidney. When the number of free $H^+$ ions secreted into the tubular fluid threatens to cause the pH of the urine to become too acidic, they must be carried in some other form. This is accomplished by combining $H^+$ ions with intratubular buffers before they are excreted in the urine. There are two important intratubular buffer systems: the phosphate buffer system and the ammonia buffer system.

The ***phosphate buffer system*** uses $HPO_4^{2-}$ and $H_2PO_4^-$ that are present in the tubular filtrate. Both become concentrated in the tubular fluid because of their relatively poor absorption and because of reabsorption of water from the tubular fluid. The combination of $H^+$ with $HPO_4^{2-}$ to form $H_2PO_4^-$ allows the kidneys to increase their secretion of $H^+$ ions. Another important but more complex buffer system is the ***ammonia buffer system***.

**The excretion of $H^+$ and generation of $HCO_3^-$ by the ammonia buffer system occurs in three major steps:**

***(1)*** *the synthesis of ammonium ($NH4^+$) from the amino acid glutamine in the proximal tubule, thick ascending loop of Henle, and distal tubules;*

*(2) the reabsorption and recycling of $NH_3$ within the medullary portion of the kidney;*

*(3) the buffering of $H^+$ ions by $NH_3$ in the collecting tubules.*

The metabolism of glutamate in the proximal tubule results in the formation of two $NH_4^+$ and two $HCO_3^-$ ions. The two $NH_4^+$ ions are secreted into the tubular fluid by a countertransport mechanism in exchange for a $Na^+$ ion. The two $HCO_3^-$ ions move out of the tubular cell along with the reabsorbed $Na^+$ ion to enter the peritubular capillaries system. Thus, for each molecule of glutamine metabolized in the proximal tubule, two $NH_4^+$ ions are secreted into the tubular filtrate, and two $HCO_3^-$ ions are reabsorbed into the blood. The $HCO_3^-$ generated by this process constitutes new $HCO_3^-$. A second buffering mechanism involves the recycling of $NH_4^+$ by tubular cells in the medullary portion of the kidney. Here, $NH_4^+$ is converted to $NH_3$ and secreted into the tubular lumen. In the collecting tubules, $H^+$ ions that are secreted into the tubular lumen combine with $NH_3$ to form $NH_4^+$ ions. However, this part of the tubule is relatively impermeable to $NH_4^+$; therefore, once the $H^+$ has reacted with $NH_3$ to $NH_4^+$, it becomes trapped in the tubular lumen and is eliminated in the urine. In the process of being converted to $NH_3$, the $H^+$ from the recycled $NH_4^+$ promotes the reabsorption of $HCO_3^-$ by combining with $HCO_3^-$ delivered from the proximal tubule.

Thus, an additional new $HCO_3^-$ is generated and added to the blood for each $NH_4^+$ that is recycled. One of the most important features of the ammonia buffer system is that it is subject to physiologic control. Under normal conditions, the amount of $H^+$ ion eliminated by the ammonia buffer system is about 50% of the acid excreted and new $HCO_3^-$ regenerated. However, with chronic acidosis, it can become the dominant mechanism for $H^+$ excretion and new $HCO_3^-$ generation.

***Hydrogen and Potassium Ions Compete for Elimination in the Urine.*** Plasma $K^+$ levels influence renal elimination of $H^+$ ions, and vice versa. When plasma $K^+$ levels fall, there is movement of $K^+$ ions from body cells into the extracellular fluid and a reciprocal movement of $H^+$ ions from the extracellular fluid into body cells. In the kidney, these movements lower the intracellular pH of tubular cells, causing an increase in $H^+$ ion secretion. Potassium depletion also stimulates ammonia synthesis by the kidney as a means of buffering the excess $H^+$ ions. The net result is an increased reabsorption of the filtered $HCO_3^-$ ions and the development of metabolic alkalosis. An elevation in plasma $K^+$ levels has the opposite effect. Plasma $K^+$ levels are similarly altered by acid-base balance. Acidosis tends to increase $H^+$ ion elimination and decrease $K^+$ ion elimination, with a resultant increase in plasma potassium levels. Alkalosis has the opposite effect.

Aldosterone also influences $H^+$ ion elimination by the kidney. It acts in the collecting duct to stimulate $H^+$ ion secretion indirectly, while increasing $Na^+$ ion reabsorption and $K^+$ ion secretion. Hyperaldosteronism tends to lead to a decrease in plasma $K^+$ levels and increased pH and alkalosis because of increased $H^+$ ion secretion. Hypoaldosteronism has the opposite effect. It leads to increased $K^+$ levels, decreased $H^+$ ion secretion, and acidosis.

***Influence of Sodium Chloride–Bicarbonate Exchange on pH.*** Body sodium levels can indirectly influence acid-base balance by way of the $Cl^-/HCO3^-$ exchange system. Sodium reabsorption in the kidneys requires the reabsorption of an accompanying anion. The two major anions in the extracellular fluid are $Cl^-$ and $HCO_3^-$. One of the mechanisms that the kidneys use in regulating the pH of the extracellular fluids is to conserve or eliminate $HCO_3^-$ ions; in the process, it often is necessary to shuffle anions. Chloride is the most abundant anion in the extracellular fluid and can substitute for $HCO_3^-$ when an anion shift is needed. As an example, plasma $HCO_3^-$ levels normally increase as hydrochloric acid is secreted into the stomach after a heavy meal, causing what is called the *postprandial alkaline tide.* Later, as the $Cl^-$ is reabsorbed in the small intestine, the pH returns to normal. *Hypochloremic alkalosis* refers to an increase in pH that is induced by a decrease in plasma $Cl^-$ levels. *Hyperchloremic acidosis* occurs when excess levels of $Cl^-$ are present.

**Carbon Dioxide and Bicarbonate Levels.** The $PCO_2^-$ of the arterial blood gases provides a means of assessing the respiratory component of acid-base balance. Arterial blood gases are used because venous blood gases are highly variable, depending on metabolic demands of the various tissues that empty into the vein from where the sample is being drawn. The dissolved $CO_2$ levels can be determined from arterial blood gas measurements using the $PCO_2^-$ and the solubility coefficient for $CO_2$ (normal arterial $PCO_2^-$ is 38 to 42 mm Hg). Arterial blood gases also provide a measure of blood oxygen ($PO_2$) levels. This can be important in assessing respiratory function. Laboratory tests include measurements of the $CO_2$ content and $HCO_3^-$ in the blood. The $CO_2$ content that is included in these measurements is different from the $PCO_2^-$ that is measured in blood gases. Instead, it refers to the total $CO_2$ content of blood, including that contained in $HCO_3^-$. More than 70 % of the $CO_2$ in the blood is in the form of bicarbonate. The $CO_2$ content is determined by adding a strong acid to a plasma sample and measuring the amount of $CO_2$ generated. The plasma $HCO_3^-$ concentration is then determined from the total $CO_2$ content of the blood. The normal range of values for venous $HCO_3^-$ concentration is 24 to 29 mEq/L (24 to 29 mmol/L).

**Base Excess or Deficit.** Base excess or deficit measures the level of all the buffer systems of the blood—hemoglobin, protein, phosphate, and $HCO_3^-$. The base excess or deficit describes the amount of a fixed acid or base that must be added to a blood sample to achieve a pH of 7.4 (normal ± 3.0 mEq/L). For practical purposes, base excess or deficit is a measurement of bicarbonate excess or deficit. Base excess indicates metabolic alkalosis, and base deficit indicates metabolic acidosis.

**Anion Gap.** The anion gap describes the difference between the plasma concentration of the major measured cation ($Na^+$) and the sum of the measured anions ($Cl^-$ and $HCO_3^-$). This difference represents the concentration of unmeasured anions, such as phosphates, sulfates, organic acids, and proteins. Normally, the anion gap ranges between 8 and 12 mEq/L (a value of 16 mEq/L is normal if both sodium and potassium concentrations are used in the calculation). The anion gap is increased in conditions such as lactic acidosis and ketoacidosis that result from elevated levels of metabolic acids. A low anion gap is found in conditions that produce a fall in unmeasured anions (primarily albumin) or rise in unmeasured cations. The latter can occur in hyperkalemia, hypercalcemia, hypermagnesemia, lithium intoxication, or multiple myeloma, in which an abnormal immunoglobulin is produced. The anion gap of urine can also be measured. It uses values for the measurable cations ($Na^+$ and $K^+$) and measurable anion ($Cl^-$) to provide an estimate of ammonium ($NH_4^+$) excretion. Because ammonium is a cation, the value of the anion gap becomes more negative as the ammonium level increases. In normal persons secreting 20 to 40 mmol of ammonium per liter, the urine anion gap is close to zero. In metabolic acidosis, the amount of unmeasurable $NH_4^+$ should increase if renal excretion of $H^+$ is intact; as a result, the urine anion gap should become more negative.

**In summary,** normal body function depends on the precise regulation of acid-base balance. The pH of the extracellular fluid is normally maintained within the narrow physiologic range of 7.35 to 7.45. Metabolic processes produce volatile and fixed or nonvolatile metabolic acids that must be buffered and eliminated from the body. The volatile acid, $H_2CO_3$, is in equilibrium with dissolved $CO_2$, which is eliminated through the lungs.

The nonvolatile metabolic acids, most of which are excreted by the kidneys, are derived mainly from protein metabolism and incomplete carbohydrate and fat metabolism. It is the ratio of the $HCO_3^-$ ion concentration to dissolved $CO_2$ ($H_2CO_3$ concentration) that determines body pH. When this ratio is 20 : 1, the pH is 7.4. The ability of the body to maintain pH within the normal physiologic range depends on intracellular and extracellular mechanisms for buffering excess $H^+$ and $HCO_3^-$ ions and on the respiratory and renal mechanisms for eliminating or conserving excess acids and bases. Proteins are the most important intracellular buffers, and the $HCO_3^-$ buffer system includes the most important extracellular buffers. The respiratory system contributes to the regulation of pH by controlling the elimination of $CO^2$. The kidney aids in regulation of pH by eliminating $H^+$ ions or conserving $HCO_3^-$ ions. In the process of eliminating $H^+$ ions, it uses the phosphate and ammonia buffer systems. Body pH is also affected by the distribution of exchangeable cations ($K^+$ and $H^+$) and anions ($Cl^-$ and $HCO_3^-$).

Laboratory tests that are used in assessing acid-base balance include arterial blood gas measurements, $CO_2$ content and $HCO_3^-$ levels, base excess or deficit, and the anion gap. The base excess or deficit describes the amount of a fixed acid or base that must be added to a blood sample to achieve a pH of 7.4. The anion gap describes the difference between the plasma concentration of the major measured cation ($Na^+$) and the sum of the measured anions ($Cl^-$ and $HCO_3^-$).

**Disorders of acid-base balance.** The terms *acidosis* and *alkalosis* describe the clinical conditions that arise as a result of changes in dissolved $CO_2$ and $HCO_3^-$ concentrations. An alkali represents a

combination of one or more alkali metals such as sodium or potassium with a highly basic ion such as a hydroxyl ion ($OH^-$). Sodium bicarbonate is the main alkali in the extracellular fluid. Although the definitions differ somewhat, the terms *alkali* and *base* are often used interchangeably. Hence, the term *alkalosis* has come to mean the opposite of *acidosis.*

**Metabolic versus respiratory acid-base disorders.** There are two types of acid-base disorders: metabolic and respiratory. *Metabolic disorders* produce an alteration in bicarbonate concentration and result from the addition or loss of nonvolatile acid or alkali to or from the extracellular fluid. A reduction in pH due to a decrease in $HCO_3^-$ is called *metabolic acidosis,* and an elevated pH due to increased $HCO_3^-$ levels is called *metabolic alkalosis. Respiratory disorders* involve an alteration in the $PCO_2$, reflecting an increase or decrease in alveolar ventilation. *Respiratory acidosis* is characterized by a decrease in pH, reflecting a decrease in ventilation and an increase in $PCO_2$. *Respiratory alkalosis* involves an increase in pH, resulting from an increase in alveolar ventilation and a decrease in $PCO_2$.

**Primary versus compensatory mechanisms.** Acidosis and alkalosis typically involve a *primary* or *initiating event* and a *compensatory* or *adaptive state* that results from homeostatic mechanisms that attempt to correct or prevent large changes in pH. For example, a person may have a primary metabolic acidosis as a result of overproduction of ketoacids and respiratory alkalosis because of a compensatory increase in ventilation.

**Acid-base imbalances.** *Compensatory mechanisms* adjust the pH toward a more normal level without correcting the underlying cause of the disorder. A mixed acid-base disorder is one in which there is both a primary and a compensatory change in acid-base balance. The respiratory mechanisms, which compensate by increasing or decreasing ventilation, are rapid but seldom able to return the pH to normal because as the pH returns toward normal, the respiratory stimulus is lost. The kidneys compensate by conserving $HCO_3^-$ or $H^+$ ions. It normally takes longer to recruit renal compensatory mechanisms than it does respiratory compensatory mechanisms. Renal mechanisms are more efficient, however, because they continue to operate until the pH has returned to a normal or near-normal value. Compensatory mechanisms provide a means to control pH when correction is impossible or cannot be immediately achieved. Often, compensatory mechanisms are interim measures that permit survival while the body attempts to correct the primary disorder. Compensation requires the use of mechanisms that are different from those that caused the primary disorder. In other words, the lungs cannot compensate for respiratory acidosis that is caused by lung disease, nor can the kidneys compensate for metabolic acidosis that occurs because of renal failure. The body can, however, use renal mechanisms to compensate for respiratory-induced changes in pH, and it can use respiratory mechanisms to compensate for metabolically induced changes in acid-base balance. Because compensatory mechanisms become more effective with time, there are often differences between the level of pH change that is present in acute and chronic acid-base disorders.

## METABOLIC ACIDOSIS

***Metabolic acidosis involves a primary deficit in base $HCO_3^-$ along with a decrease in plasma pH.*** In metabolic acidosis, the body compensates for the decrease in pH by increasing the respiratory rate in an effort to decrease $CO_2$ and $H_2CO_3$ levels. The $PCO_2$ can be expected to fall by 1 to 1.5 mm Hg for each 1 mEq/L fall in $HCO_3^-$

**Causes** Metabolic acidosis can be caused by one of four mechanisms: increased production of nonvolatile metabolic acids, decreased acid secretion by the kidney, excessive loss of bicarbonate, or an increase in $Cl^-$. The anion gap is often useful in determining the cause of the metabolic acidosis. The presence of excess metabolic acids produces an increase in the anion gap as sodium bicarbonate is replaced by the sodium salt of the offending acid (*e.g.,* sodium lactate). When acidosis results from increased chloride levels (*e.g.,* hyperchloremic acidosis), the anion gap remains within normal levels.

***Increased Production of Metabolic Acids.*** Metabolic acids increase when there is an accumulation of lactic acid, overproduction of ketoacids, or drug or chemical anion ingestion.

*Lactic Acidosis.* Acute lactic acidosis is one of the most common types of metabolic acidosis. Lactic acidosis develops when there is excess production of lactic acid or diminished lactic acid removal from the blood. Lactic acid is produced by the anaerobic metabolism of glucose. Virtually all tissues can produce lactic acid under appropriate circumstances.

Tissues such as red blood cells, intestine, and skeletal muscle do so under normal conditions. Excess lactate is produced with vigorous exercise, during which there is a local disproportion between oxygen supply and demand in the contracting muscles. The liver and, to a lesser extent, the kidney normally remove lactic acid from the blood and use it for energy or convert it back to glucose. Most cases of lactic acidosis are caused by inadequate oxygen delivery, as in shock or cardiac arrest. Such conditions

increase lactic acid production, and they impair lactic acid clearance because of poor liver perfusion. Mortality rates are high for persons with lactic acidosis because of shock and tissue hypoxia. Lactic acidosis is also associated with disorders in which tissue hypoxia does not appear to be present. It has been reported in patients with leukemia, lymphomas, andother cancers; those with poorly controlled diabetes; and patients with severe liver failure. Mechanisms causing lactic acidosis in these conditions are poorly understood. Some conditions, such as neoplasms, may produce local increases in tissue metabolism and lactate production or interfere with blood flow to noncancerous cells. Ethanol produces a slight elevation in lactic acid, but clinically significant lactic acidosis does not occur in alcohol intoxication unless other problems, such as liver failure, are present. Lactic acidosis may also occur in mitochondrial disorders that impair oxidative metabolism. Lactic acidosis occurs in genetic mitochondrial disorders that impair lactate metabolism. One of these disorders, referred to by the acronym MELAS, involves mitochondrial encephalopathy (ME), lactic acidosis (LA), and strokelike episodes (S). Children with the disorder function normally for the first few years of their lives and then begin to display impaired motor and cognitive development. The mitochondrial defect also leads to short stature, seizure disorders, and multiple strokes. Lowering the plasma lactate level of children with severe lactic acidosis may result in marked clinical improvement. A variety of drugs can also produce life-threatening lactic acidosis by inhibiting mitochondrial function (biguanide antidiabetic drugs and the antiretroviral nucleoside analogs that are used to treat acquired immunodeficiency syndrome (AIDS)).

A unique form of lactic acidosis, called D-lactic acidosis, can occur in persons with intestinal disorders that involve the generation and absorption of D-lactic acid (L-lactic acid is the usual cause of lactic acidosis). D-Lactic acidosis can occur in persons with jejunoileal bypass, smallbowel resection, or short bowel syndrome, in which thereis impaired reabsorption of carbohydrate in the small intestine.

In these cases, the unabsorbed carbohydrate is delivered to the colon, where it is converted to D-lactic acid by an overgrowth of gram-positive anaerobes. Persons with D-lactic acidosis experience episodic periods of metabolic acidosis often brought on by eating a meal high in carbohydrates. Manifestations include confusion, cerebellar ataxia, slurred speech, and loss of memory. They may complain of feeling (or may appear) intoxicated. Treatment includes use of antimicrobial agents to decrease the number of D-lactic acid–producing microorganisms in the bowel along with a low-carbohydrate diet. *Ketoacidosis.* Ketoacids (*i.e.,* acetoacetic and hydroxybutyric acid), produced in the liver from fatty acids, are the source of fuel for many body tissues. An overproduction of ketoacids occurs when carbohydrate stores are inadequate or when the body cannot use available carbohydrates as a fuel. Under these conditions, fatty acids are mobilized from adipose tissue and delivered to the liver, where they are converted to ketones. Ketoacidosis develops when ketone production exceeds tissue use. The most common cause of ketoacidosis is uncontrolled diabetes mellitus, in which an insulin deficiency leads to the release of fatty acids from adipose cells with subsequent production of excess ketoacids. Ketoacidosis may also develop as the result of fasting or food deprivation, during which the lack of carbohydrates produces a self-limited state of ketoacidosis. The selflimited nature of ketoacidosis results from a decrease in insulin, which further suppresses the release of fatty acids from fat cells. Ketones are also formed during the oxidation of alcohol, a process that occurs in the liver. A condition called *alcoholic ketoacidosis* can develop in persons who engage in excess alcohol consumption.It usually follows prolonged alcohol ingestion, particularly if accompanied by decreased food intake and vomitingconditions that result in using fatty acids as an energy source. The ketoacids responsible for alcoholic ketoacidosis are formed in part as a result of alcohol metabolism. Ketone formation may be further enhanced by the hypoglycemia that results from alcoholinduced inhibition of glucose synthesis (*i.e.,* gluconeogenesis) by the liver and impaired ketone elimination by the kidneys because of dehydration. An extracellular fluid volume deficit caused by vomiting and decreased fluid intake often contributes to the acidosis.

*Salicylate Toxicity.* Salicylates are another potential source of metabolic acids. Aspirin (acetylsalicylic acid) is rapidly converted to salicylic acid in the body. Although aspirin is the most common cause of salicylate toxicity, other salicylate preparations such as methyl salicylate, sodium salicylate, and salicylic acid may be involved. Salicylate overdose produces serious toxic effects, including death. A fatal overdose can occur with as little as 10 to 30 g in adults and 3 g in children. A variety of acid-base disturbances occur with salicylate toxicity. The salicylates cross the blood–brain barrier and directly stimulate the respiratory center, causing hyperventilation and respiratory alkalosis. The kidneys compensate by secreting increased amounts of $HCO_3^-$, $K^+$, and $Na^+$, thereby contributing to the development of metabolic acidosis. Salicylates also interfere with carbohydrate metabolism, which results in increased production of metabolic acids.

*Methanol and Ethylene Glycol Toxicity.* Ingestion of methanol and ethylene glycol results in the production of metabolic acids and causes metabolic acidosis. Both produce an osmolar gap because of their small size and osmotic properties. Methanol (wood alcohol) is a component of shellac, varnish, deicing solutions, sterno, and other commercial products. Methanol can be absorbed through the skin or gastrointestinal tract or inhaled through the lungs. A dose as small as 30 mL can be fatal. In addition to metabolic acidosis, methanol produces severe optic nerve and central nervous system toxicity. Organ system damage occurs after a 24-hour period in which methanol is converted to formaldehyde and formic acid.

***Decreased Renal Function.*** Kidney disease is the most common cause of chronic metabolic acidosis. The kidneys normally conserve $HCO_3^-$ and secrete $H^+$ ions into the urine as a means of regulating acid-base balance. In renal failure, there is loss of glomerular and tubular function, with retention of nitrogenous wastes and metabolic acids. In a condition called *renal tubular acidosis*, glomerular function is normal, but the tubular secretion of $H^+$ or reabsorption of $HCO_3^-$ is abnormal.

***Increased Bicarbonate Losses.*** Increased $HCO_3^-$ losses occur with the loss of bicarbonate-rich body fluids or with impaired conservation of $HCO_3^-$ by the kidney. Intestinal secretions have a high $HCO_3^-$ concentration. Consequently, excessive loss of $HCO_3^-$ ions occur with severe diarrhea; small bowel, pancreatic, or biliary fistula drainage; ileostomy drainage; and intestinal suction. In diarrhea of microbial origin, $HCO_3^-$ is also secreted into the bowel as a means of neutralizing the metabolic acids produced by the microorganisms causing the diarrhea. Creation of an ileal bladder, which is done for conditions such as neurogenic bladder or surgical removal of the bladder because of cancer, involves the implantation of the ureters into a short, isolated loop of ileum that serves as a conduit for urine collection. With this procedure, contact time between the urine and ileal bladder is normally too short for significant anion exchange, and $HCO_3^-$ is lost in the urine.

***Hyperchloremic Acidosis.*** Hyperchloremic acidosis occurs when $Cl^-$ ion levels are increased. Because $Cl^-$ and $HCO_3^-$ are anions, the $HCO_3^-$ ion concentration decreases when there is an increase in $Cl^-$ ions. Hyperchloremic acidosis can occur as the result of abnormal absorption of chloride by the kidneys or as a result of treatment with chloridecontaining medications (*i.e.,* sodium chloride, amino acid– chloride hyperalimentation solutions, and ammonium chloride). Ammonium chloride is broken down into $NH_4^-$ and $Cl^-$. The ammonium ion is converted to urea in the liver, leaving the $Cl^-$ ion free to react with $H^-$ to form HCl. The administration of intravenous sodium chloride or parenteral hyperalimentation solutions that contain an amino acid–chloride combination can cause acidosis in a similar manner. With hyperchloremic acidosis, the anion gap is within the normal range, whereas the chloride levels are increased, and bicarbonate levels are decreased.

## METABOLIC ALKALOSIS

***Metabolic alkalosis is a systemic disorder caused by an increase in pH due to a primary excess of plasma $HCO_3^-$ ions.***

It can be caused by a loss of $H^+$ ions, net gain in $HCO_3^-$ ions, or loss of $Cl^-$ ions in excess of $HCO_3^-$ ions. Metabolic alkalosis is reported to be the second most common acid-base disorder in hospitalized adults, accounting for about 32 % of all acid-base disorders.

**Causes.** Most of the body's plasma $HCO_3^-$ is obtained from three sources: from $CO_2$ that is produced during metabolic processes, from reabsorption of filtered $HCO_3^-$, or from generation of new $HCO_3^-$ by the kidney. Usually, $HCO_3^-$ production and renal reabsorption are balanced in a manner that prevents alkalosis from occurring. The proximal tubule reabsorbs 99.9 % of the filtered $HCO_3^-$. When the plasma levels of $HCO_3^-$ rise above the threshold for tubular reabsorption, the excess is excreted in the urine. Many of the conditions that increase plasma $HCO_3^-$ also raise the level for $HCO_3^-$ reabsorption; thus, an increase in $HCO_3^-$ contributes not only to the generation of metabolic alkalosis but also to its maintenance. Metabolic alkalosis involves both the factors that generate the loss of $H^+$ or gain of $HCO_3^-$ ions and those that maintain it by interfering with excretion of the excess $HCO_3^-$. Factors that serve to maintain metabolic alkalosis include extracellular fluid volume contraction accompanied by hypokalemia and hypochloremia and mineralocorticoid (aldosterone) excess.

**Alkalosis**

***Excess Alkali Intake.*** Excessive alkali ingestion, as in the use of bicarbonate-containing antacids or $NaHCO_3$ administration during cardiopulmonary resuscitation, can cause metabolic alkalosis. Other sources of alkali intake are acetate in hyperalimentation solutions, lactate in parenteral solutions such as Ringer's lactate, and citrate used in blood transfusions. A condition called the *milk-alkali syndrome* may develop in persons who consume excessive amounts of milk along with an antacid such as calcium carbonate. In this case, the carbonate raises the plasma **$HCO_3^-$** while the hypercalcemia

prevents the excretion of excess $\mathbf{HCO_3^-}$. The most common cause at present is the use of calcium carbonate as a phosphate buffer in persons with renal failure.

***Hydrogen, Chloride, and Potassium Ion Loss Associated With Bicarbonate Ion.*** Vomiting, removal of gastric secretions through use of nasogastric suction, and low potassium levels resulting from diuretic therapy are the most common causes of metabolic alkalosis in hospitalized patients. The binge and purge syndrome, or self-induced vomiting, also is associated with metabolic alkalosis. Gastric secretions contain high concentrations of HCl and lesser concentrations of potassium chloride (KCL). As $Cl^-$ is taken from the blood and secreted into the stomach with the $H^+$ ion, it is replaced by $\mathbf{HCO_3^-}$. Under normal conditions, each 1 mEq of $H^+$ ion that is secreted into the stomach generates 1 mEq of plasma $\mathbf{HCO_3^-}$. Because the entry of acid into the duodenum stimulates an equal amount of pancreatic $\mathbf{HCO_3^-}$ secretion, the increase in plasma $\mathbf{HCO_3^-}$ concentration is usually transient, and pH returns to normal within a matter of hours. However, loss of $H^+$ and $Cl^-$ ions from the stomach due to vomiting or gastric suction stimulates continued production of gastric acid and thus the addition of more bicarbonate into the blood.

***Maintenance of Metabolic Alkalasis by Volume Contraction***

***Hypokalemia, and Hypochloremia.*** Vomiting also results in the loss of water, sodium, and potassium. The resultant volume depletion and hypokalemia maintain the generated metabolic alkalosis by increasing the renal reabsorption of $\mathbf{HCO_3^-}$ ion. Administration of diuretics (thiazide diuretics) is often associated with metabolic alkalosis. Loop diuretics decrease $Na^+$, $K^+$, and $Cl^+$ reabsorption, leading to volume contraction and hypokalemia. The thiazide diuretics increase renal $K^+$ loss, leading to increased $\mathbf{HCO_3^-}$ reabsorption. Extracellular volume depletion is one of the most important factors affecting $\mathbf{HCO_3^-}$ reabsorption in the proximal tubule. A decrease in extracellular fluid volume activates the renin-angiotensin-aldosterone system, which increases $Na^+$ reabsorption as a means of maintaining extracellular fluid volume. The reabsorption of $Na^+$ requires concomitant anion reabsorption; because there is a $Cl^-$ deficit, $\mathbf{HCO_3^-}$ is reabsorbed along with $Na^+$. Hypokalemia is a potent stimulus for $H^+$ secretion and $\mathbf{HCO_3^-}$ reabsorption. The mechanisms by which hypokalemia increases $\mathbf{HCO_3^-}$ reabsorption are likely the effects of tubular $K^+/H^+$ ion exchange. In hypokalemia, $K^+$ moves out of the tubular cell into the blood and is replaced by the $H^+$ ion. This results in intracellular acidosis and increased $\mathbf{HCO_3^-}$ reabsorption. For some unknown reason, severe hypokalemia may cause a reduction in $Cl^-$reabsorption by the distal tubule. As a result, $Na^+$ reabsorption at this sit is associated with greater tubular electronegativity and greater tendency to $H^+$secretion. It has been proposed recently that hypochloremia and the reduced delivery of $Cl^-$ to the distal tubule of the kidney are responsible for maintaining metabolic alkalosis, rather than volume depletion per se. A low intraluminal concentration of $Cl^-$ ion is interpreted by the kidney as a sign of low extracellular fluid volume, thereby serving as a stimulus for activation of the renin-angiotensin-aldosterone system. Low intraluminal concentrations of $Cl^-$-ion also reduce the driving force for bicarbonate reabsorption. Metabolic alkalosis can also result from excessive adrenocorticosteroid hormones (*e.g.,* hyperaldosteronism, Cushing's syndrome). The hormone aldosterone increases $H^+$ ion secretion as it increases $Na^+$ and $\mathbf{HCO_3^-}$ ion reabsorption. In hyperaldosteronism, the concurrent loss of $K^+$ in the urine serves to perpetuate the alkalosis. Chronic respiratory acidosis produces a compensatory loss of $H^+$ and $Cl^-$ ions in the urine along with $\mathbf{HCO_3^-}$ retention. When respiratory acidosis is corrected abruptly, as with mechanical ventilation, a "posthypercapneic" metabolic alkalosis may develop because of a rapid drop in $PCO_2$; however, the concentration of $\mathbf{HCO_3^-}$ ions, which are eliminated renally, remains elevated.

**RESPIRATORY ACIDOSIS** occurs in conditions that impair alveolar ventilation and cause an increase in plasma $PCO_2$, also known as *hypercapnia,* along with a decrease in pH. Respiratory acidosis can occur as an acute or chronic disorder. Acute respiratory failure is associated with a rapid rise in arterial $PCO_2$ with a minimal increase in plasma $\mathbf{HCO_3^-}$ and large decrease in pH. Chronic respiratory acidosis is characterized by a sustained increase in arterial $PCO_2$, resulting in renal adaptation and a more marked increase in plasma $\mathbf{HCO_3^-}$ **.** Respiratory acidosis occurs in acute or chronic conditions that impair effective alveolar ventilation and cause an accumulation of $PCO_2$. Impaired ventilation can occur as the result of decreased respiratory drive, lung disease, or disorders of chest wall and respiratory muscle. Less commonly, it results from excess $CO_2$ production.

***Acute Disorders of Ventilation.*** Acute respiratory acidosis can be caused by impaired function of the respiratory center in the medulla (as in narcotic overdose), lung disease, chest injury, weakness of the respiratory muscles, or airway obstruction. Almost all persons with acute respiratory acidosis are hypoxemic if they are breathing room air. In many cases, signs of hypoxemia develop before those of respiratory acidosis because $CO_2$ diffuses across the alveolar capillary membrane 20 times more rapidly than oxygen.

***Chronic Disorders of Ventilation.*** Chronic respiratory acidosis is a relatively common disturbance in patients with chronic obstructive lung disease. In these persons, the persistent elevation of $PCO_2$ stimulates renal $H^+$ ion secretion and $\mathbf{HCO_3^-}$ reabsorption. The effectiveness of these compensatory mechanisms can often return the pH to near-normal values as long as oxygen levels are maintained within a range that does not unduly suppress chemoreceptor control of respirations. An acute episode of respiratory acidosis can develop in patients with chronic lung disease who have chronically elevated $PCO_2$ levels. This is sometimes called *carbon dioxide narcosis.* In these persons, the medullary respiratory center has become adapted to the elevated levels of $CO_2$ and no longer responds to increases in $PCO_2$. Instead, the oxygen content of their blood becomes the major stimulus for respiration. When oxygen is administered at a flow rate that suppresses this stimulus, the rate and depth of respiration decrease, and the $CO_2$ content of the blood increases.

***Increased Carbon Dioxide Production.*** Carbon dioxide is a product of the body's metabolic processes, generating a substantial amount of acid that must be excreted by the lungs or kidney to prevent acidosis. An increase in $CO_2$ production can result from numerous processes, including exercise, fever, sepsis, and burns. For example, $CO_2$ production increases by approximately 13% for each $1^0$C rise in temperature above normal. Nutrition also affects the production of carbon dioxide. A carbohydrate-rich diet produces larger amounts of $CO_2$ than one containing reasonable amounts of protein and fat. Although excess carbon dioxide production can lead to an increase in $PCO_2$, it seldom does. In cases of healthy persons, an increase in $CO_2$ is usually matched by an increase in $CO_2$ elimination by the lungs. In contrast, persons with respiratory diseases may be unable to eliminate the excess $CO_2$.

**Respiratory alkalosis** is a systemic acid-base disorder characterized by a primary decrease in plasma $PCO_2$, also referred to as *hypocapnia*, which produces an elevation in pH and a subsequent decrease in $HCO_3^-$. Because respiratory alkalosis can occur suddenly, a compensatory decrease in bicarbonate level may not occur before respiratory correction has taken place.

**Causes** Respiratory alkalosis is caused by hyperventilation or a respiratory rate in excess of that needed to maintain normal plasma $PCO_2$ levels. It may occur as the result of central stimulation of the medullary respiratory center or stimulation of peripheral (*e.g.,* carotid chemoreceptor) pathways to the medullary respiratory center. Mechanical ventilation may produce respiratory alkalosis if the rate and tidal volume are set so that $CO_2$ elimination exceeds $CO_2$ production. Carbon dioxide crosses the alveolar capillary membrane 20 times more rapidly than oxygen. Therefore, the increased minute ventilation may be necessary to maintain adequate oxygen levels while producing a concomitant decrease in $CO_2$ levels. In some cases, respiratory alkalosis may be induced medically as a means of controlling disorders such as severe intracranial hypertension. Central stimulation of the medullary respiratory center occurs with anxiety, pain, pregnancy, febrile states, sepsis, encephalitis, and salicylate toxicity. Respiratory alkalosis has long been recognized as a common acid-base disorder in critically ill patients and is a consistent finding in both septic shock and the systemic inflammatory response syndrome. Progesterone increases ventilation in women; during the progesterone phase of the menstrual cycle, normal women increase their $PCO_2$ values by 2 to 4 mm Hg and their pH by 0.01 to 0.02. Women also develop substantial hypocapnia during pregnancy, most notably during the last trimester, with $PCO_2$ values of 29 to 32 mm Hg. One of the most common causes of respiratory alkalosis is the hyperventilation syndrome, which is characterized by recurring episodes of overbreathing often associated with anxiety. Persons experiencing panic attacks frequently present in the emergency room with manifestations of acute respiratory alkalosis. Hypoxemia exerts its effect on pH through the peripheral chemoreceptors in the carotid bodies. Stimulation of peripheral chemoreceptors occurs in conditions that cause hypoxemia with relatively unimpaired $CO_2$ transport such as exposure to high altitudes, asthma, respiratory disorders.

| The full student's name | The date | The marks | Teacher's signature |
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## PRACTICAL LESSON № 16 (18 stomat.)
## The final control of students' knowledge on topics «TYPICAL VIOLATIONS OF METABOLISM»

**On the Moodle platform, in the section corresponding to the lesson number, control questions and tasks of the KROK-1 database are presented.**
**https://distance.knmu.edu.ua/mod/folder/view.php?id=92477**

# RATING OF STUDENT

**Student** _____

**Faculty** _____

**Course** _____

**Group** _____

| № lesson | | Theme of lesson | Amount of points | Signature of teacher |
|---|---|---|---|---|
| med. | stomat. | | | |
| 1 | 1 | Subject and objectives of pathophysiology. Methods of pathophysiological studies. Main stages of pathophysiology development | | |
| 2 | 2 | Pathogenic effect of physical factors on the organism | | |
| 3 | 3 | The pathology of reactivity. The biological barriers. The abnormalities during phagocytosis. The role of a mononuclear phagocyte system | | |
| 4 | 4 | The violations of immunological reactivity | | |
| 5 | 5 | Allergy | | |
| 6 | 6 | *The final control of students' knowledge on topics «General nosology – general studies about illness, etiology and pathogenesis. Pathogenic action factors of environment. A role of internal factors in pathology»* | | |
| 7 | 7 | Standard violations of peripheral blood circulation and microcirculation. | | |
| | 8 | | | |
| 8 | 9 | Inflammation. The vascular phenomena at the inflammation | | |
| | 10 | | | |
| 9 | 11 | Fever | | |
| 10 | 12 | Tumors | | |
| 11 | 13 | Hypoxia | | |
| 12 | 14 | *The final control of students' knowledge on topics «Typical pathological processes».* | | |
| 13 | 15 | Disorders of carbohydrate metabolism | | |
| 14 | 16 | Disorders of water-electrolyte metabolism | | |
| 15 | 17 | Disorders of acid-base balance | | |
| 16 | 18 | *The final control of students' knowledge on topics «Typical violations metabolism»* | | |
| | | **COMPUTER** | | |

***Навчальне видання***

# ЗАГАЛЬНА ПАТОФІЗІОЛОГІЯ

***Методичні вказівки***
***для самостійної позааудиторної підготовки іноземних студентів***
***(спеціальність «Медицина» та «Стоматологія»)***


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