**NORMAL PHYSIOLOGY 1**

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| **№** |  **Themes** | **Hours** |
|
| 1. | Physiology is science about the dynamics of whole organism.History of physiology development. Methods of investigations in physiology.General peculiarities of living organisms. Excitability. Excitation. Inhibition. General physiological principles of organism structure: correlation, regulation, reflex reaction, self organization, self regulation, functional system.  | 2 |
| 2. | Morphophysiological properties of muscles. Types of muscle contraction. Summation of muscle contractions. Mechanism of tetanic muscle contraction. Motor unit. Muscular tone. Modern idea about mechanism of muscle contraction. Muscle work and strength. Muscle fatigue. Morphophysiological properties of smooth muscles. Nerve-muscle junction.  | 2 |
| 3. | Receptors, their classification. Morphophysiological peculiarities of nerves.Peculiarities of transmission of excitation in nerve fibers. Classification of nerve fibers. Components of nerve trunk action potential. Nerve indefatigability. Parabiosis. Coordination of reflex processes. Convergence and occlusion. Irradiation of excitation in central nervous system. Reciprocal innervation. Principle of dominant. Methods of research of the CNS activity. | 2 |
| 4. | Physiology of spinal cord. Spinal shock. Medulla oblongata and mesencephalon. Decerebrate rigidity. Physiology of reticular formation. Diencephalon. Specific and non-specific nuclei. Functions of hypothalamus. Limbic system. Subcortical nuclei. Physiology of cerebellum.Morphological properties of vegetative nervous system. Differences between sympathetic and parasympathetic divisions, their synergism and relative antagonism. Effects of sympathetic and parasympathetic divisions. | 2 |
| 5. | Physiology of blood. Blood volume, hematocrit, pH of blood, osmotic pressure. Functional systems regulating the constancy of homeostatic parameters of blood etc. Defense functions of blood. |  |
| 6. | Significance of blood circulation for organism. Valvular apparatus. Phases of cardiac cycle. Stroke volume of the heart and cardiac output. Physiological properties of cardiac muscle. Neurohumoral regulation of heart activity. Role of reflexogenic zones and cerebral cortex in regulation of heart activity.  | 2 |
| 7. | External manifestations of heart activity, methods of research. Electrocardiography. Heart sounds. Phonocadiography.  Basic principles of hemodynamics.Rate of blood flow and its determination. Measure of arterial pressure in human and animal. Arterial pulse and its main parameters. Vasomotor centers. Neurohumoral regulation of vasomotor center. Role of reflexogenic zones and cerebral cortex in regulation of vascular tone. Limph circulation and its regulation mechanisms.  | 2 |

**NORMAL PHYSIOLOGY 1**

**LECTURE 1**

**The Subject of Physiology and its Relation to other Disciplines.**

**The Methods of Physiology.**

**Physiology** (Gr. “physis”- nature, “logos” - science, learning) is one of the most important biological sciences. It is a science about the dynamics of life processes of organism. Physiology studies the functions of living organism and its parts: functional systems, organs, tissues, cells and structural elements of the cells. Physiology aspires to reveal the mechanisms of realization of living organism’s functions, the relations among them, their regulation, adaptation to external environment, their origin and evolution.

Thus, the principal **problems** which the physiology studies, are:

**1.** Functions of living organism and its systems of organs, organs, cells and structural elements of the cells.

**2.** Correlation of functions of organism’s systems of organs, organs, cells and so on.

**3.** Interrelation between the whole organism and the environment.

**The final aim of physiology** is to acquire the profound knowledge of functions with the purpose of providing the possibility of active influence on them in desired direction.

Taking into consideration that each type of organism, from the every simple virus to the largest tree or to the complicated human being, has its own functional characteristics, the vast field of physiology is accordingly divided into parts and their subdivisions.

First of all, we distinguish the general physiology, comparative physiology and special physiology.

**The general physiology** studies the nature of basic living processes and regularities of organism’s and its structures’ reactions to the influence of environment. One of its parts is the cellular physiology.

**The comparative physiology** studies the specific features of functions of

organisms belonging to different species or standing on different stages of development. Now the evolutionary physiology is formed and studies the regularities of specific and individual development of functions.

**The special parts of physiology** study the separate species or groups of animals, systems,organs or tissues of organism.

**The normal physiology** studies the functions of healthy human organism. The branches of human physiology are labor physiology, sports physiology, feeding physiology, age physiology,cosmic physiology and others.

**The pathological physiology** or the general pathology is the science about the functional disturbances in the diseased organism and establishes general regularities of pathological processes. Since pathological physiology studies the vital activities of the diseased organism it can be referred to as physiology of the diseased organism.

The physiology has close relations to many other disciplines - the biophysics and the biochemistry. Therefore, the physiologist must know the anatomy, histology and cytology well. Physiology relies also on biology, doctrine of evolution, embryology. The living organism is a self-regulating system. Therefore, physiology applies the methods of cybernetics - the science about the control of automated processes.

**Physiology is the theoretical basis of medicine.** To diagnose the disease the physician must know well the normal indices describing the sound organism. This information is necessary also when he evaluates the result of treatment. On the other hand, the clinic has a great number of valuable materials which are interesting for physiologists. The clinical physiology as a special branch of physiology applies its theoretical and experimental methodical achievements in clinic. On the other hand, it uses the clinical observations to explain and analyze the physiological processes.

The achievements of physiology, especially in sphere of higher nervous activity, are very important for psychology and education science.

Physiology is the science based on **experiments**. Trying to study the functions of organism the physiologist uses in his investigations *observations and experiments*. It is possible to observe such functions of man as heart activity, respiratory indices, blood pressure and so on. Because the measurement of blood pressure, blood count, ECG recording do not harm the organism. But it is impossible to experimentalize on man. Therefore, in order to study the functions of human organism more deeply it is necessary to carry out experiments on different animals, such as frogs, rabbits, cats, dog etc. Then the results are compared with the data obtained in clinic and only after this they can be used in clinical practice.

In physiological investigations acute and chronic experiments are carried out.

The acute experiments for the first time were used widely by Claudius Galenus in the

second century AD.

**Acute experiment** (vivisection) permits to observe visually some functions of organism (for instance, heart contraction) and register it during a short time. At the end the experimental animal usually perishes.

For a long time the acute experiment facilitated study of many functions of organism, though it suffers from grave shortcomings: loss of blood, pain, narcosis exert the negative influence on experimental animals’ vital functions and the facts are misrepresented.

**The chronic experiments** permit to study the functions of experimental animals during a long period of time, even for many months or years. The ways of chronic experiment were greatly improved in the laboratory of I. P. Pavlov.

There are numerous methods of chronic experiment. Actually almost every action of physiologist can be regarded as a method. For example if the nerve is cut, it is the method of *denervation* and the physiologist has an opportunity to study the changes in organs’ activity when it is not controlled by nervous system.

The methods of *ligation, perfusion, catheterization, fistula*, vascular *anastomosis* are used to study the functions of different organs.

Some methods of physiological investigations are very ancient: *extirpation (removal or extraction of organs or tissues), transplantation (grafting), stimulation (irritation), damaging* and others.

The electron and *stereotaxic* equipment makes it possible to stimulate or destroy not only separate structures of brain, but even small groups of neurons.

*The graphic recordings* of functions also has been improved significantly. Now the

physiologist can record not only the mechanical or bioelectrical activity of organs, but also the activity of single neurons. For this aim he possesses varied converters, sensing elements, amplifiers, sensitive recorders. The *electroencephalography*, *electromyography, electrocardiography, electrogastrography* are widely used in physiological investigations. Owing to the method of *radiotelemetry* it is possible to record the physiological functions of organism at a great distance. For instance, the physiologist can register the temperature, pressure and active reaction in the stomach of sportsman, pilot or cosmonaut when they are doing their usual work far away from researches. The *conditioned reflex* method elaborated by I. P. Pavlov enriched the physiology significantly. Thanks to this method it became possible to study the higher nervous activity without hurting the organism.

The existence of physiology as an independent science with its experimental methods dates from the XVII century, exactly from 1628 when English physician, anatomist and physiologist William Harvey (1578-1657) discovered the blood circulation (greater or systemic circulation and lesser or pulmonary circulation).

In Azerbaijan the first physiology chair was founded in 1920 at medical faculty of Azerbaijan University.

At Azerbaijan Medical University the physiology chair (1930) was headed by P.J. Rostovtsev, then A. A. Amirov, S. R. Ojagverdizade, G. M. Gahramanov, F. I. Jafarov.

**The Basic Ideas of the Physiology.Organism. Homeostasis. Physiologycal Functions. Biological Reactions. Reflex. Regulation of Body Functions**

As it was stated in the definition of physiology, it studies functions of organism. Besides the organism and the physiological functions the other **basic ideas** of physiology are: homeostasis, biological reactions, irritation, irritability, excitability, excitation, reflex.

Organism is the independently existing unit of the organic world which is the selfregulating system and reacts to the different changes of environment as the integral whole.

This definition of organism gives us some of its **principal features**.

1- organism is the *independently existing unit of the organic world*. This means that the size and other pecularities of organism are not decisive. For instance, amoeba, though microscopic, is the organism, because it can exist independently. But the half of the elephant, though million and milliard times bigger than amoeba, is no longer the organism, because it cannot exist in this form by itself.

2- the *organism must react to the different changes* of environment as the integral whole. The result of the interaction of organism with the environment is the selfrenewal of organism. This means that *organism cannot exist without the constant interaction with the environment.*

3- the organism is the *self- regulating system*. This is very important pecularity of organism and the necessary condition of its existence. Self - regulating systems are such systems where any deviation from the norm becomes the cause of restoration of that norm. It reminds the relay. For example, if the blood pressure has risen, then the baroceptors localized in aortic arch and carotid sinus are irritated, the excitation is conducted to the vasomotor center in brain (in medulla oblongata). From there the vasodilative impulses come to arteries. They dilate and the blood pressure decreases to the normal level. And all of this is done by the organism itself without any outside intervention and help.

There is a large number of such self-regulating mechanisms controlling every function of organism (active reaction of blood, blood cells number, rate of the heart beat, respiration rate, muscular tension and so on).

Every organism exists in environment, that is, in external medium. But extracellular fluid of organism, i. e. blood, lymph and tissue fluid form the **internal environment or internal medium** of organism. So, the cells of organism exist in its internal environment. The cells of organism can exist only in constant conditions. But the parameters of external medium (temperature, humidity and so on) change within great limits. This evokes the changes in one or other direction in the indices of internal environment. Thanks to the activity of selfregulating machanisms these deviations are normalized and the relative constancy of internal environment is maintained. To mean the maintenance of static or constant conditions (the chemical composition, physical and chemical properties) of internal environment W. Cannon offered the term homeostasis. But *Claude Bernard* as long ago as in the XIX century with genius farsightedness noted that the constancy of internal environment of organism is the necessary condition of free and independent life. This means that if the homeostasis is broken, the death may follow. For example, let us imagine a man with normal maximum arterial pressure 120 mm Hg. If under some circumstances (negative emotions, anger, other influences) his pressure rises, let us say, to 170 mm Hg, after some time owing to the activity of self-regulating systems the pressure decreases to normal 120 mm Hg. Undoubtedly, such negative influences effect repeatedly and every time after the rise of blood pressure it is decreased by the help of self-regulation systems.

Now let us imagine the man whose blood pressure self-regulation mechanisms, for instance, aortic arch and carotid sinus baroceptors are hurted and cannot fulfil their function. Then every negative influence will rise the arterial pressure which will remain on that high level. Thus, after some influences of this kind the blood pressure may reach such high figures which is enough to tear the arteries and cause death.

This example clearly demonstrates the significance of the homeostasis for safety and wellbeing of organism. Owing to homeostasis there are biological constants, which characterize the normal state of organism, for instance, the blood pressure (120/80 mm Hg), pulse rate (70-75 in 1 minute), the number of erythrocytes (4-5 millions in 1 mm) and so on.

We must once more emphasize that there is not absolute constancy of life functions indices and internal medium of organism. Because they are always changing under the influence of different agents. Therefore, the constancy of physical, chemical and biological properties of internal environment of organism is relative and dynamic.

From evolutionary point of view we distinguish different levels of organization of organisms: the molecular, cell, tissue, organ, system levels. Higher the level of evolutionary development of organism - higher the level of homeostasis and more complicated are its mechanisms. All the organs and tissues of the body perform certain functions that help to maintain homeostasis. The lungs continually provide to the extracellular fluid oxygen that is being used by the cells, the kidneys maintain constant ion concetrations, the gastrointestinal system provides nutrients. The possibilities of homeostasis are not boundless. If the organism remains in unfavourable conditions for a long time, then homeostasis is disturbed, disease and even the death (as we saw in our example) can follow.

To prevent such a tragic end, the human body has thousands of control systems, that is, homeostatic control mechanisms. The most intricate of them are the genetic ones, operating in all cells. Many other control systems operate within the organs, others- throughout the entire body to control the interrelationships between the organs.

Most of control systems of the body act by process of negative feedback. For instance, a high concentration of carbon dioxide in the extracellular fluid causes increased pulmonary ventilation, lungs excrete greater amounts of carbon dioxide out of the body and this causes decreased carbon dioxide concentration. So, the high concentration causes a decreased concentration, which is negative to the initiating stimulus. Conversely, if the carbon dioxide concentration falls too low, this causes a feedback increase of its concentration. The high blood pressure also causes a series of reactions that promote a lowered pressure, and a low pressure causes a series of reactions that promote an elevated pressure.

**Generally** speaking, if some factor becomes excessive or too little, a control *system initiates negative feedback*, which consists of a series of changes that return the factor toward a certain mean value, thus maintaining homeostasis.

All the control systems of the body operate by negative rather than positive feedback. Because positive feedback does not lead to stability but to instability and often to death. Positive feedback is better known as a “vicious circle”. For example, the normal human heart pumps about 5 liters of blood per minute. If the person is suddenly bled 2 liters, the amount of blood in the body is decreased to such a low level that not enough is available for the heart to pump effectively. As a result, the arterial pressure falls, and the flow of blod to the heart muscle through the coronary vessels also diminishes. This results in weakening of the heart, further diminished pumping, further diminished pumping, further decrease in coronary blood flow, and still more weakness of the heart; the cycle repeats itself again and again until death. Each cycle in the feedback results in further weakening of the heart. In other words, the initiating stimulus causes more of the same, which is positive feedback.

But sometimes the positive feedback can be useful. For example, when a blood vessel is ruptured and a clot begins to form, clotting factors within the clot itself are activated. Some of these enzymes act on unactivated enzymes of the immediately adjacent blood, activate them and cause still more clot. This process continues until the hole in the vessel is plugged and bleeding stops.

Some movements of the body are so rapid that nerve signals have not enough time to pass the way from the peripheral parts of the body to the brain, and then back again in time to control the movements. In such cases to cause the required muscle contractions the brain uses a principle called *feed - forward control*. Then, sensory nerve signals from the moving parts inform the brain whether the appropriate movement as planned by brain actually has been performed correctly or not. If not, the brain corrects the feed - forward signals. Then, if still further correction needs to be made, this too will be done. This is called adaptive control and, in a sense it is delayed

negative feedback.

**Thus,** each functional structure has its share in the maintenance of homeostasis. As long as normal conditions are maintained in the internal environment, the cells of the body continue to live and function properly. When one or more functional systems lose their ability to contribute their share of function, all the cells of the body suffer. Extreme dysfunction leads to death, moderate dysfunction - to sickness.

Now, when we have acquainted in details with organism as the subject of physiology, it is just time to answer the question - *what are the physiological functions?*

***Physiological functions*** are vital activity manifestations of adaptability significance. Fulfilling different functions the organism adapts itself to the environment or fits up the environment to its own requirements. The physiology studies not only the functions, but also the functiogenesis, that is, the origin and development of every function.

**The main function of living organism** is the ***metabolism***, including energy metabolism. The metabolism is the necessary condition of the life, though such metabolism can take place also in inorganic bodies. The difference is that the metabolism destroys the inorganic bodies, but the organism cannot exist without this function. Cessation of metabolism is end of the life, i. e. results in death.

All the other physiological functions of the organism are also connected with the metabolism.

The basis of any physiological function is formed by the certain totality of the conversion of substances and energy. In the time of fulfilment of any function as a result of physical and chemical processes and chemical conversions in the cells of organism the structural changes take place. These changes may be macroscopic, visual, or microscopic and even so insignificant that they can be revealed only with the aid of electronic microscope. Just using the electronic microscope it was possible to establish the submicroscopic changes in muscle cell during its contraction and in teleneuron during the nerve impulse transmission.

So, realization of every physiological function without fail evokes the changes in the structure of cells. As a rule, these changes are reversible and they are quickly recovered. But in rare cases the irreversible changes can take place (for instance, the destruction of some cells during the secretion).

The living organisms and their cells are able to respond to the influence of environment by the changes of their own structure and activity. This ability is called **irritability.** The process of influence of environmental agents to the living tissue is called irritation or stimulation. The agents themselves which cause the irritation, are **stimuli (stimulants) or irritants**.

They can be divided in 5 large groups:

1) the physical stimuli (temperature, mechanical, electrical, light, sound),

2) the chemical stimuli (nutritives, medicinal preparations, poisons and many chemical combinations, which are able to change the metabolism in cells and evoke physiological reactions),

3) the physical-chemical stimuli (the changes of the active reaction of environment, electrolyte composition, colloidal state, osmotic pressure). The natural irritants of cells are the nerve impulses.

4) biological (viruses, microbes)

5) information (speech, emotions, signals about danger etc.)

Accroding to the physiological significance of stimulants they are divided in 2 groups:

1) the adequate stimuli - they are specific or special irritants for certain biological structure, which is adapted to perceive them (for the gustatory lingual papilla - different chemical substances, for the retinal rod - cells and cones-shaft of light, for the organ of hearing - sound),

2) the inadequate general irritants, which can exercise influence on any tissue (electric current, temperature, mechanical blow).

In the process of evolution the cells became more sensitive to their adequate stimuli than inadequate ones.

In physiological experiments the electrical current is used more oftenly. It has some advantages: the effect of electrical current begins and ends instantly, it can be exactly regulated by many parameters, electric current exercises its influence in such doses that does not damage the tissues and can be repeated many times.

The tissues can be irritated directly or indirectly (through the nerve).

The living tissue answers any influence by changing its form, structure, growth, division, by formation of different chemical compounds. Any changes of structure and functions of organism and its cells in response to different influences are called biological reactions.

But there is a special form of the biological reaction, characteristic only for excitable tissues. It is called **excitation.** The obligatory sign of the excitation is change of the electric state of cell membrane which causes rise of action potential.

The excitable tissues are: nervous, muscular and glandular tissues. Excitation of nervous tissue manifests itself by the rise of nerve impulse, muscular - by contraction, glandular – by secretion.

Ability of excitable tissues to answer the irritation by excitation is called **excitability**.

The minimal strength of the stimulus which is necessary to cause excitation is called the excitation **threshold.** It is natural that the lower is the excitation threshold, the higher is the excitability and vice versa.

Excitability of receptors is especially high regarding their adequate stimuli. For instance, the rod cells of retina react even on 3-4 quantum of light, and the influence of several molecules of aromatic substance is enough to excite the olfactory cells.

It is possible to influence on the living cells or organs not only directly, but also through the central nervous system. Any response of organism to irritation which is realized with participation of the central nervous system is called **reflex.** The way of nerve impulses which cause reflex is called the **reflex arch**.

The reflex arch consists of the following parts:

1) the receptor - perceives the certain type of influences of external and internal environment,

2) the afferent (sensory) nerve,

3) the nervous and synapses in central nervous system,

4) the efferent (motor) nerve,

5) the working organ - its activity changes as the result of reflex.

Irritation not always stimulates activity of the cells or organs.

Cessation or weakening of nervous activity under the influence of nerve impulses is called **inhibition.**

There is one more idea, though it is studied chiefly by pathological physiology. That is reactivity. The organism’s reactivity is its ability to respond in a definite manner to the action of ordinary and pathological stimuli in every concrete situation. Reactivity is more extensive idea that the preceding ones.The irritation and excitation can be regarded as the indices of reactivity.

Now we became acquainted with several basic ideas of physiology which we shall use frequently. Some of them are very like. Therefore it is necessary to imagine them clearly and tell one from the other.

For instance, the irritability, as well as excitability, is the ability of organism or its tissues. But the irritability is the ability of any living tissue to respond to stimulus while the excitability is the ability of only excitable tissues to specific response.

We mentioned several forms of response of organism and its tissues. They also must be distinguished.

When we irritate any living tissue and observe any changes, it is a **biological**

**reaction.**

When we irritate the muscle and it contracts - it is excitation. But when we observe the same contraction of muscle as a response to the irritation of corresponding receptors - it is a reflex. When such an irritation causes cessation or weakening of organ’s activity- it is inhibition.

**Reactivity** is more extensive and complicated idea. It characterizes the response of whole organism in every concrete situation.

Unity and integrity of organism, intercommunication of its functions are achieved by **two mechanisms of regulation**: humoral and nervous mechanisms.

The ***humoral or chemical*** mechanism of regualtion is phylogenetically more ancient. Hormonal regulation is its part. The humoral regualtion is based on the fact that some chemical compounds, possessing a great physiological activity, are transported by blood to whole organism and exercise their influence on different cells and organs. These chemical stimulants, have not definite addressee, though the electoral sensitivity of cells to them is obvious.

The ***nervous*** mechanism is phylogenetically younger and more perfect. It is more exact and quick.

Both regulatory mechanisms are interconnected. On the one hand, different chemical compounds influence on nerve cells and change their state. The hormones are a system of regulation that complements the nervous system. On the other hand, the humoral regulation in certain degree submits to the nervous system.

The nervous system, in general, regulates mainly muscular and secretory activities of the body, whereas the hormonal system regulates mainly the metabolic functions. They form a single neurohumoral mechanism of regulation of organism’s functions.

**GENERAL PHYSIOLOGY OF EXCITABLE TISSUES**

**Bioelectrical Phenomena. Membrane Potential and Action Potential**

**The excitable tissues** are: the nervous, muscular and glandular tissues. In response to irritation they are able to change from the physiological resting state to the state of the activity, that is, to generate the specialized forms of vibration of the electric potentials.

**Excitation** is characterized by an aggregate of electric, temperature, functional, structural changes. Among these the electrical phenomena are most important, because they provide transmission of excitation - the electric impulse spreads along the cell membrane.

The living organism consists of approximately hundred trillions (billions) cells. The normal functioning of every cell, as well as of the organism on the whole, is possible owing to continuous exchange of information among the cells. This exchange is realized by direct interaction among the cells by the humoral way and by the help of the bioelectrical potentials. Transmission of bioelectrical potentials from one cell to another is the most rapid way of transmission of the information in the organism.

The nervous system, which is most developed in the human being, provides perception, transmission, storage, conversion and reproduction of the information which is enclosed in the electric signals.

The doctrine about the “animal” electricity, that is, the electrical phenomena in living tissues, has been originated in the second half of the XVIII century. By the help of the Leyden jar it was observed that some fishes (electric rays, electric cells) stunned their prey with a strong electric shock. Priestley made a supposition that the spreading of the nerve impulse was the flow of the “electrical fluid” along the nerve. Bertolon tried to explain the cause of the diseases by surplus or deficiency of this fluid. As a result of the scientific dispute about the nature of the “animal electricity” between

physiologist Galvani and physicist Volta, lasting several years (1791-1797), the facts were ascertained that testified to the existence of the electrical potentials in nervous and muscular tissues. Besides, the galvanic element (“Volta’s column”) was invented.

To study the physiological influence of the atmospheric electricity during thunderstorms, **Galvani** used a preparation of hind legs of a frog linked with the spine. After suspending it on a copper hook from the iron railing of the balcony he noticed that the muscles of the frog’s legs, swinging in the wind, contracted each time they touched the railing. Galvani came to a conclusion that these contractions were caused by the “animal electricity” which originated in the spinal cord of the frog and was transmitted to the muscles of the legs through the metal conductors (hook and railing).

**Volta** pointed out that the current source in this experiment of Galvani was not the spinal cord of the frog, but the circuit formed by heterogeneous metals (iron and copper), and therefore, the phenomena described by Galvani could not be regarded as caused by “animal electricity”.

Galvani carried out the **new experiment**. He stripped the skin from the frog’s legs,

dissected the sciatic nerve in the place where it leaved the spinal cord and prepared the nerve along the thigh to the crus. When he threw the nerve on the bare muscles of the crus, the muscles

contracted.

This ***second experiment of Galvani***, carried out without metal, was called by Du Bois-Reymond “the chief true experiment of neuromuscular physiology”.

Thanks to invention of the galvanometer, in the twenties of the last century the measurement of the bioelectric currents was possible, and K. **Matteucci** investigated the mechanism of the electrical phenomena in the living tissues. In 1838 he ascertained that in the second experiment of Galvani the muscles contracted only in the cases when in the process of the preparation they were damaged. This paradox he explained by the fact that the external surface of the muscle was charged positively and the internal contents-negatively. The resting membrane potential is conditioned by this potential difference. When the muscle is damaged, the negative charges are uncovered, and if the nerve of the another muscle is thrown on this damaged muscle in such a manner that it gets in touch with the damaged and intact parts, the resting membrane potential causes contraction of the second muscle.

In 1840 Matteucci demonstrated his second experiment known as the “second contraction”, which proved existence of the action potentials. He threw the nerve of one muscle on the second muscle. When the nerve of this second muscle was stimulated, both muscles contracted. The contraction of the first muscle is caused by the action potential that occurs when the second muscle is contracted under the influence of the stimulation.

This method was used to reveal the action potentials by the help of the “rheoscopic paw” or “physiological rheoscope”. For instance, when the nerve of the neuromuscular preparation was thrown on the contracting heart, the muscle also contracted in the rhythm of the heart activity.

The further investigations (in 1875) revealed that the brain activity is also followed by the bioelectrical currents. In 1887 for the first time the electrocardiogram was recorded. In 1913 electroencephalogram of the animal and then-that of the man were recorded.

As far back as in 1896 Chagovets expressed his opinion about **ionic nature of the bioelectrical processes**. In 1902 Bernstein developed the membrane-ionic theory which was modified and proved in experiments in 1949-1952 by Hodgkin, Huxley and Katz.

When the cell (or fiber) is in the physiological resting state, its internal potential is negative in relation to the external potential. Such state is called polarization and this transmembrane potential difference is called the **resting potential or the membrane potential.**

To measure the membrane potential intracellular microelectrode technique is applied. A

small pipette filled with electrolyte solution is impaled through the cell membrane to the interior

of the fiber. Another electrode (indifferent electrode) is placed in the interstitial fluids. The

potential difference between the inside and outside of the fiber is measured using voltmeter. For recording rapid changes in the membrane potential during the transmission of nerve impulses, the microelectrode is connected to an oscilloscope.

In different cells the resting membrane potential varies from 50 to 90mV.

**The basic structure of the cell membrane** is a lipid bilayer, which is a thin film of lipids only 2 molecules thick. It is composed almost entirely of phospholipids and cholesterol. Interspersed in this lipid film are large globular protein molecules, most of which are glycoproteins. **Two types of proteins** occur: the integral proteins that protrude all the way through the membrane and the peripheral proteins that are attached only to the surface of the membrane and do not penetrate.

Many of the integral proteins provide **structural channels** **(pores)** through which water soluble substances (especially the ions) can diffuse between the extracellular and intracellular fluid. These proteins have selective properties that cause preferential diffusion of some substances more than others.

Others of the integral proteins act as carrier proteins for transporting substances in the direction opposite to their natural direction of diffusion, which is called active transport. Still others act as enzymes.

The peripheral proteins are attached to one of the integral proteins and function almost entirely as enzymes.

The membrane carbohydrates occur in combination with proteins and lipids (glycoproteins and glycolipids). Many of the carbohydrates act as receptor substances. Some enter into immune reactions.

***The main factor in the origin of membrane potential*** is the large potassium ion ***concentration*** gradient from the inside toward the outside of the cell. Because the potassium ions concentration in the nerve and muscle cell cytoplasm is 30-50 times higher than that of in the extracellular fluid. But the concentration of the sodium ions is 8-15 times higher and the concentration of chlorine ions 10-50 times higher in the extracellular fluid than those in the cytoplasm.

In the resting state the membrane ***permeability*** for the *potassium* ions is on the whole, 25 times higher than that of for the sodium ions. In the nerve fibers the permeability of the membrane to potassium is even 100 times as great as to sodium.

So, there is a strong tendency for potassium ions to diffuse outward. Doing so, they carry positive charges to the outside, thus creating a state of electropositivity outside the membrane and electronegativity on the inside because of the negative anions that remain behind and do not diffuse outward along with the potassium.

Simultaneous diffusion of the *sodium* ions into the cell is very weak and it decreases the absolute value of the resting potential slightly.

In nerve fibers *chlorine* ions do not play significant role in the origin of resting potential. But in skeletal muscle fibers the permeability of membrane in resting state for the chlorine ions is comparable to that of for potassium ions and therefore, diffusion of chlorine ions into the cell increases value of the resting potential.

**So**, the value of the membrane potential is determined by two main factors such as correlation of the concentrations of cathions and anions diffusing through the resting membrane and correlation of the membrane permeability for these ions.

A channel protein in the cell membrane, through which potassium and sodium ions can leak is called a potassium-sodium leak channel. There are many different proteins of this type with different leak characteristics. But on the average the channels are far more permeable (about 100 times) to potassium than to sodium. This differential in permeability is exceedingly important in determining the level of the normal resting membrane potential.

Despite the fact that the sodium and potassium streams in the resting state are not strong, in the end the concentration difference of these ions in the cell and in the extracellular fluid had to be equalized, if the **sodium-potassium pump** was not present in the membrane. It pumps sodium ions out of cytoplasm and potassium ions into it. There is continuous pumping of three sodium ions to the outside for each two potassium ions pumped to the inside of the membrane. The fact that more sodium ions are being pumped to the outside than potassium to the inside causes a continual loss of positive charges from inside the membrane. This creates an additional degree (about - 4 mV) of negativity on the inside beyond that which can be accounted for by diffusion alone.

**In summary**, the diffusion potentials alone caused by potassium and sodium diffusion would give a membrane potential of approximately - 86 mV almost all of this being determined by potassium diffusion. Then, an additional - 4mV is contributed to the membrane potential by the electrogenic sodium-potassium pump, giving a net resting membrane potential of -90mV.

The energy for the activity of the sodium-potassium pump is provided by the ATP, which is the universal source of energy of living cells.

The resting membrane potential in large skeletal muscle fibers is approximately the same as that in large nerve fibers (-90 mV). But in small nerve and muscle fibers (smooth muscle) as well as in many neurons of the central nervous system, the membrane potential is often as little as -40 to -60 mV.

Nerve signals are transmitted by **action potentials** – rapid changes in the

membrane potential caused by stimulation of the excitable tissues.

To cause the action potential the stimulus must be no less than certain critical level (**threshold of stimulation**). In the natural conditions action potentials are generated in nerve fibers when receptors are stimulated or nerve cells are excited.

The changes of the cell membrane ion permeability form the basis of action potential.

When the cell is stimulated, the membrane permeability for sodium sharply increases. Therefore, the stream of sodium ions into the cytoplasm begins to exceed that of potassium ions directed on the outside.

Each action potential begins with a sudden change from the normal resting negative potential to a positive membrane potential and then ends with an almost equally rapid change back again to the negative potential. To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the fiber’s end.

The successive **stages of the action potential** are as follows:

**1.** *Resting stage* - this is the resting membrane potential before the action potential occurs. During this stage the membrane is polarized.

**2.** *Depolarization stage (local an regenerative*) - the membrane becomes very permeable to sodium ions, the tremendous numbers of which flow to the interior of the axon. The normal “polarized” state of -90 mV is lost, with the potential rising rapidly in the positive direction. This is called depolarization. In large nerve fibers the membrane potential actually overshoots beyond the zero level and becomes somewhat positive, but in some smaller fibers as well as many central nervous system neurons, the potential merely approaches the zero level and does not overshoot to the positive state.

**3.** *Repolarization stage* - within a few 10000 ths of a second after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close, and the potassium channels open more than normally. Rapid diffusion potassium ions to the exterior re-establishes

the normal negative resting membrane potential. This is called repolarization of the membrane.

The necessary actor in causing depolarization and repolarization of the nerve membrane

during the action potential is the voltage-gated sodium channel. But the voltage-gated potassium channel also plays an important role in increasing the rapidity of repolarization of the membrane.

These two volage-gated channels are in addition to the sodium-potassium pump and sodium potassium leak channels.

**The voltage-gated sodium channel** has two gates - one near the outside of the channel called the *activation* gate and another near the inside called the *inactivation* gate. In the resting membrane (when the membrane potential is - 90 mV) the activation gate is closed, and this prevents the entry of sodium ions to the interior of the fiber. When the membrane potential becomes less negative, rising from -90 mV toward zero, it finally reachs a voltage between – 70 and - 50 mV, and this causes a sudden conformational change in the activation gate, flipping it to the open position. During this activated state sodium ions can literally pour inward through the channel, the sodium permebility of the membrane is increased as much as 500-fold to 5000-fold.

The same increase in voltage that opens the activation gate also closes the inactivation gate. But closure of the inactivation gate is a slower process and occurs a few 10000 this of a second after the activation gate opens. Thus, after the sodium channel has remained open for a few 10000 this of a second, it closes and sodium ions can no longer pour to the inside of the membrane. The membrane potential begins to recover back toward the resting membrane state (repolarization process).

It is not possible for the sodium channels to open again without the nerve fiber first repolarizing. Because the inactivation gate will not reopen again until the membrane potential returns nearly to the original resting membrane level. This is very important characteristic of the sodium channel inactivation process.

During the resting state the gate of the voltage-gated potassium channel is closed, and potassium ions are prevented from passing through this channel to the exterior. When the membrane potential rises from - 90mV toward zero, this voltage change causes a slow conformational opening of the gate and allows increased potasium diffusion outward through the channel. The potassium channels mainly open just at the same time that the sodium channels are closing. So, the decrease in sodium entry to the cell and simulateneous increase in potassium exit from the cell greatly speeds the repolarization process, leading within a few 10000 ths of a second to full recovery of the resting membrane potential.

For a few milliseconds after the action potential is over, the membrane potential becomes even more negative than the original resting membrane potential. Because many potassium channels remain open for several milliseconds after the repolarization process of the membrane is complete, and excess potassium ions diffuse out of the nerve fiber, leaving an extra deficit of positive ions on the inside, which means more negativity. This state is called the **positive afterpotential (trace potential)**. Because historically, when measured on the outside, this potential caused a positive record. The positive afterpotential is called also *hyperpolarization afterpotential*.

The **negative afterpotential** also occurs, which is called *depolarizaion afterpotential.*

**So,** in the action potential the spike and afterpotential are distinguished. The spike consists of ascending (depolarization – local and regenerative) and descending (repolarization) phases.

The **all-or-nothing (all-or none) principle** applies to all normal excitable tissues. This means that once an action potential has been elicited at any point on the membrane, the depolarization process will travel over the enire membrane if conditions are right, or it might not travel at all if conditions are not right.

If the membrane potential rises very slowly (over many milliseconds instead of a fraction of a millisecond), the slow, inactivating gates of the sodium channels will have time to close at the same time that the activating gates are opening.

Consequently, the opening of the activating gates will not be as effective in increasing the flow of sodium ions as normally. Therefore, a slow increase in the internal potential of a nerve fiber either requires a higher threshold voltage than normal to cause firing or prevents firing entirely, even with a voltage rise to zero or even to positive voltage. This phenomenon is called **accomodation** of the membrane to stimulus.

Some factors can decrease nerve **excitability**. These are called membrane-stabilizing factors. For instance, calcium ions are a stabilizer, because a high extracellular fluid calcium ion concentration decreases the membrane permeability and simulatneously reduces its excitability.

Low potassium ion concentration in the extracellular fluids also acts as a stabilizer and reduces membrane excitability. because it has a direct effect of decreasing the permeability of the potasium channels. Among the most important stabilizers are local anesthetics (procaine, tetracaine) and many other drugs. Most of these act directly on the activation gates of the sodium channels, making it difficult for this gates to open and thereby reducing the membrane excitability.

**Critical Level of Depolarization and Local Reply. Chronaxy. Polar Rule of Excitation. Physiological Electrotonus. Pfluger’s Rule of Contraction. Refractory Period. Lability**

For the action potential to occur the ion permeability of the membrane must be increased under the influence of some stimulus. But this is possible only when the stimulus is sufficiently powerful. A weak electrical stimulus is not able to excite a fiber. But when the stimulus is progressively increased, there comes a point (threshold level) at which excitation takes place. Such stimuli are called liminal (**threshold)** stimuli. The weaker stimuli are called subliminal (**subthreshold**) and the stronger ones-supraliminal (**superthreshold**) stimuli.

The action potential occurs at the moment when the depolarization of the membrane reaches the *critical level*. This critical level does not depend on the character of the stimulus applied or the distance between electrodes, but is determined only by the properties of membrane itself. If the critical level is reached the action potential (as well as excitation) occurs after a short latent period.

A weak stimulus is not able to change the membrane potential sufficiently for the automatic regenerative processes of the action potential to develop. Nevertheless, it does disturb the membrane potential locally. The local potential changes, which fail to elicit an action potential, are called subthreshold potential or **local reply**.

The first signs of the local reply appear when the stimulus applied makes 50-75% of the threshold level.

So, even a weak stimulus causes a local potential change at the membrane, but the intensity of the local potential must rise to a threshold level before the action potential will be set off.

The threshold level of any stimulus in certain limits is inversely proportional to the duration of its influence. But the stimuli weaker than certain minimum level do not cause excitation even though their influence is continued for a long time.

The dependence of the threshold power of the stimulus on the duration of its influence on the tissues to cause an excitation, is presented in the **curve “ power - duration ”** (or “ power - time”).

The minimum level of the direct current which is able to cause the excitation (threshold of stimulation), is called **rheobase.**

The minimal interval of the time, during which the stimulus of one rheobase must influence on the tissue to cause an excitation, is called the **useful (effective) time**. This means that the further increasing of the duration is useless for the origin of the action potential.

Increasing of the power of the current leads to decreasing of the minimal time of the stimulation. But when the time is excessively short, even very powerful stimulus cannot cause the excitation. Therefore, the idea of chronaxy is used.

The **chronaxy** is the time during which the stimulus of double rheobase must influence the tissue to cause the excitation. The values of rheobase and chronaxy of nerve fibers are markedly less than those of muscle fibers.

The chronaximetry is applied in the neurology practice to establish the organic affection of the motor nerves.

When the nerve or muscle is stimulated by the **direct current**, the excitation occurs only at the moments of closing and breaking of the circuit. Between these moments, though the current flows through the living tissue and causes certain changes in it, the excitation does not occurs.

Moreover, the excitation occurs not under both electrodes, but each time only under one of two electrodes.

At the moment of closing of the circuit the excitation occurs under the cathode and at the moment of breaking of the circuit - under the anode. This is called the **polar rule of excitation.**

The polar rule of excitation is demonstrated in several ways. For instance, the area of the tissue is damaged. When this area is under cathode, and anode is on the intact tissue, the excitation of intact area occurs only at the moment of the breaking of the circuit (under anode).

When anode is on the damaged area, the excitation occurs only at the moment of closing of the circuit (under cathode).

If two microelectrodes are introduced into the cell for stimulation and recording of

potentials, the closing of circuit causes action potential only when cathode is outside and anode is inside. When the positive and negative poles are situated in reverse order, at the moment of closing of circuit (even of the powerful current) the excitation does not occur.

The polar rule of excitation is explained in the following way. The negative current from the negative electrode reduces the voltage immediately outside the membrane, that is, causes depolarization. This allows activation of the sodium channels, thus resulting in an action potential. Conversely, at the anode injection of positive charges on the outside of the membrane heightens the voltage difference across the membrane, that is, causes hyperpolarization, which decreases excitability of the tissue.

The electric current not only excites the tissue, but also changes its physiological properties, such as excitability and conduction.

When the direct current flows through the nerve or muscle fiber its excitability and conduction change. They increase under the cathode (cathelectrotonus) and decrease under the anode (anelectrotonus). On the whole these phenomena are called the **physiological electrotonus.**

**So,** cathode increases excitability and excites but anode does not excite and decreases excitability.

The electrotonic changes may be studied by the way of measuring the excitation threshold at different areas of the fiber when the direct current is flowing through it. Higher the threshold lower the excitability and vice versa. In this way it was established that the threshold is lowest, that is, the excitability is highest at the point of the fiber where the cathode touches it. And the highest threshold, that is, the lowest excitability was found at the point where the anode touches the tissue. Farther from cathode and anode - weaker these changes are marked.

Between the electrodes there is a point where the flow of the current does not cause the change of excitability and conduction. It is called the indifferent point. The indifferent point is situated in the middle way between electrodes at the average power current. When the current is weak it is nearer to the anode, and for the powerful current the indifferent point is nearer to the cathode.

The mechanism of physiological electrotonus is connected with the fact that the value of excitation threshold depends on the correlation between the initial and critical levels of the membrane potential.

At the point where the **cathode** touches the nerve or muscle fibers, the resting potential (E0) approaches to the critical level (Ec), that is, the partial depolarization occurs and the depolarization threshold (V) decreases. Therefore, the excitability increases and the excitation is facilitated.

At the point where the **anode** is put to the tissue, the level of E0 moves away from Ec, that is, hyperpolarization occurs and ∆V increases. This causes decrease of excitability, and rise of excitation becomes more difficult.

Under the **prolonged influence of the direct current** on the tissue the electrotonic phenolmena are inversed. The initial increase of the excitability under the cathode is replaced by its decrease. This is called the ***cathodic depression***. Simultaneously the initial decreased excitability under the anode gradually increases, excitation develops (**anodic exaltation**). These changes are connected with inactivation of the sodium permeability caused by the prolonged depolarization of the membrane and increase of the membrane permeability for the potassium ions.

So, depolarization of the membrane is the electrophysiological proof of the excitation and its hyperpolarization - that of **inhibition**. But protracted depolarization also causes inhibition.

According to Pfluger’s **rule of contraction**, not only the power of the direct current and the moments of closing and breaking of the circuit are important, but the direction of the current also must be taken into consideration (especially when the muscle contraction is learned). Because the powerful current can cause a temporary paralysis in the nerve fiber, and if this area turns out to be between the stimulating electrodes and the muscle, it prevents the impulses to be transmitted.

Besides, as it was mentioned, when the current is weak, the indifferent point is situated nearer to the anode, that, is the anodic area is smaller than the cathodic area. Therefore, the depolarization under the anode does not reach the critical level and the excitation does not occur.

Two directions of the current are distinguished: ascending (when the anode is situated near the muscle) and descending (cathode is near the muscle).

In both directions (ascending and descending) of the **average power** current at the moments of closing as well as breaking of the circuit the muscle always contracts.

The **weak current** of both directions causes the contractions only at the moment of the closing of circuit.

For the **powerful current** the direction of the current is decisive. The ascending current causes the contraction only at the moment of breaking of the circuit, but the descending current only at the moment of closing.

Shortly after the initiation of action potential the sodium and calcium channels become inactivated. The only condition that will reopen them is for the membrane potential to return to the original resting membrane potential level. Therefore, a new action potential cannot occur in an excitable fiber as long as the membrane is still depolarized by the preceding action potential.

The period of time during which a second action potential cannot be elicited, even under a very strong stimulus, is called the **absolute refractory period**. This period is about 0.4msec for rapid conductive nerve fibers of the worm-blooded animals, but very long for the heart muscle fibers (250-300 msec).

Following the absolute refractory period is **a relative refractory period**, lasting about one quarter to one half as long as the absolute refractory period. During this time stronger than normal stimuli can excite the fiber. The cause of relative refractoriness is twofold: 1) some of the sodium channels still have not been reversed from their inactivation state, 2) the potassium channels are wide open, causing a state of hypolarization that makes it more difficult to stimulate the fiber.

The relative refractory period is followed by the period of **supernormal excitability**. This is caused by depolarization afterpotential. If the depolarization afterpotential is followed by hyperpolarization afterpotential, the period of supernormal excitability is replaced by the period of **subnormal excitability**.

The absolute refractory period for large myelinated nerve is about 1/2500 second. This means that such a fiber can carry no more than 2500 impulses per second (even less than this number). So, the amount of the excitations of the living tissue in a unit of time is limited.

The velocity of the elementary reactions following the physiological activity of the given apparatus of the body was called by Vvedenski the **lability or functional mobility**.

**So, the lability** is the maximum number of the action potentials (“maximum rhythm”) that the excitable tissue is able to generate in 1 second in accordance with the frequency of the stimulations.

To reproduce the rhythm of the stimulations the intervals between them must be

even more than duration of the absolute refractory period.

The lability of the nerve fibers is the greatest. For the muscle fibers it is less, and the least lability is that of neuromuscular synapses and especially that of the central nervous system synapses.

The lability is very variable index. It is changed even for one and the same tissue in its different physiological states or in the course of the rhythmical stimulation. For instance, the single nerve fiber was irritated by the rhythmical stimuli of the frequency 460 in 1 second, and it responsed to each stimulus. Then the frequency was increased up to 740 in 1 second, and the fiber answered only to every second stimulus. But after several seconds the fiber began to response to each stimulus, and the frequency of the impulses increased to 740 in 1 second. This phenomenon was called by Ukhtomski the **assimilation of the rhythm**.

**LECTURE 2**

**Functions and Properties of Cross-Striated Muscles. Mechanism of Muscle**

**Contraction. Functions and Properties of Smooth Muscles**

About 40% of the body is cross-striated or skeletal muscle and almost 10% is smooth and cardiac muscle. Though these different types of muscle differ by their structure and physiological properties, many of the same principles of contraction apply to all of them.

The skeletal muscles are the active part of the locomotor system which includes also bones, ligaments and tendons. As a result of the contractile activity of the skeletal muscles the following **functions** are realized: 1) movement of the organism in the space, 2) shift of the parts of the body regarding each other, 3) support of the posture.

The most important **physiological properties** of the skeletal muscle fibers are excitability, conduction and contractibility. One of the results of the muscle contraction is production of the heat.

In natural conditions excitation and contraction of muscle are due to the impulses coming from the central nervous system. To cause muscle contraction in experiment the electrical stimulation is applied. The muscle may be stimulated directly or indirectly (through the motor nerve).

Since the excitability of the muscular tissue is lower than that of nervous tissue, the direct stimulation is not provided even when the stimulating electrodes are put immediately to the muscle: the motor nerve endings are excited in the first place, and this causes the contractions of the muscle. To observe truly direct stimulation, the motor nerve endings in the muscle must be paralyzed (by the poison curare) or the stimulation must be carried out through microelectrode introduced into the muscle fiber.

The electrical activity of the whole muscle may be recorded by the help of the electrodes put on the muscle or introduced into the muscle by the further amplification of the potentials. This method is called **electromyography**. It is widely used in the sports physiology and medicine to evaluate the state of the locomotor system and for the diagnosis of a number of diseases. The electromyography permits to reveal different disturbances in the innervation of the muscles and in control of their activity by the central nervous system.

The method of recording of the mechanical activity of the muscles is called **myography**.

Isotonic, isometric and auxotonic contractions of muscles are distinguished.

During the **isotonic** contraction the fibers of the muscle are changed, but the tension remains constant.

When both ends of the muscle are fixed motionless, it cannot shorten, and during the contraction the length of the muscle fibers remains constant, but the tension increases. This is called **isometric** contraction.

During the **auxotonic** contraction the fibers of the muscle are changed, and the tension increases.

During the natural motor acts in the whole organism three types of the muscle contractions are observed:

1) isometric contraction (the length of the muscle does not change),

2) concentric contraction (the muscle is shortened),

3) eccentric contraction (the muscle grows longer – for instance, when the load is slowly put down). Although the critical level (Ec), when the spreading potentials in muscle and nerve fibers are generated, is almost the same, the excitability of the muscle fiber is lower than that of nerve fiber. Because the resting potential (Eo) of muscle fiber is about 20 mV more negative (-90 mV) than that of nerve fiber. Therefore, for action potential to be generated, the membrane potential of muscle fiber must be displaced more (∆V=40 mV) than that of nerve fiber (∆V=20 mV).

Consequently, the threshold of stimulation is also higher for the muscle fiber than for the nerve fiber.

The action potential is spread bilaterally from the point of stimulation and does not fade along the fiber.

Each muscle fiber contains several hundreds to several thousands myofibrils, and each myofibril in turn has, lying side - by - side, about 1500 myosin filaments and 3000 actin filaments.

These are large polymerized protein molecules that are responsible for muscle contraction.

The myosin and actin filaments partially interdigitate and thus cause the myofibrils to have alternate light and dark bands. The light bands (I bands) contain only actin filaments and are isotropic to polarized light. The dark bands (A bands) contain the myosin filaments as well as the ends of the actin filaments and are anisotropic to polarized light.

The small projections protrude from the surfaces of the myosin filaments along the entire extent of the filament except in the very center. It is interaction between these crossbridges and the actin filaments that causes contraction.

The ends of the actin filaments are attached to Z disk from which they extend in both directions to interdigitate with the myosin filaments. This Z disk passes from myofibril to myofibril, attaching them to each other all the way across the muscle fiber. Therefore, the entire muscle fiber has light and dark bands, as do the individual myofibrils. These bands give skeletal and cardiac muscle their striated appearance.

The portion of a myofibril (or of the whole muscle fiber) that lies between two successive Z discs is called **a sacromere.**

In the sarcoplasm is the **sarcoplasmic reticulum** which has a special organization. The more rapidly contracting types of muscle have especially extensive sarcoplasmic reticula. In the sarcoplasmic reticulum calcium ions are stored. They are in T tubule systems (triads). If the end of microelectrode is put to the muscle fiber surface in the area of the Z membrane, the I discs begin to shorten in both sides of the membrane and the contraction is spread along Z membrane. Stimulation of other areas of the myofibrils does not cause such effect. Consequently, when the action potential is spread, depolarization of muscle fiber superficial membrane in the area of I discs is the Starting mechanism of the contraction process.

**The muscle contraction** is initiated and executed in the following sequential steps. An action potential travels along a motor nerve to its endings on muscle fibers, and at each ending the nerve secretes the neurotransmitter substance - **acetylcholine.** The acetylcholine acts on a local area of the muscle fiber membrane and opens multiple acetylcholine - gated protein channels in it. Opening of these channels allows large quantities of sodium ions to flow to the interior of the muscle fiber membrane at the point of the nerve terminal. This initiates an action potential in the muscle fiber. The action potential travels along the muscle fiber membrane (in the same way that it travels along nerve membrane), depolarizes it and also travels deeply within the muscle fiber. It causes the sarcoplasmic reticulum to release into the myofibrils large quantities of calcium ions. The calcium ions initiate attractive forces between the actin and myosin filaments, causing them to slide together (contractile process).

A result of repolarization calciuw pump is activated, the calcium ions are pumped back into the sarcoplasmic reticulum (they remain here stored until a new muscle action potential comes along). Muscle contraction ceases.

In the relaxed state of sarcomere the ends of the actin filaments derived from two

successive Z discs barely begin to overlap each other, but completely overlap the myosin filaments. In the contracted state these actin filaments are pulled inward among the myosin filaments and overlap each other to a major extent. Also, the Z discs are pulled by the actin filaments up to the ends of the myosin filaments (these buckle during very intense contraction).

So, muscle contraction occurs by a sliding filament mechanism, that is, the length of the actin and myosin filaments does not change. But when they slide, the I discs disappear and this leads to the diminution of the total length of the muscle.

Sliding of the actin filaments inward among the myosin filaments is caused by mechanical forces generated by the interaction of the crossbridges of the myosin filaments with the actin filaments.

The actin filament is composed of three different protein components : actin, tropomyosin and troponin. Troponin is a complex of three loosely bound protein subunits, each of which plays a specific role in the control of muscular contraction: troponin I has a strong affinity for actin, troponin T - for tropomyosin, troponin C - for calcium ions. The strong affinity of the troponin for calcium ions is believed to initiate the contraction process.

A pure actin filament without the presence of troponin - tropomyosin complex binds strongly with myosin molecules in the presence of magnesium ions and ATP. If the troponin -tropomyosin complex is added to the actin filament, this binding does not take place. Thus, the active sites of the normal actin filament of the relaxed muscle are inhibited or actually physically covered by the troponin - tropomyosin complex, and therefore, they cannot attach to the myosin filaments to cause contraction.

**So,** before contraction can take place, the inhibitory effect of the troponin – tropomyosin complex itself must be inhibited. This takes place in the presence of large quantities of calcium ions. As soon as the actin filament becomes activated by the calcium ions, the heads of the cross - bridges from the myosin filaments immediately become attracted to the active sites of the actin filament, and this causes contraction to occur. The presice manner by which this interaction causes contraction is explained by the “ walk along “ (or “ ratchet”) theory of contraction..

The energy for the contractile process is derived from the high - energy bonds of ATP. The myosin head functions as an ATP ase enzyme. This property allows the head to cleave ATP and to use the energy to energize the contraction process. Greater the amount of work performed by the muscle, greater the quantity of ATP that is cleaved. This is called the Fenn effect. Here also the trigger mechanism functions: part of the energy originated from the cleavage of ATP is expended on the resynthesis of ATP itself.

So, during the muscle contraction the **energy of ATP** is used for the following main processes:

1) work of the sodium - potassium pumps,

2)sliding of the actin and myosin filaments,

3) work of the calcium pump,

4) resynthesis of ATP.

The contraction process is followed by the formation of heat. The **thermogenesis** in muscle is divided into two phases:

**1)** The initial heat production - from the moment when excitation of the muscle begins to the end of the contraction, including the relaxation. This phase is 1000 times shorter than the second phase and the heat that is produced consists of three parts, corresponding to the phases of muscle contraction: the heat of activation, the heat of contraction and the heat of relaxation.

**2)** The delayed or recovery heat production - occurs during few minutes after the muscle is relaxed. It is connected with the chemical processes, which provide the resynthesis of ATP.

**The smooth muscles** are in the internal organs, blood vessels and skin. They are able to perform relatively slow and protracted tonic movements.

The relatively slow, more often rhythmical contractions of the smooth muscles of hollow organs (stomach, intenstine, urinary bladder, bile cyst etc.) walls provide the shifts of their contents (for instance, pendular and peristaltic movements of the intestine).

The protracted tonic contractions of sphincters smooth muscles prevent the contents of hollow organs to go out. This secures accumulation of bile in bile cyst, of urine - in urinary bladder and so forth.

Tonic contractions of the vascular wall smooth muscles (especially those of arteries and arterioles) regulate size of the lumen of blood vessels and in this way- the level of blood presssure and blood supply of organs.

Smooth muscles are composed of far smaller fibers (2-5 micrometers in diameter and 20 -500 micrometers in length) in contrast to the skeletal muscle fibers (which are 20 times larger in diameter and thousands times longer). Nevertheless, many of the principles of contraction apply to smooth muscle the same as to skeletal muscle. And though the internal physical arrangement of smooth muscle fibers is entirely different, but essentially the same attractive forces between myosin and actin filaments cause contraction in smooth muscle as in skeletal muscle.

The smooth muscle of each organ is distinctive from that of most other organs in several different ways (physical dimensions, organization into bundles or sheets, response to different types of stimuli, characteristics of innervation, function).

Generally, smooth muscles can be divided into **two major types**: multiunit and single - unit smooth muscles.

**Multiunit** smooth muscle is composed of discrete smooth muscle fibers each of which operates entirely independently of the others and is often innervated by a single nerve ending, as occurs for skeletal muscle fibers. Therefore, each fiber can contract independently of the others, and their control is exerted mainly by nerve signals. This is in contrast to a major share of the control of visceral smooth muscle by non - nervous stimuli. The smooth muscle fibers of the ciliary muscle of the eye, the iris of the eye, the piloerector muscles that cause erection of the hairs when stimulated by the sympathetic nervous system, are of multiunit type of mooth muscle.

The term “single - unit” does not mean single muscle fiber, but a whole mass of hundreds to millions of muscle fibers that contract together as a single unit. The fibers are aggregated into sheets or bundles, and their cell membranes are adherent to each other at multiple points so that force generated in one muscle fiber can be transmitted to the next. The cell membranes are joined by many gap junctions through which ions can flow freely from one cell to the next so that action potentials travel from one fiber to the next and cause the muscle fibers all to contract together.

Such muscle is found in the walls of most viscera of the body (the gut, bile ducts, ureters, uterus, many blood vessels), and therefore, it is also called visceral smooth muscle. Because of interconnections among fibers this type of smooth muscle is also called **syncytial** smooth muscle.

Unlike the most skeletal muscles, most smooth muscles provide prolonged tonic

contraction., often lasting hours or even days. The rapidity of cycling of the cross- bridges (their attachment to actin, then release and attachment again for the next cycle) is much slower in smooth muscle than in skeletal muscle (as little as 1/ 10 to 1/ 300 the frequency in skeletal muscle).

Only 1/10 to 1/300 as much energy is required to sustain the same tension of contraction in smooth muscle as in skeletal muscle. This economy of energy is exceedingly important, because organs such as intestines, the urinary bladder, the gallbladder and others must maintain tonic muscle contraction on a daily basis.

A typical smooth muscle tissue begins to contract 50 -100 milliseconds after it is excited, reaches full contraction approximately 0.5 second later and then declines in contractile force in another 1-2 seconds (a total contraction time - 1-3 seconds). This is about 30 times as longs as a single contraction of an average skeletal muscle. But contractions of some types can be as short as 0.2 second or as long as 30 seconds.

The maximum force of contraction of smooth muscle is often even greater than that of

skeletal muscle - as great as 4-6 kg/cm2 in comparison with 3-4 kilograms for skeletal muscle.

Characteristic of smooth muscle is its ability to shorten a far greater percentage of its length (more than two thirds its stretched length) than can skeletal muscle (only about one third its stretched length) while still maintaining almost full force of contraction. This allows the gut, bladder, blood vessels and other internal bodily structures to change their lumen diameters from very large down to almost zero.

Once smooth muscle has developed full contraction the degree of activation of the muscle can be reduced to far less than the initial level and yet the muscle will still maintain its full strength of contraction.

The energy consumed to maintain contraction is sometimes as little as 1/300 the energy required for comparable skeletal muscle continuous contraction. This is called the “latch” mechanism.

The importance of the latch mechanism is that it can maintain prolonged tonic contraction in smooth muscle for hours and hours with very little use of energy. Also, very little excitatory signal is required from nerve fibers or hormonal sources.

Smooth muscle, especially the visceral type of smooth muscle in many hollow organs, is able to return nearly to its original force of contraction seconds or minutes after it has been elongated or shortened. For instance, a sudden increase in volume of fluid in the urinary bladder causes an immediate large increase in pressure in the bladder. But during the next 15 seconds to a minute or so, despite continued stretch of the bladder wall, the pressure returns back to the original level. When the volume increases by another step, the same effect occurs again. If the volume is suddenly decreased, the pressure falls very low at first, but then returns in another few seconds or minutes back to the original level.

This phenomenon is called **stress- relaxation**.

It allows a hollow organ to maintain approximately the same amount of pressure inside its lumen regardless of length of the muscle fibers.

Ability of smooth muscle to preserve the length given by the stretch without changing the tension, is called the ***plasticity*.** So, the plasticity of smooth muscle provides the normal activity of hollow organs.

Because while the organ is being filled, the pressure in it does not increase significantly and the reflex for its emptying does not occur before the proper time.

Like the skeletal muscle, the initiating event in most smooth muscle contractions is an increase in intracellular calcium ions. But smooth muscle does not contain troponin, the regulatory protein that is activated by calcium ions to cause skeletal muscle contraction. Instead, smooth muscle cells contain large quantities of another regulatory protein- ***calmodulin***. The calcium ions bind with calmodulin. The calmodulin - calcium combination joins with myosin kinase (a phosphorylating enzyme) and activates it. In response to the myosin kinase one of the light chains of each myosin head, called the regulatory chain, becomes phosphorylated. As a result, the head has the capability of binding with the actin filament and proceeding through the entire cycling process, thus causing muscle contraction. When the calcium ion concentration falls below a critical level, all these processes automatically reverse except for the phosphorylation of the myosin head. Reversal of this requires another enzyme, myosin phosphatase, which splits the phosphate from the regulatory light chain. Then, the cycling stops and the contraction ceases.

Unlike skeletal muscle, which is activated exclusively by the nervous system, smooth muscle can be stimulated to contract also by hormonal stimulation and in several other ways. Because the smooth muscle membrane contains many different types of receptor proteins that can initiate the contractile process. Still other receptor proteins inhibit smooth muscle contraction which is another difference from skeletal muscle.

Neuromuscular junctions of the type that are on skeletal muscle fibers are not found in smooth muscle. The nerve fibers that innervate smooth muscle generally branch diffusely on top of a sheet of muscle fibers. In most instances these fibers do not make direct contact with the smooth muscle fibers at all but form ***diffuse junctions*** that secrete their transmitter substance into the cells. If there are many layers of muscle cells, the nerve fibers often innervate only the outer layer, and the muscle excitation travels to the inner layers by action potential conduction in the muscle mass or by subsequent diffusion of the transmitter substance.

The axons innervating smooth muscle fibers also do not have typical branching end-feet of the type in the motor end-plate on skeletal muscle fibers. Instead, most of the terminal axons have multiple varicosities distributed along their axes. At these points the Schwann cells are interrupted so that transmitter substance can be secreted through the walls of the varicosities, in which are vesicles similar to those in the skeletal muscle end-plate containing transmitter substance. But in contrast to those vesicles which contain only acetylcholine, the vesicles of the nerve fiber endings innervating smooth muscles, contain acetylcholine in some fibers and norepinephrine in others.

In a few instances (especially in the multiunit type of smooth muscle) the varicosities lie directly on the muscle fiber membrane with a separation from it of the same width as the synaptic cleft in the skeletal muscle junction. These contact junctions function in much the same way as the skeletal muscle neuromuscular junction, and the latent period of contraction of these smooth muscle fibers is considerably shorter than of those stimulated by the diffuse junctions.

*Acetylcholine* is an excitatory transmitter substance for smooth muscle fibers in some organs, but an inhibitory substance in other organs. When acetylcholine excites a muscle fiber, *norepinephrine* inhibits it and vice versa.

It is the type of receptor that determines whether the smooth muscle will be inhibited or excited and also determines which of the two transmitters will be effective in causing this influence.

In the resting state *the membrane potential* in smooth muscles is usually - 50 to - 60mV, that is, about 30 millivolts less negative than in skeletal muscles.

In single - unit smooth muscle *action potentials* occur in the same way that in skeletal muscle. Action potentials of *visceral* smooth muscle occur in two different forms: spike potential and action potential *with plateau*.

Typical spike action potentials, such as those in skeletal muscle, occur in most types of single - unit smooth muscle. They can be elicited in many ways (electrical stimulation, action of hormones or transmitter substances, or as a result of spontaneous generation in the muscle fiber itself).

The onset of action potential with plateau is similar of that of spike potential. But instead of rapid repolarization of the muscle fiber membrane, the repolarization is delayed for several hundred to several thousand milliseconds. The plateau can account for the prolonged periods of contraction in some types of smooth muscle (ureter, uterus, some vascular smooth muscle).

The smooth muscle cell membrane has far more voltage-gated calcium channels than does skeletal muscle, but very few voltage-gated sodium channels. Therefore, sodium participates very little if any in generation of the action potential in most smooth muscle. The flow of calcium ions to the interior of the fiber is mainly responsible for the action potential. But calcium channels open many times more slowly than do sodium channels and this accounts in large measure for the slow action potentials of smooth muscle fibers.

This same calcium acts directly on the smooth muscle contractile mechanism to cause contraction. So, the calcium performs two tasks at once. The special feature of smooth muscles, distinguishing them from skeletal muscles, is the ability of spontaneous automatic activity. The spontaneous contractions may be observed in the

smooth muscle of the stomach, intestine, bile cyst, ureters etc. The automatic activity of the smooth muscles is regulated by the nervous elements which are in the walls of the organs.

So, some smooth muscles are self – excitatory, that is, action potentials arise within the smooth muscle itself without an extrinsic stimulus. This is usually associated with a basic slow wave rhythm of the membrane potential. It is a local property of the smooth muscle fibers.

The slow waves themselves cannot cause muscle contraction, but when the potential of the slow wave rises above the level of approximately – 35 mV, an action potential develops and spreads over the muscle mass, and then contraction occurs. This effect can promote a series of rhythmical contractions of the smooth muscle mass. Therefore, the slow waves are called also pacemaker waves. For instance, this type of activity controls the rhythmical contractions of the gut.

When visceral smooth muscle is stretched sufficiently, spontaneous action potentials are generated, which result from a combination of the normal slow wave potentials plus a decrease in the negativity of the membrane potential caused by the stretch itself. This response of stretch allows a hollow organ that is excessively stretched to contract automatically and to resist the stretch. For example, when the gut is overstretched by intestinal contents, a local automatic contraction sets up a peristaltic wave that moves the contents away from the excessively stretched intestine.

*Multiunit* smooth muscle fibers contract mainly in response to nerve stimuli. Transmitter substances (acetylcholine or norepinephrine) cause depolarization of the smooth muscle membrane, and this local depolarization, called the “junctional potential”, itself spreads “electrotonically” over the entire fiber. It is all that is needed to cause the muscle contraction. Action potentials most often do not develop (because the fibers are too small to generate an action potential).

Half or more of all smooth muscle contraction is initiated not by action potentials but by stimulatory factors acting directly on the smooth muscle contractile machinery. The two types of nonnervous and nonaction potential stimulating factors are local tissue factors and various hormones.

The smaller of blood vessels have little or no nervous supply. But the smooth muscle is highly cintractile, responding rapidly to changes in local conditions in the surroundding interstitial fluid. In this way, a powerful local feedback control system controls the blood flow to the local tissue area. Some of the specific control factors causing vasodilatation are: lack of oxygen in the local tissues, excess of carbon dioxide, increased hydrogen ion concentration. Local vasodilatation is caused also by adenosine, lactic acid, increased potassium ions, diminished calcium ion concentration, decreased body temperature.

Most of the hormones affect smooth muscle contraction at least to some degree, some have very profound effects. More important hormones that affect contraction are: norepinephrine, epinephrine, acetylcholine, angiotensin, vasopressin, oxytocin, serotonin, histamine.

When the muscle cell membrane contains hormone-gated excitatory receptors for the respective hormone, it causes contraction of smooth muscle. If the membrane contains inhibiting receptors, the hormone causes inhibition.

Some hormone receptors in the smooth muscle membrane open sodium or calcium ion channels and depolarize the membrane the same as nerve stimulation. Occasionally, action potentials result, or rhythmical action potentials, that are already occurring, may be enhanced.

Activation of other membrane receptors inhibits contraction by closing sodium and calcium channels or by opening potassium channels, in both instances increasing the degree of negativity inside the muscle cell (hyperpolarization).

Sometimes contraction or inhibition is initiated by hormones without causing any change at all in the membrane potential. For instance, the hormone activates a membrane receptor that causes an internal change in the muscle fiber (release of calcium ions from the sarcoplasmic reticulum). Or to inhibit contraction other receptor mechanisms activate in the cell membrane the enzymes that cause formation of second messengers (c AMP, c GMP). These indirectly promote the inhibition of contraction.

The smooth muscles are innervated by the parasympathetic and sympathetic nerves, which exercise opposite influences on the muscle fibers.

**Motor Unit. Skeletal Muscle Tone. Solitary Contraction of the Muscle and Tetanization. Power and Work of Muscle. Muscle Fatigue**

Each motor nerve fiber is the outgrowth (process) of the motoneuron which is situated in the anterior horn of the spinal cord or in the motor nucleus of cranial nerve. Such fiber innervates not one, but many muscle fibers, the number depending on the type of the muscle. Motor nerve fiber together with all the muscle fibers innervated by this single motor nerve fiber, are called motor unit.

The muscle fibers in each motor unit are not all bunched together in a muscle but are spread out in the muscle in microbundles of 3-15 fibers. Therefore, these lie among similar microbundles of other motor units. This interdigitation allows the separate motor units to contract in support of each other rather than entirely as individual segments.

An average figure for all the muscles of the body can be considered to be about 100 muscle fibers to the motor unit. But small muscles that react rapidly, perform exact movements and whose control also must be exact, have few muscle fibers in each motor unit. Whereas the large muscles that do not require very fine control may have several hundred muscle fibers in a motor unit. For instance, eyeball have less than 10 muscle fibers in a motor unit, but gastrocnemius muscle - several hundred muscle fibers.

When the action potential is spread along the motor nerve fiber, all the muscle fibers of the motor unit are excited almost simultaneously.

Every muscle of the body is composed of a mixture of fast and slow muscle fibers, with still other fibers graduated between these two extremes. The muscles that react very rapidly are composed mainly of the fast fibers with only small numbers of the slow variety. Conversely, the muscles that respond slowly but with prolonged contraction are composed mainly of slow fibers.

Fast fibers are much larger fibers for great strength of contraction. Lack of red (myoglobin) gives tha name white muscle. The slow fibers are smaller fibers also innervated by smaller nerve fibers. The myoglobin gives the slow muscle a reddish appearance.

The fast fibers are adapted for very rapid and powerful muscle contractions, such as for jumping or for short - distance powerful running. The slow fibers are adapted for prolonged, continued muscle activity, such as support of the body against gravity, long-continuing athletic events, marathon races.

Even when muscles are at rest, they do not relax completely, and a certain amount of tautness remains This is called muscle tone. Skeletal muscle tone results entirely from nerve impulses coming from the spinal cord. These in turn are controlled partly by impulses transmitted from the brain to the appropriate anterior motoneurons and partly by impulses that originate in muscle spindles located in the muscle itself.

Dissection of the posterior roots by which sensory impulses from muscle spindles come to the spinal cord, causes complete relaxation of the muscle. This fact proves the reflex nature of the skeletal muscle tone.

In human being the muscle tone can be regulated at will within certain limits: it is possible to relax the muscles almost completely or tauten them.

Irritation of the muscle or the motor nerve that innervates it by single stimulus causes the solitary contraction of the muscle. Although duration of the solitary contraction differs in wide limits, on the average it lasts 0.11-0.12 seconds. Three phases of the solitary contraction are distinguished: 1)the latent period (0.01 sec), 2) the period of contraction (0.04 - 0.05 sec), 3) the period of relaxation (0.05 - 0.06 sec).

The contraction of muscle fiber begins already during the ascending phase of the action potential when the spreading action potential reaches certain threshold level. Duration of the contraction is thousand times more than that of action potential.

Amplitude of the solitary contraction of the isolated muscle fiber does not depend on the strength of the stimulation, that is, it obeys “all- or nothing” principle. But the contraction of the whole muscle (which consists of many fibers) depends on the power of the stimulation. Its threshold power causes contraction of several fibers. Stronger the stimulation - more fibers are excited, until the maximal contraction is reached.

If the muscle is irritated by two stimuli in quick succession, summation occurs and its amplitude is greater than that of maximal contraction during the single irritation.

Two types of the summation are distinguished: 1) if the second stimulation is caused when the muscle already began to relax, the summation will have two peaks, 2) if the second stimulation is caused during the contraction, the summation will have only one peak.

When the rhythmical stimuli are applied to the muscle, their effects are summarized and tetanization occurs. When the frequency of the stimulation is within 10-20 stimuli in 1 sec, the denticulated tetanus is observed. More frequent (more than 30-40 in 1 sec) stimuli cause the smooth tetanus.

During the tetanization contractile responses of the muscle are summarized, but not its electrical reactions (action potentials).

Amplitude of tetanus may be several times greater than that of maximal solitary contraction.

The power of muscle is determined by the maximum load which the muscle is able to lift or the maximum tension which it can develop in the condition of isometric contraction. This power is very great. For instance, dog can lift by the muscles of jaws the load 8.3 times greater than its own body mass.

The solitary muscle fiber is able to develop the tension up to 100-200 mg. Considering that the total number of muscle fibers in human body is about 15-30 millions, they could develop the tension equal to 20-30 tons, pulling simultaneously in one direction.

If the other conditions are equal, power of a muscle depends on its cross-section. Greater the physiological cross-section of the muscle, that is, the sum of transverse section of all its fibers, larger the maximum load that the muscle is able to lift.

The physiological and geometrical cross-sections are the same in the muscles with the longitudianl fibers. But the physiological cross-section of the muscle with the oblique fibers is more times greater than its geometrical cros-section. Therefore, these muscles are more powerful than those with longitudinal fibers.

To calculate the absolute power of the muscle, the maximum load that the muscle is able to lift, is divided by its physiological cross-section. The absolute power of the human gastrocnemius muscle is 5.9 kg/cm2, that of the three-headed brachial muscle - 16.8 kg/cm2. But the absolute power of the smooth muscles is much lower - 1 kg/cm2.

When a muscle contracts against a load, it performs work, which may be defined by the following equation:

W = L●D

In this equation W is the work output, L - the load, D - the distance of movement against the load.

If the load is gradually increased, the distance is decreased until the moment comes when the muscle cannot lift the next load, that is, the distance becomes zero.

When a muscle contracts and does not lift a load, its work is zero. Increase of the load causes increase of the work till certain limit after which the load decreases again and at last becomes zero (when the muscle cannot lift the next load).

So, the maximum work of the muscle is performed when it lifts the average loads. This is called the rule of the average loads.

Prolonged and strong contraction of a muscle leads to the muscle fatigue, that is, temporary decrease of capacity for work.

If the isolated muscle to which a small load is suspended, is irritated by the rhythmical electrical stimuli, the amplitude of its contractions gradually decreases down to zero. Recording of the contractions that is registered during such experiment, is called the curve of fatigue.

During the muscle fatigue besides decrease of the amplitude of contractions, the latent period and the relaxation period are lengthened.

The muscle fatigue in the human organism is studied by the help of ergograph.

The following experiment demonstrates that the fatigue occurs in the first place in the nerve centers, then in the neuromuscular synapses and at last in the muscle itself. The afferent nerve is stimulated and the muscle contraction is observed until the muscle ceases to reply to the stimuli. Then the efferent nerve is stimulated and the muscle begins to contract again. This means that it was the nerve center where the fatigue ocurred. When the muscle ceases to react to the stimulations, this time the electrodes are put immediately on the muscle, and it contracts. Consequently, after the nerve center (the central synapses) the fatigue occured in the neuromuscular synapses.

I. M. Sechenov established that the capacity for work of the tired muscles of the hand is recovered more rapidly, if during the rest the work is continued by the other hand. Sechenov regarded this effect of such active rest as the proof of the supposition that the fatigue was developed, in the first place, in nerve centers.

Role of the cerebral cortex in the muscle fatigue is demonstrated on the persons under the hypnosis. When such a person is suggested that he is performing a hard work, the fatigue develops rapidly, though the person is sitting still.

The fatigue of the isolated muscle is caused mainly by two factors: 1) oppressive effect of the metabolic products that are accumulated during the contraction (lactic acid, phosphoric acid etc.) on the muscle fibers capacity for work; 2) gradual depletion of reserves (glycogen) of the muscle.

But the fatigue of the muscles in the whole organism is more intricate process and depends on many factors. The immidiate cause of the fatigue is the change of the physiological properties of the muscle, such as excitability, conduction, lability and so forth.

The systematic intensive work of muscle causes increase of the muscle tissue mass. This is called work hypertrophy of the muscle. The power of the hypertrophied muscle and velocity of its contractions are increased.

In trained persons with many hypertrophied muscles the musculature may come to 50% of the body mass (instead of normal 35-40%).

If a muscle does not perform its normal work for a long time, such inactivity causes atrophy of the muscle. The special type of muscular atrophy is observed when the muscle is denervated.

**LECTURE 3**

**Conduction of Impulses in Unmyelinated Nerve Fibers. Saltatory Conduction in Myelinated Nerve Fibers. Laws of Transmission of Excitation. Classification of Nerve Fibers. Neuromuscular Transmission. Physiology of Synapses. Ephapses. Pessimal Inhibition. Parabiosis. Relative Indefatigability of Nerve**

An action potential elicited at any point of an excitable membrane, excites adjacent portions of the membrane, resulting in propagation of action potential. In the nerve and muscle fibers the action potential is transmitted by the help of the local currents.

Transmission of nerve impulses is the specialized function of nerve fibers. The nerve fibers are divided into two groups: 1) myelinated nerve fibers, 2) unmyelinated nerve fibers. The small fibers are unmyelinated, and the large fibers are myelinated. The average nerve trunk contains about twice as many unmyelinated fibers than myelinated fibers.

In the unmyelinated fibers, as well as in muscle fibers, between the polarized (excited) areas of the membrane and the adjacent resting membrane areas a “local circuit” of current flow occurs. It causes depolarization of the adjacent area. The depolarization reaches the critical level and evokes the action potential. Then these newly depolarized areas cause local circuits of current flow still farther along the membrane causing progressively more and more depolarization. Thus, the depolarization process travels along the entire extent of the fiber.

Transmission of depolarization process along a nerve or muscle fiber is called a nerve or muscle impulse.

An excitable membrane has no single direction of propagation, and the action potential can travel in both directions away from the stimulus - and even along all branches of a nerve fiber, until the entire membrane has become depolarized.

The theory explaining transmission of excitation was confirmed in many experiments. For instance, if the area of the nerve fiber is placed into the medium deprived of ions (saccharose solution), transmission of excitation through this area ceases completely.

The velocity of the transmission depends also on the internal resistance of the fiber. Greater the diameter of the fiber - lower the resistance and more the velocity of the transmission.

Once an action potential has been elicited at any point on the membrane of a normal fiber, the depolarization process will travel over the entire membrane if conditions are right, or it might not travel at all if conditions are not right. This is called the all-or-nothing principle. The all-ornothing principle applies to all normal excitable tissues.

If an action potential will reach a point on the membrane at which it does not generate sufficient voltage to stimulate the next area, the spread if depolarization stops. Therefore, for continued propagation of an impulse to occur, the ratio of action potential to threshold for excitation must at all times be greater than 1. This is called the safety factor for propagation.

Spreading action potential is a strong stimulus for the resting areas of the membrane. Its safety factor is equal to 5-6. Therefore, to blockade the transmission of the nerve impulse, it is necessary to increase powerfully the polarization threshold of the nerve fiber or significantly decrease the amplitude of the action potential. Local anesthetic preparations (novocain, cocaine) cause both of these changes simultaneously.

So, in muscular and unmyelinated nerve fibers excitation is realized continuously from "point to point”, that is, every point of the fiber takes part in the transmission of the action potential and is excited.

But in myelinated fibers this is impossible. Because ions cannot flow significantly through the thick myelin sheath of myelinated nerves. They can flow with considerable ease through the nodes of Ranvier. Therefore, action potentials can occur only at the nodes, and they are conducted from node to node. This is called saltatory conduction. That is, electrical current flows through the surrounding extracellular fluids and also through the axoplasm from node to node, exciting successive nodes one after another. Thus, the nerve impulse jumps down the fiber, which is the origin of the term “saltatory”.

Saltatory conduction has two advantages:

1. Causing the depolarization process to jump long intervals along the axis of the nerve fiber, this mechanism increases the velocity of nerve transmission in myelinated fibers from 5 to 50 times.
2. Since only the nodes depolarize, the energy is conserved for the axon, allowing hundred times smaller loss of ions than would otherwise be neccessary and therefore requiring little extra metabolism for re-establishing the sodium and potassium concentration differences across the membrane after a series of nerve impulses.

There are three laws of transmission of excitation:

1. The law of the physiological safety.
2. The law of the isolated conduction.
3. The law of the two-way conduction.

Since the transmission of nerve impulses is the physiological function of the fiber, to conduct impulses the fiber must be intact not only anatomically, but also from the physiological point of view. Therefore, conduction of the fiber is disturbed not only when it is cut or its surface membrane is damaged. Even when the fiber is intact physically, its ligation or excessive stretching, cooling or warming, influence of the local anesthetics, as well as the stable depolarization, cause disturbance of the conduction, and nerve impulses are not transmitted.

To prove the law of the physiological safety the neuromuscular preparation is made and the nerve is stimulated by the electrical current. The muscle contracts. Then between the electrodes and muscle the nerve is ligated or a cotton wool moistened in ammonia is put on it. Further stimulations do not cause contraction of the muscle.

In muscular and nerve fibers impulses are spread separately and do not pass into neighbouring fibers. This law of the isolated conduction is very important. Because peripheral nerves contain many different fibers, and in each of them impulses are transmitted separately along the fiber only to the cells that are innervated by this fiber. Otherwise, the normal functioning of the peripheral organs and tissues would be impossible.

This law may be proved on the skeletal muscle that is innervated by the mixed nerve. If one of the spinal nerve roots is stimulated, not the whole muscle is contracted, but only the fibers that are innervated by this root.

The law of the isolated conduction may be demonstrated also by the following way. In the middle of the muscle triangular transverse cut is made. When one side of the muscle is stimulated and contracts, in other side from the cut contraction is observed only in the intact fibers. This means that the excitation does not pass from them to the neighbouring fibers that are cut in the middle.

When the nerve fiber is stimulated, the excitation is transmitted in both centripetal and centrifugal directions. This is called the law of the two-way conduction. It can be proved and demonstrated by different ways. For instance, two pairs of recording electrodes are applied to the nerve, and between them the nerve is stimulated. In both sides from the stimulating electrodes the action potential is recorded.

The electrical response of the whole nerve to the stimulation is the algebraical sum of action potentials of its separate fibers. If several pairs of recording electrodes are placed on the nerve in different distances from the stimulating electrodes and the nerve is stimulated, all of them will record the action potential. But farther from the stimulating electrodes, the recorded potentials will be more divided. Because the velocity of conduction in different fibers is not the same, and therefore, the excitation does not reach each pair of recording electrodes simultaneously by all fibers. Farther from the point of stimulation- longer is the time interval between the impulses transmitted by the rapid and slow fibers.

The velocity of conduction in nerve fibers varies from as little as 0.5 m/sec in very small unmyelinated fibers to as high as 100 m/sec and more in very large myelinated fibers. The velocity increases depending on the fiber diameter in myelinated nerve fibers and depending on the square root of fiber diameter in unmyelinated fibers.

Taking into consideration the velocity of conduction, duration of different phases of the action potential and structure of the nerve fibers, they are divided into three groups: A, B and C type fibers.

1. type fibers are divided into 4 subgroups: A, A, A, A. They are myelinated fibers. The thickest are A fibers (12-22 mcm) with maximal velocity of conduction (70-120m/sec). These are mainly the motor fibers and partly the fibers transmitting the excitation from receptors of muscles to the corresponding nerve centers. Diameter of the fibers in other subgroups (A, A, A) is smaller, the velocity of conduction is less, but the duration of action potential is longer. These are mainly sensory fibers transmitting excitation from different receptors to the central nervous system.
2. type fibers (diameter - 1 - 3.5 mcm, velocity of conduction - 3 - 18 m/sec) are myelinated fibers, mainly the preganglionic fibers of the vegetative nervous system.
3. type fibers are unmyelinated fibers of the smallest diameter (0.5 - 2 mcm) and of the least velocity of conduction (0.5 - 3 m/sec). These are mainly the postganglionic fibers of the vegetative nervous system, and also the fibers transmitting excitation from the pain receptors and some thermal, cold and pressure receptors to the central nervous system.

Each nerve fiber branches many times and stimulates from three to several hundred skeletal muscle fibers. The nerve ending makes a junction called the neuromuscular junction (synapse), with the muscle fiber near its midpoint, and the action potential in the fiber travels in both directions toward the muscle fiber ends (with the exception of about 2% of the muscle fibers).

The nerve fiber branches at its end to form a complex of branching nerve terminals, which invaginate into the muscle fiber but lie entirely outside the muscle fiber plasma membrane. The entire structure is called the motor end - plate. It is covered by one or more Schwann cells that insulate it from the surrounding fluids.

Invagination of the membrane is called the synaptic gutter or synaptic through, and the space between the terminal (presynaptic membrane) and the fiber membrane (postsynaptic membrane) is called the synaptic cleft. The synaptic cleft is 20-30 monometers wide and is occupied by a basal lamina which is a thin layer of spongy reticular fibers through which diffuses extracellular fluid. At the bottom of the gutter there are numerous smaller folds of the muscle membrane called subneural clefts, which greatly increase the surface area at which the synaptic transmitter can act.

In the axon terminal there are many mitochondria that supply energy mainly for synthesis of the excitatory transmitter acetylcholine that, in turn, excites the muscle fiber. The acetylcholine is synthesized in the cytoplasm of the terminal but is rapidly absorbed into many small synaptic vesicles, approximately 300000 of which are normally in the terminals of a single end-plate. Attached to the matrix of the basal lamina are large quantities of the enzyme acetylcholinesterase (which is capable of destroying acetylcholine).

When a nerve impulse reaches the neuromuscular junction, about 300 vesicles of acetylcholine are released from the terminals into the synaptic trough.

On the inside surface of the neural membrane are linear dense bars. To each side of each dense bar are protein particles that penetrate the membrane, believed to be voltage-gated calcium channels. When the action potential spreads over the terminal, these channels open and allow large quantities of calcium to diffuse to the interior of the terminal. The calcium ions in turn exert an attractive influence on the acetylcholine vesicles, drawing them to the neural membrane adjacent to the dense bars. Some of the vesicles fuse with the neural membrane and empty their acetylcholine into the synaptic trough by the process of exocytosis.

In the muscle membrane there are many acetylcholine receptors, which are acetylcholinegated ion channels, located near the mouth of the subneural clefts lying immediately below the dense bar areas, where the acetylcholine vesicles empty into the synaptic trough.

The channel remains constricted until acetylcholine attaches to one of its subunits. This causes a conformational change that opens the channel. Diameter of the acetylcholine channel is large enough to allow all the important positive ions (sodium, potassium and calcium) to move easily through the opening. But negative (chloride) ions do not pass through because of strong negative charges in the mouth of the channel.

The net effect of opening the acetylcholine-gated channels is to allow large numbers of sodium ions to pour to the inside of the fiber, carrying with them large numbers of positive charges. This creates a local potential inside the fiber called end-plate potential that initiates an action potential at the muscle membrane and thus causes muscle contraction.

The acetylcholine, once released into the synaptic trough,continues to activate the acetylcholine receptors as long as it persists in the trough.But it is rapidly removed:most of the acetylcholine is destroyed by the acetylcholinesterase and its small amount diffuses out of the synaptic trough.

Small amounts of acetylcholine are secreted by the motor nerve endings not only during the excitation, but also in the resting state.They cause weak depolarization of short duration in the muscle fiber postsynaptic membrane.Its amplitude is 50-80 times smaller than that of end – plate potential, and therefore, such depolarization is called the miniature potential.

Artificial stimulation of the nerve fiber at rates greater than 100 times per second for several minutes diminishes the number of vesicles of acetylcholine released with each impulse so much that impulses fail to pass into the muscle fiber. This is fatigue of the neuromuscular junction, and it is similar to fatigue of the synapse in the central nervous system. Under normal functioning conditions fatigue of the neuromuscular junction occurs very rarely (at the most exhausting levels of muscular activity).

Many different compounds(methacholine, carbachol, nicotine)have the same effect on the muscle fiber as does acetylcholine.But they are not destroyed by cholinesterase or are destroyed very slowly, so that when once applied to the muscle fiber the action persists for many minutes to several hours. These drugs work by causing localized areas of depolarization at the motor end- plate, where the acetylcholine receptors are located. Then, every time the muscle fiber becomes repolarized elsewhere, these depolarized areas, by virtue of their leaking ions, cause new action potentials, thereby causing a state of spasm.

The curariform drugs prevent passage of impulses from the end-plate into the muscle. For instance, D-tubocurarine affects the membrane by competing with acetylcholine for the recoptor sites of the membrane, so that the acetylcholine cannot increase the permeability of the acetylcholine channels sufficiently to initiate a depolarization wave.

Some drugs (neostigmine, physostigmine, diisopropyl fluorophosphate) inactivate acetylcholinesterase so that the cholinesterase in the synapses will not hydrolyse the acetylcholine rebased at the end-plate.As a result,the amount of acetylcholine increases under the influence of successive nerve impulses so that its extreme quantities can accumulate and then repetitively stimulate the muscle fiber. This causes muscular spasm when even a few nerve impulses reach the muscle.

Two main characteristics of the synapses are:

**1.**The one- way conduction (unlike the two-way conduction in the nerve and muscle fibers)of the excitation- because the nerve endind products the mediator which excites the postsynaptic membrane,but the nerve fiber does not produce the mediator and cannot excite the presynaptic membrane through the synaptic cleft.

**2.**The synaptic delay of the conduction of the excitation-this is connected with the processes occurring in the synapse (the diffusion of the mediator from the presynaptic membrane to the postsynaptic membrane and so forth)which require the certain time.

These characteristics of synapses are absent in ephapses. Ephapse is the synapse with the electrical conduction of the signals. The mechanism of the ephaptic conduction is similar to that of spreading of the depolarization wave along the nerve fiber. The structural base of the ephapse is highly permeable contact in the cleft providing the electrical connection between the elements. Unlike the chemical synapse, in ephapse the post-synaptic current generator is in the presynaptic membrane, where the action potential occurs and then it spreads to the postsynaptic membrane by the electrical way. As distinct from the chemical synapses, the ephapses are able to conduct mainly the exciting potentials.

Ephapses are found in the epithelial, glandular tissues, smooth muscles, heart muscle, central nervous system. In some interneuronal synapses electrical and chemical conductions are realized simultaneously.

Increase of stimulation frequency in certain limits causes increase of the height of the tetanic contraction and at some optimal frequency the tetanus reaches the maximal size.But the further increase of frequency leads to the sharp weakining of the tetanic contraction and at the certain pessimal frequency the muscle is almost completely relaxed, though the stimulation is continued. This phenomenon is called the pessimal inhibition or Vvedensky’s inhibition.

For instance, the frequency of stimulation about 40 stimuli per 1 second is optimal for neuromuscular preparation of frog and causes the smooth tetanic contraction of maximal height.But increase of frequency up to 120 stimuli per 1 second causes the sudden relaxation of the muscle, that is, this frequency is pessimal for that preparation.

The stable depolarization of the postsynaptic membrane and block of conduction caused by too frequent impulses form the basis of the pessimal inhibition.

Role of acetylcholine in development of the pessimal inhibition is confirmed by the fact that it can be caused by the poisons which inactivate the cholinesterase and promote accumulation of the acetylcholine in synapse.

Causing alteration in the nerve by the way of intoxication (chemical agents such as cocaine, chloroform, phenol) or damage(powerful faradic current, mechanical injury), Vvedensky observed sharp decrease of its lability. Then conduction of the rhythmical impulses was blocked.

To emphasize the disturbance of vital activity, he called such state of lowered lability **parabiosis** (from Gr. para- beside, bios- life).

Parabiosis is a reversible process.But if the factor that causes it, becomes exceedingly powerful, the death of the tissue may occur.

The parabiotic changes occur in three consecutive stages:

**1.**Provisory(equalizing) phase- the capasity of the nerve to transmit rhythmic impulses is reduced with stimulation of any strenth; but the reduction has a greater influence on the effect of frequent(strong)stimuli than on those of infrequent(moderate strengh),so that the effect of both is almost equal.

**2.**Paradoxical phase-strong impulses emanating from normal points of the nerve are not conveyed to the muscle through the narcotized portion, or cause only initial contractions, whereas very moderaty stimuli can produce quite considerable tetanic contraction.Thus, response to the strong stimlation is weaker than that to weak stimulation.

**3.** Inhibitory phase- the nerve completely loses capacity to transmit impulses of any intensity.

The mechanism of parabiosis is explaied in the following way.

With stimuli of slow rhythm(or low strength)every impulse arising in the intact portion of a nerve is conducted through the parabiotic portion because by the time it arrives there, excitability, reduced after the preceeding impulse, has already been restored.

During frequent(or strong) stimulation when impulses follow one another in rapid succession each next impulse arriving at the parabiotic portion enters the refractory stage following the previous one, when excitability is zero (the absolute refractory period)or much reduced(the relative refractory period), and the amplitude of response diminishes. Therefore, no wave of excitation appears, or even a greater reduction of excitability occurs.

So, in the parabiotic portion of the nerve impulses arriving quickly one after another get in each others way. In the equalizing phase all these phenomena are still weak, so the rapid rhythm is only transformed into a slower one, as a result, the effects of frequent(strong) stimulation and relatively infrequent(moderate) are equalized.But in the paradoxical phase the cycles of restoration of excitability are so prolonged that frequent (strong) stimulation has little effect in general.

Vvedensky considered the parabiosis to be the prototype of the transition from excitation to inhibition in nerve centers. In his opinion, inhibition was the result of overexcitation of a nerve fiber or nerve cell.

During the excitation the nerve fiber expends relatively small energy. Therefore, unlike the nerve centers, where the fatigue occurs in the fist place, the nerves are practically indefatigable(tireless).The relative indefatigability of nerve is demonstrated in the following way. The nerves of two neuromuscular preparations are stimulated simultaneously, and both muscles contract. Then one of the nerves is stimulated in addition by the powerful ascending direct current, and because of anelectrotonic decrease of excitability and conduction, the contractions of this muscle cease. So, this muscle rests, while its nerve is irritated all the time. When the other muscle ceases to contract in response to the stimulation, the direct current electrodes are taken away and the muscle, that was resting, begins to contract. This means that in the other preparation the fatigue of muscle occurred, but not of the nerve, and nerves are practically indefatigable.

**LECTURE 4**

# PHYSIOLOGY OF THE CENTRAL NERVOUS SYSTEM

**Neurons and the Central Synapses. Excitation and Inhibition in the Central Nervous System**

Unlike the endocrine system, regulating principally the metabolic functions of the body, the nervous system controls the rapid activities of the body, such as muscular contractions, rapidly changing visceral events. But since the nervous system controls even the rates of secretion of endocrine glands (in direct or indirect way), in the end, practically all the functions of the organism are controlled by the nervous system.

The central nervous system coordinates activity of all organs and systems of the organism, provides the effective adaptation of the organism to the changes of the environment, forms the purposive behaviour. It receives millions of bits of information from different sensory organs and then integrates all these to determine the response to be made by the body.

These most complicated functions of vital importance are performed by the neurons, which are specialized for the perception, processing, storage and transmission of the information.

They are united in the nerve centers forming different functional systems of the organism.

The consolidation of the neurons is realized by the help of the synaptic junctions.

The central nervous system is composed of more than 100 billion neurons.

According to the number of processes (outgrowths) the neurons may be unipolar, bipolar or multipolar. Bipolar neurons are the primary afferent neurons. Usually their body is in the periphery, but the central process enters the central nervous system. The multipolar neurons are characteristic of central nervous system.

Afferent, intercalary and efferent neurons are distinguished.The primary afferent neurons perceive the signals from the receptors and transmit them to the central nervous system. Here the endings of the processes of these neurons form the synaptic contacts by the intercalary neurons (sometimes even immediately by the efferent neurons). The intercalary neurons are localized within the central nervous system. They realize the connection between different afferent and efferent neurons.

Axons of the afferent neurons, for instance, motor neurons, leave the central nervous system and innervate skeletal muscle fibers. However, many efferent neurons transmit the signals to peripheral organs not directly, but through other neurons.

The efferent neurons of the vegetative nervous system are situated in the vegetative ganglia (out of the central nervous system).

In every neuron four main elements are distinguished and each of them performs certain function: body (soma), dentrites (dendrons), axon and presynaptic ending (termination) of axon.

The body of neuron contains different intracellular organellas necessary to provide the vital activity of the cell. Its membrane is covered by the synapses, that is, plays an important role in the perception and integration of the signals.

The dentrites transmit signals in the direction to the body of the neuron. They are powerfully branched, and their total surface surpasses significantly the surface of the neuron’s body. This allows more synapses to locate on the dentrites.

The axon transmits nerve impulses in the direction from the body of the neuron.The action potentials are transmitted along the axon to its end (sometimes several dozens of centrimetres). So, transmitting signals to the great distances, axon connects the neurons with each other and with the effector organs.

Termination of axon is specialized to transmit signals to other neurons or to the cells of effector organs. It contains synaptic vesicles full of mediators and many calcium channels.

The incoming information enters the cell almost entirely through synapses on the neuronal dentrites or cell body ; there may be from a few hundred to 200 000 such synaptic connections from the input fibers. The total amount of the synaptic contacts in the human central nervous system is about 1015-1016.

However, the output signal travels by way of a single axon, but this axon gives off many separate branches to other parts of the brain, the spinal cord or the peripheral body. These terminals then provide synapses with the next order of neurons or with muscle cells or secretary cells.

The central nervous system functions as a united co-ordinated mechanism, owing to which the reactions of the organism to different stimulations have a character of whole, integrated behaviour. In every such act motor, sensory and vegetative components may be distinguished.

Most activities of the nervous system are initiated by sensory experience emanating from sensory receptors (visual, auditory, tactile receptors, etc.) This sensory experience can cause an immediate reaction or its memory can be stored in the brain for minutes, weeks or years and then can help to determine the bodily reaction at some future date.

Sensory information from the receptors of the entire surface of the body and some deep structures enters the central nervous system and is conducted to multiple “primary” sensory areas in the spinal cord at all levels,the reticular substance of the medulla oblongata, pons, mesencephalon, the cerebellum,the thalamus and some areas of the cerebral cortex. But in addition to these primary sensory areas, signals are then relayed to essentially all other parts of the nervous system.

The nervous system controls various bodily activities.This is achieved by controlling contractions of skeletal and smooth muscles and secretion by both exocrine and endocrine glands. This activities are collectively called motor functions of the nervous system, and the muscles and glands are called effectors.

Operating parallel to the motor axis of the nervous system for controlling skeletal muscle contraction, is another similar system for control of smooth muscle and glands, called the vegetative nervous system or autonomic nervous system.

The skeletal muscles can be controlled from many different levels of the central nervous system, including the spinal cord, the reticular substance of the medulla, pons, mesencephalon, the basal ganglia, the cerebellum and the motor cortex. Each of these different areas plays its own specific role in the control of body movements :the lower regions are concerned primarily with automatic, instantaneous responses of the body to sensory stimuli, and the higher regionswith deliberate movements controlled by the thought process of the cerebrum.

The major function of the central nervous system is to process incoming information in such a way that appropriated motor responses occur. More than 99% of all sensory information is discarded by the brain as irrelevant and unimportant. After the important sensory information has been selected, it is channeled into proper motor regions of the brain to cause the desired responses.This channeling of information is called the integrative function of nervous system.

The direction that the nervous signals spread in the nervous system are determined by synapses. Signals are transmitted from one neuron to the next with ease in some synapses and with difficulty in others.Synaptic activity can be controlled also by the facilitatory and inhibitory signals from other areas in the nervous system which sometimes cause opening of the synapses for transmission and at other times-closing.

Besides, some postsynaptic neurons respond with large numbers of impulses, and others respond with only a few.

So, synapses perform a selective action, blocking the weak signals and allowing the strong ones to pass or selecting and amplifying certain weak signals or channeling the signals in many different directions.

Only a small fraction of the important sensory information causes an immediate motor response. Much of the remainder is stored for future control of motor activities and for use in the thinking processes. Most of the information is stored in the cerebral cortex, but the basal regions of the brain and even the spinal cord can store small amounts of information.

Synapses participate in storage of information (memory) : each time certain types of sensory signals pass through sequences of synapses, they become more capable of transmitting the same signals the next time. This is called facilitation.

Each impulse may be blocked in its transmission from one neuron to the next, changed from a single impulse into repetitive impulses or integrated with impulses from other neurons to cause highly intricate patterns of impulses in successive neurons.These are the synaptic functions of neurons.

In the central nervous system there are chemical, electrical and mixed synapses. Also axosomatic, axondentritic, axoaxonal, dendrodendritic, somatodentritic and dendrosomatic synapses are distinguished.

Some postsynaptic receptors, when activated, cause excitation of the postsynaptic neuron and others cause inhibition.The effect depends on the different molecular and membrane mechanisms.

Excitation is caused by the opening of sodium channels to allow large numbers of positive electrical charges to flow to the interior of the postsynaptic cell. That is, depolarization occurs, and the membrane potential is raised up toward the threshold level for excitation. Conduction through potassium and chloride channels is depressed. Various changes in the internal metabolism of the cell excite cell activity, increase the number of excitatory membrane receptors and decrease the number of inhibitory membrane receptors.

Inhibition is caused by opening of potassium channels through the receptor molecule. Increase in the conductance of chloride ions through the receptor allows these negative ions to diffuse to the interior. Rapid diffusion of positively charged ions from inside the postsynaptic neuron to the outside and increase of the negativity inside (hyperpolarization) is inhibitory. Activation of receptor enzymes that inhibit cellular metabolic functions increase the number of excitatory receptors.

Over 40 different transmitter substances have been discovered. Two different groups of synaptic transmitters are distinguished:

1. Small –molecule,rapidly acting transmitters:

Class I –acetylcholine.

Class II - the amines (norepinephrine, epinephrine, dopamine, serotonin, histamine). Class III - amino acids (-aminobutyric acid-GABA, glycine, glutamate, aspartate).

1. Neuropeptide, slowly acting transmitters:
	1. Hypothalamic releasing hormones (thyrotropin-releasing hormone, luteinizing, hormone-releasing hormone, growth hormone-inhibitory factor-somatostatin).
	2. Pituitary peptides (ACTH, -endorphin, -melanocyte-stimulating hormone, prolactin, luteinizing hormone, thyrotropin, growth hormone, vasopressin, oxytocin).
	3. Peptides that act on gut and brain (leucine enkephalin, methionine enkephalin, substance P, gastrin, cholecystokinin, vasoactive intestinal polypeptide-VIP, neurotensin, insulin, glucagon).
	4. From other tissues (angiotensin II, bradykinin,carnosine,sleep peptides, calcitonin).

The small –molecule,rapidly acting transmitters cause most of acute responses of the nervous system, such as transmission of sensory signals to and inside brain and motor signals back to the muscles. The neuropeptides cause more prolonged actions,such as long-term changes in number of receptors, long-term closure of certain ion channels,and possibly even long-term changes in number of synapses.

The small-molecule types of transmitters are synthesized in the cytosol of the presynaptic terminal and then are absorbed into the transmitter vesicles. Each time an action potential reaches the presynaptic terminal, a few vesicles at a time release their transmitter into the synaptic cleft within millisecond or less. The subsequent action of the transmitter on the postsynaptic membrane receptors also occurs within another millisecond or less. Most often the effect is to increase or decrease conductance through ion channels. Occasionally these transmitters can stimulate receptor-activated enzymes, thus changing the internal metabolic machinery of cell.

After the vesicles fuse with the synaptic membrane and open to release their transmitters, the visicle membrane at first simply becomes part of the synaptic membrane. But within seconds to minutes the vesicle portion of the membrane invaginates back to the inside of the presynaptic terminal and pinches off to form a new vesicle.

The most important of the small-molecule transmitters are the following:

Acetylcholine is secreted by neurons in many areas of the brain (specifically by the large pyramidal cells of the motor cortex, many different neurons in the basal ganglia, the motor neurons that innervate the skeletal muscles, the preganglionic neurons of the vegetative nervous system, the postganglionic neurons of the parasympathetic nervous system and some of the postganglionic neurons of the sympathetic nervous system). In most instances acetylcholine has an excitatory effect, but it has inhibitory effects at some of the peripheral parasympathetic nerve endings (inhibition of the heart by the vagus nerves).

Norepinepherine is secreted by many neurons whose cell bodies are located in the brain stem and hypothalamus. Specifically, norepinephrine-secreting neurons located in the pons send nerve fibers to widespread areas of the brain and help control the overall activity and mood of the mind. In most of these areas it activates excitatory receptors, but in a few areas - inhibitory receptors. Norepinephrine is also secreted by most of the postganglionic neurons of the sympathetic nervous system, where it excites some organs and inhibits others.

Dopamine is secreted by neurons originating in the substantia nigra. Termination of these neurons is mainly in the striatal region of the basal ganglia.The effect of dopamine is inhibition. Glycine is secreted mainly at synapses in spinal cord and acts as an inhibitory transmitter.

Gamma-aminobutyric acid (GABA) is secreted by nerve terminals in the spinal cord,the cerebellum, the basal ganglia and many areas of the cotex. It causes in inhibition.

Glutamate is secreted by the presynaptic terminals in many of the sensory pathways as well as in many areas of the cortex. It causes excitation.

Serotonin is secreted by nuclei that originate in the median raphe of the brain stem and projects to many brain areas, especially to the dorsal horns of the spinal cord and to the hypothalamus. It acts as an inhibitor of pain pathways in the cord, and also helps control the mood of the person, perhaps even to cause sleep.

The neuropeptides are synthesized as integral parts of large protein molecules by the ribosomes in the neuronal cell body. The protein molecules are transported into the endoplasmic reticulum of the cell body,are split into smaller fragments, the neuropeptide is packaged into minute transmitter vesicles that are released into the cytoplasm. The transmitter vesicles are transported all the way to the tips of the nerve fibers by axonal streaming of the axon cytoplasm, traveling at the slow rate of only a few centimeters per day. Finally, these vesicles release their transmitter in response to action potentials in the same manner as for small-molecule transmitters. But the vesicle is autolysed and is not used once again.

Because of this laborious method of forming, much smaller quantities of the neuropeptides are released than that of the small –molecule transmitters. But the neuropeptides are a thousand or more times as potent as the small –molecule transmitters and they cause much more prolonged actions: closure of calcium pores, changes in the metabolic machinery of cells, changes in activation or deactivation of specific genes in the cell nucleus, alterations in numbers of excitatory or inhibitory receptors. Some of these effects can last for days or even months or years.

Only a single small-molecule type of transmitter is realised by each type of neuron. But the terminals of the same neuron may also release one or more neuropeptides at the same time.Yet according to the principle of Dale, whatever small-molecule transmitters and neuropeptides are released at one terminal of the neuron, these same transmitters will be realised at all other terminals of the same neuron, whatever these are few in number or many thousand and also wherever these terminate within the nervous system or in peripheral organs. Therefore, for instance, cholinergic and serotoninergic neurons, cholinergic and adrenergic synapses are distinguished.

After a transmitter is released at a nerve ending, it is destroyed or removed to prevent continued action forever thereafter. The neuropeptides are removed mainly by diffusion into the surrounding tissues, followed by destruction within a few minutes to several hours by enzymes. The small-molecule, rapidly acting transmitters are removed within a few milliseconds in three different ways:

1. by diffusion of the transmitter out of the cleft into the surrounding fluids;
2. by enzymatic destruction within the cleft itself;
3. by active transport back into the presynaptic terminal itself and reuse. This is called transmitter re-uptake. It occurs especially prominently at the presynaptic terminals of the sympathetic nervous system for the re-uptake of norepinephrine.

The electrical events in neuronal excitation have been studied especially in the large motor neurons of the anterior horns of the spinal cord. But except for some quantitative differences, they apply to most other neurons of the nervous system as well.

The resting membrane potential of the neuronal soma is about-65 millivolts. This is somewhat less than that of large peripheral nerve fibers and skeletal muscle fibers. The lower voltage is important because it allows both positive and negative control of the degree of excitability of the neuron. Decreasing the voltage to a less negative value makes the membrane of the neuron more excitable, where-as increasing this voltage to a more negative value makes the neuron less excitable.

The interior of the neuronal soma contains a very highly conductive electrolytic solution (the intracellular fluid of the neuron), and its diameter is very large (10-80 mm)-there is almost no resistance to conduction of electrical current from one part of the somal interior to another part Therefore,any change in potential in any part of the intrasomal fluid causes an almost equal change in potential at all other points inside the soma. This principle plays a major role in the summation of signals entering the neuron from multiple sources.

When a transmitter is secreted in the synaptic cleft and acts on a membrane excitatory receptor to increase the membrane’s permeability to sodium ions, these ions rush to the inside of the membrane. The rapid influx of the positive charged sodium ions to the interior neutralizes part of the negativity of the resting membrane potential. This increase in voltage above the normal resting neuronal potential (to a less negative value) is called the excitatory postsynaptic potential (EPSP) because if this potential rises high enough it will elicit an action potential in the neuron,thus exciting it. An increase of this magnitude requires the simultaneous discharge of many terminals (40-80 for the antenior motor neuron) at the same time or in rapid succession. This occurs by a process called summation.

When the excitatory postsynaptic potential rises high enough, action potential origins in the initial segment (axon hillock) of the axon leaving the neuronal soma. Because the soma has relatively few voltage-gated sodium channels,but the membrane of the initial segment has seven times as great a concentration of voltage-gated sodium channels and therefore can generate an action potential with much greater ease than can the soma. The excitatory postsynaptic potential that will elicit action potential at the initial segment is between +15 and + 20 millivolts (in contrast to the + 30 mv or more required on the soma).

The action potential travels both peripherally along the axon and often also backward over the soma and even into some dentrites (not into all of them because they also have very few voltage-gated sodium channels).

Inhibitory synapses open potassium and chloride channels (instead of sodium channels). Opening the potassium channels will allow positive charged potassium ions to move to the exterior, and opening the chloride channels will allow negative charged chloride ions to move to the interior. Both effects cause hyperpolarization and inhibit the neuron because the membrane potential is now farther away than ever from the threshold for excitation. Therefore, an increase in negativity beyond the normal resting membrane potential level is called the inhibitory postsynaptic potential (IPSP).For instance, when the activation of inhibitory synapses decreases the membrane potential from its normal value of –65mV to the more negative value of –70mV, IPSP is –5mV.

Sometimes activation of the inhibitory synapses causes little or no inhibitory postsynaptic potential but inhibits the neuron.The tendency for the potassium and chloride ions to maintain the membrane potential near the resting value when the inhibitory channels are wide open is called “short circuiting” of the membrane,thus making the sodium current flow caused by excitatory synapses ineffective in exciting the cell.

Besides the postsynaptic inhibition caused by inhibitory synapses operating at the neuronal memebrane, the presynaptic inhibition occurs in the presynaptic terminals before the signal reaches the synapse. This type of inhibition is caused by “presynaptic” synapses that lie on the terminal nerve fibrils before they themselves terminate on the following neuron. Activation of these synapses decreases the ability of the calcium channels in the terminals to open.

Unlike the postsynaptic inhibition which lasts for only a few milliseconds, the presynaptic inhibition requires many milliseconds to develop and can last for minutes or even hours.

In the spinal cord, as well as in different parts of the brain, the inhibitory neurons were found. For instance, the Renshaw cells cause the recurrent inhibition. The collaterals of motor neurons end in these cells,the axons of which form the inhibitory synapses on the motor neurons of the same segments of the spinal cord. Thus,the excitation originating in the motor neuron by the direct way spreads to the periphery (to the skeletal muscle),but by the collaterals they activate the inhibitory cell which suppresses the excitation of motor neuron. This mechanism of recurrent inhibition protects neurons from excessive excitation.

The central inhibition was discovered by I. M. Sechenov in 1861.His experiment was performed on the thalamic frog, that is, after dissection of the brain and removal of the cerebral hemispheres above the thalami. The hind leg of the frog was irritated by the weak acid solution and reflex time was determined. Then NaCl crystal was put on the thalamus or it was stimulated by the weak electric current. When the reflex time was determinated after the stimulation of the thalamus, it was lengthened. On the strength of this fact Sechenov came to the conclusion that in the thalamic area of the brain centers exist which inhibit the spinal cord reflexes.

Holts demonstrated that the reflex of jerking back of frog’s hind leg when irritated by the acid solution, may be inhibited by the simultaneous powerful mechanical irritation of the second leg (for instance compression by the pincers). In his opinion, there are no inhibitory centers,and the inhibition may develop in any part of the central nervous system when two or more irritations meet.

Inhibition is the independent nervous process which is caused by the excitation and manifests in the suppression of another excitation.

Different contradictory suppositions were voiced about the mechanism of the central inhibition. Some scientists believed that in the central nervous system there were the structures specialized in the inhibition, and the inhibition was opposite to the excitation. Other researchers considered that inhibition in the central nervous system was resulted in by the conflict of several excitations or owing to the exceedingly powerful (or protracted) excitation (by the mechanism of Vvedensky’s pessimum).

The modern electrophysiological researches showed that all of these researches were right in certain degree. Because in the central nervous system several types of inhibition of different nature and localization exist:

1)presynaptic inhibition;

2) postsynaptic inhibition; recurrent inhibition;

3) pessimal inhibition;

4**)** inhibition after excitation.

**Methods of Investigation of Central Nervous System Functions.**

**Reflex. Reflex Arc. Types of Reflexes**

The method of extirpation (removal), the method of dissection (cutting) and the method of stimulation (irritation) are the oldest methods of investigation of the central nervous system functions. But these methods have not lost their significance up to the present when the electrophysiological methods are successfully used.

The method of extirpation and the method of dissection applied in the acute and chronic experiments allow to form a true notion of physiological importance of different parts of the central nervous system. They permit to ascertain which of the central nervous system functions disappear and which of them are preserved after the operative intervention.

The brain can be cut at different levels. The complete transverse dissection of the spinal cord or brain stem dissociates the upper parts of the central nervous system from its lower parts and permits to study the reflex reactions which are realized by the brain and spinal cord centers situated below the dissection. It allows also to study the significance of the impulses coming from the upper parts of the central nervous system to its lower parts.

Depending on the level of the dissection the experimental animals ar called:

1. the spinal animal - the dissection is performed at the level of the upper segments of the spinal cord;
2. the bulbar animal - the medulla oblongata is separated from the midbrain by the transverse section;
3. the mesencephalic animal - the brain stem is dissected between the midbrain and diencephalon;
4. the diencephalic animal - by the section above the diencephalon it is separated from the cerebral hemispheres.

To study the functions of different areas of brain usually the method of local damaging was applied which was carried out by the help of needle or scalpel. Now the local damaging of nerve centers is performed by the way of electrolytic destruction of the tissues, that is, the thin electrodes are introduced into the brain through which the direct current is put.

In the experiments the brain tissues are destroyed also by means of the thermocoagulation, narrow powerful pencil of x-rays, ultrasounds, freezing.

One of the widespread methods of investigation of neurons functions is the electrical stimulation of the afferent nerve fibers. In this case the excitation is transmitted in the central nervous system from one neuron to another through the excitatory synapses, which is similar to natural conditions. This way of conduction of the excitation is called the orthodromic conduction.

Excitation of the neuron may be caused also by the way of the stimulation of its axon, and the action potential is transmitted not only in the peripheral direction but also to the neuron. This is called the antidromic way of conduction.

Reactions of organs innervated by corresponding parts of the central nervous system are the proof of the excitation of the neurons. In modern researches the electrophysiological methods of recording of excitation are used.

Weak electrical current applied to certain areas of the cerebral cortex causes different motor reactions (contractions of separate muscle groups or even isolated contractions of single muscle).

By the help of the electrodes implanted in different structures of the brain, certain centers of the cerebral cortex, basal ganglia, brain stem and spinal cord are stimulated, and the functional changes caused by this stimulations are studied.

Brain structures are stimulated also by different chemical substances (narcotics, strychnine, etc.). The chemical substances are introduced into the central nervous system by the method of electrophoretic microinjection. The thin micropipette filled with solution is introduced into the nerve center. One electrode is put into other end of the micropipette and other electrode is applied to the body surface. When weak direct current is put through the electrodes, the substance in solution filled into the micropipette enters the tissue.

To introduce the electrodes, micropipettes, etc. into the deep structures of the brain, the stereotaxic (Gr. stereos - volumetric, taxis - situation technique is applied. With that aim in view the localizations of the cerebral structures are expressed in the three - coordinate system which helps to determine the spatial situation of the nerve centers. These co-ordinates are determined in the special stereotaxic albums.

The head of the animal is fixed in the stereotaxic apparatus, and according to the coordinates indicated in the stereotaxic album, the electrodes are introduced into the sought - for point of the brain.

Using the implanted electrodes, it is possible to record the bioelectrical potentials of the brain Unipolar (one electrode is in the nerve center that is studied and another electrode is on the skin) and bipolar (both electrodes are in the area of the brain that is studied) leads are applied.

Electrophysiological investigation of the central nervous system functions includes recording of the background electrical activity, the evoked (generated) potentials, etc.

Since the background electrical activity is observed in all parts of the central nervous system even without apparent stimulations, it is called also the spontaneous activity. The typical waves of the background activity with the frequency of 10-40 in 1 second and amplitude of 100 microvolts are recorded in the electroencephalogram, which is the total expression of different electrical processes in the neurons and synapses.

The electrical reaction of the certain areas of the central nervous system (spinal cord, cerebellum, thalamus, cerebral cortex, etc.) in response to the afferent impulses (when the receptors or afferent nerves are stimulated) is called the evoked potential.

Recording of evoked potentials allows to study the exact ways of conduction of the information to the different structures of the brain.

The evoked potentials recorded in the nerve centers, where the afferent impulses from certain group of receptors enter, are called the primary replies. They have shortest latent period. In the nerve centers, for instance, in different areas of the cerebral cortex more late responses are also recorded, which are called the secondary reply.

To study the activity of separate neurons intracellular potentials are recorded with the help of microelectrodes.

The principal form of the nervous activity are reflexes. Reflex (from Latin reflectoreflection) is the law - governed reaction of organism to the change of the external or internal environment which is realized with the participation of central nervous system as a response to the stimulation of receptors. Reflex manifests itself by onset or ceasing of some activity of organism (contraction or relaxation of muscles, secretion or ceasing of secretion of glands, constriction or dilatation of vessels and so forth).

Thanks to the reflex activity organism is able to react rapidly to different changes of the external environment or its own internal state and adapt itself to these changes.

The structural basis of the reflex activity is the neuronal chain of receptor, intercalary and effector neurons. They form the way from receptor to the effector organ for nerve impulses causing the reflex. This way is called the reflex arc. So, the following parts of the reflex arc are distinguished:

1. the receptor which perceives the external or internal stimuli;
2. the afferent (sensory) nerve;
3. the nerve center, that is, the central part of the reflex arc;
4. the efferent (motor) nerve;
5. the effector, that is, the working organ (muscle, gland) realizing proper activity.

The idea of reflex activity principle of the nervous system was first introduced in the middle of the XVII century by R. Descartes - the great French naturalist and philosopher. The reflex theory was an important step in the development of the materialistic ideas about the mechanism of organism's reactions. Because this theory showed that in the basis of the responses of the organism was the principle of determinism, that is, the principle of the cause and effect relationships. But Descartes was dualist. He could not explain the expendiency (purposefulness) of reflex and though materialis at the beginning of the reflex arc, he became idealist at its end.

The term “reflex” was suggested in the XVIII century by Czech physiologist G. Prochaska. **I.** M. Sechenov proved the reflex nature of the psychical activity.

**I.** P. Pavlov discovered the conditioned reflexes and showed that conditioned reflex can connect any stimulation with any effector organ. He saw in the conditioned reflex the factor of future.

P. K. Anokhin discovered the feedback in the reflex arc. He pointed out that thanks to the feedback, the nerve center receives information about the result of the reflex and makes corresponding corrections. After any repetition of the reflex the nerve center itself becomes more experienced.

So, as distinct from the three-component (afferent, central, efferent parts) reflex arc of Descartes that of Anokhin's is four component (afferent, central, efferent parts and the feedback). However, there is also an important qualitative difference between them. It turns out that actually the reflex arc is not arc at all, but it is a kind of turn of spiral.

Thus, the mechanism of expediency of reflex act was explained and the dualism of Descartes was got over.

The totality of receptors, stimulation of which cause the certain reflex, is called the receptive field (or zone) of the reflex. Stimulation of the same receptors may cause different reflexes depending on the power of the stimulation and to which central structures the impulses are transmitted. Besides, in the receptive field of one reflex may be receptors performing different functions. For instance, the flexor reflex may be caused by the stimulation of tactile receptors of the skin as well as the muscular receptors.

The simplest reflex arc consists of two neurons (receptor and effector neurons) and one synapse between them. Such reflex arc is called two - neuronal and monosynaptic arc. But arcs of the most reflexes include more than two neurons (receptor neuron, one or several intercalary neurons and effector neuron). These are called multineuronal and polysynaptic arcs.

Reflex arcs consist of the number of receptor, intercalary and effector neurons. So, even the simplest reflex arc includes a number of parallel synapses connecting a group of receptor neurons with a group of effector neurons causing the same reaction.

The monosynaptic reflex arcs are very rare, for instance,that of myotatic (or stretch) reflex. The stretch of muscle causes generation of nerve impulses in muscular receptors (muscle spindles), which are conducted to the spinal cord by the outgrowths of the receptor neurons and immediately, without participation of intercalary neurons, are transmitted to the motor neurons. From these the impulses are directed to the end-plates in the same muscle. As a result, the stretch of the muscle causes its reflex shortening.

Since in monosynaptic reflex arc the excitation passes only through one interneuronal synapse, such reflexes are realized more rapidly than those with polysynatic reflex arc.

The polysynaptic reflex arcs include several successively united series of neurons and synapses between them. For instance, the arc of the withdrawal reflex (jerking back the limb in response to the painful stimulation of the skin) is polysynaptic reflex arc.

The schemes of the reflex arcs (even those of polysynaptic reflex arcs) form a simplified notion of composition of neurons taking part in reflex act. Because in reality the nerve impulses are widely spread in the central nervous system along numerous conduction tracts. For example, the excitation caused by the painful stimulation spreads also to the nuclei of brain stem, to cerebral cortex and from there the impulses are transmitted to the spinal cord centers by the efferent ways.

Thanks to the participation of the brain stem and cerebral cortex neurons in the protective reactions against the painful stimulation, the sensation of pain is accompanied by a number of vegetative reactions (the changes of pulse rate, respiration rate, vascular tension, etc.).

Even in such simple reflex reactions as the propriorecetive reflexes, for realization of which participation of two neurons is quite enough, the excitation widely spreads in the central nervous system. For instance, the blow on the tendon causes the change of cerebral cortex electrical activity.

Degree of drawing of neurons in different parts of the central nervous system into reaction to the stimulation depends on the power and duration of stimulation, the state of the central nervous system.

The first reflex reactions of the human fetus are revealed in the second half of the III month of the intrauterine life. The earliest are the reflex movements in response to the irritation of the head, then to that of upper extremities and trunk, later to that of lower extremities. The plantar reflex, knee reflex and grasping reflex are revealed in early period of the human fetus development.

In this period of the embryonic development the wide spreading (irradiation) of the excitation in the central nervous system is observed. That is, any area of the body is the reflexogen zone which is able, when stimulated, to cause the movements of the signifycant part of the body or even of the whole body.

Development of the limited and localized motor reactions and decrease of irradiation of the nerve impulses is connected with the myelinization of the nerve fibers. Improvement of the process of inhibition is also important.

Reflexes or reflex acts are extremely varied. They can be classified by the number of signs.

According to the biological significance of the reflexes they are divided into following groups:

1. food reflexes;
2. defence reflexes;
3. sexual reflexes;
4. orientation reflexes;
5. posture and tonus reflexes;
6. locomotor reflexes (reflexes of the position and movements of the body in the space).

Depending on receptors, causing the reflex act the following reflexes are distinguished:

**1)** exteroceptive reflexes; **2)** interoceptive reflexes;

**3)** proprioceptive refelxes.

In every reflex act realized by the higher parts of the central nervous system the neurons of the lower parts of the brain also take part and vice versa, i.e., in the reflexes realized by the lower centers, the nerve impulses reach the highest cerebral centers, including the brain cortex. But in every reflex the center may be distinguished which is necessary for its realization. Therefore, the reflexes are classified also by the following way: **1)** spinal (spinal cord) reflexes;

1. bulbar (medulla oblongata) reflexes;
2. mesencephalic (midbrain) reflexes;
3. diencephalic reflexes;
4. cortical (cerebral cortex) reflexes.

Depending on the organs, taking part in the reflex, the reflexes are divided into following groups:

1. motor reflexes (the effector organs are muscles);
2. secretory reflexes (the effector organs are glands);
3. vasomotor reflexes (these manifest themselves by the constriction or dilatation of blood vessels).

According to duration of the response reaction the motor reflexes are divided into: **1)** phasic reflexes (rapid movements of short duration); **2)** tonic reflexes (prolonged holding of some posture).

All the reflexes of the whole organism are divided into two groups: **1)** unconditioned reflexes; **2)** conditioned reflexes.

Some relatively simple reflexes frequently studied in the laboratory conditions of experiment or investigated in the clinic are the following. Spinal reflexes:

1. The flexor reflex (the withdrawal reflex) - in the spinal animal any type of cutaneous sensory stimulus on a limb causes contraction of its flexor muscles, thereby withdrawing the limb from the stimulus.
2. The rubbing reflex - a piece of filtering paper moistened in the weak acid solution is put on the skin on the side of the body of spinal frog. This stimulation causes the reflex contraction of the muscles of the limb which rubs the place of irritation and throws off the paper.
3. The scratch reflex - electrical stimulation of the skin of dog's leg causes the rhythmical (toand-fro) scratching movements.
4. The plantar (sole) reflex - irritation of the skin of the human foot sole causes reflex flexion of the foot and toes. In healthy infants in first months of their life and in adult persons during some diseases of central nervous system such irritation causes opposite action - extension of great toe and fan-like divergence of other toes of the foot. This is called Babinsky's reflex.
5. The knee jerk or patellar reflex - is elicited by simply striking the patellar tendon with a reflex hammer. This stretches the quadriceps muscle and initiates a dynamic stretch reflex that in turn causes the leg to jerk forward.
6. The Achilles reflex - the blow on the Achilles tendon causes contraction of the gastrochemius muscle.

The last two reflexes are classified as muscle stretch (tendon) reflexes or myotatic reflexes.

1. The micturition (urinary) reflex.
2. The defecation reflex. Bulbar reflexes:
3. The sucking reflex - the touch to the lips of baby causes the rhythmical sucking movements.
4. The vomiting reflex - irritation of the back wall of gullet causes vomiting.
5. The corneal reflex - the touch to the eye cornea causes closing of the eye. Mesencephalic reflex:

The pupillary reflex - when light is shone into the eyes, the pupils constrict.

**Nerve Centers and their Properties**

Totality of neurons necessary for realization of certain reflex or for regulation of certain function is called the nerve center.

Localization of nerve center is determoned in experiments by the way of stimulation, narowly limited detruction, expiration or dissection of different parts of the central nervous system. If stimulation of any area of the brain or spinal cord causes certain physiological function and removal or destruction of this area is followed by disappearance of that function, then it is considered that in this area the nerve center is situated which regulates the function in question.

For instance, stimulation of certain area of the parietal lobe of hemispheres causes flexion of the anterior paw of the dog and therefore, it is considered that in this area is the center of the flexion of the paw.

The cortical visual center is situated in the occipital lobe of hemispheres - the removal of this area causes loss of vision.

Dissection of the brain stem above the medulla oblongata does not cause cessation of the breathing, but when dissected below, the breathing stops. Besides, destruction of certain area of the medulla oblongata causes irreversible stopping of the breathing. All these facts permit to consider that the respiratory center is localized in the medulla oblongata.

It must be taken into consideration that in every reflex act of the organism not only separate group of neurons situated in the limited area of the brain takes part, but it is realized by the participation of many other neurons widely scattered all over the central nervous system. For instance, the neurons, controlling breathing, are situated not only in the medulla oblongata, but also in the spinal cord, as well as in the pons, reticular formation of the midbrain and diencephalon, cerebral cortex.

Therefore, in wide sense of the word, the nerve centers must be regarded as the functional systems.

Characteristics of nerve centers are determined by the structure of the neuronal chains forming these centers and properties of synaptic conduction.

Unlike the nerve fibers, conducting impulses in both directions, in nerve centers excitation can be transmitted only in one direction - from the receptor neuron and through the intercalary neurons to the effector neuron. This phenomenon is called one-way conduction of excitation. The one-way conduction is conditioned by existence od synapses in the nerve centers, and synapses transmit impulses only in one direction.

The one-way conduction in nerve centers is demonstrated in the following experiment. Anterior and posterior roots of any segment of the spinal cord are cut. Since in the posterior root there are afferent fibers and in the anterior root-efferent ones, the electric stimulation of the central end of the posterior root causes excitation in the central end of the anterior root (the action potential is recorded). However, when the anterior root is stimulated, no action potential is recorded in the posterior root.

The one-way conduction determines direction of the conduction of impulses in the reflex arc.

Another characteristics of the synapses, that is, the synaptic delay of conduction of the excitation also manifests itself in nerve centers. Excitation is conducted along the reflex arc more slowly than along the nerve fiber.

For secretion of transmitter in nerve terminal in response to the impulse, its diffusion through synaptic cleft to the postsynaptic membrane and originating of the excitatory postsynaptic potential (EPSP) about 0.3-0.5 msec is required. After EPSP has been generated, 1.2 msec passes until the spreading action potential is originated. So, conduction of excitation through one synapse requires approximately 1.5-2 msec.

Owing to the delay of conduction of excitation in synapses the reflex time or latent period of reflex is relatively long. This is the time from the moment of stimulation of receptor to the moment when the reflex is observed. During this time receptors are excited, the excitation is conducted through the afferent nerve fibers to the nerve centers, it is transmitted from the afferent neuron through one or a number of synapses to the efferent neuron, then the excitation is conducted from the nerve center through the efferent nerve fibers and peripheral synapse to the effector organ. When the own latent period of effector organ is up, the reflex appears.

The considerable part of reflex time goes on the central time (or true time) of the reflex, that is, the time necessary for the intracentral transmission of the excitation through the central synapses. To calculate the central time of the reflex the sum of times spent on all other processes must be subtracted from reflex time.

Since the transmission of the excitation through one synapse requires 1.5-2msec, the number of synapses in reflex arc may be determined if the central time of the reflex is known.

The time of most human tendon reflexes is the shortest. For instance, the time of knee reflex is only 20-24 msec, but that of wink reflex - 50-200 msec, though the distance between the receptor and effector in the first case is considerably longer. This is explained by the fact that the central time of the knee reflex is 3 msec, and that of wink reflex - 36-186 msec. Consequently, the arc of knee reflex is monosynaptic and that of wink reflex is polysynaptic.

The reflex time depends also on the power of stimulation, the state of central nervous system, the latent period of effector organ’s excitation. Stronger the stimulation-shroter is the reflex time. Increase of nerve center excitability considerably shortens the reflex time and fatigue lengthens it.

The time of reflex reactions of the internal organs, blood vessels and sweat glands is the longest. These are the effector organs to which impulses are transmitted through the vegetative nervous system and which response slowly. For instance, the reflex time of flushing of the skin caused by dilatation of its blood vessels, is 20 seconds or more.

Unlike the nerve fiber in which the subliminal (subthreshold) stimulations disappear completely leaving no trace, in nerve centers summation of excitations occurs. The temporal summation and spatial summation are distinguished.

Some reflexes do not occur when the single stimulus is applied to the receptor. For instance, the scratch reflex cannot be caused by the single stimulation even though it is very strong. But when the skin receptive field of this reflex is stimulated rhythmically by the weak induced current, the scratch reflex is observed. This is called the temporal summation.

The same reflex can be caused by simultaneous subliminal stimulation of two areas of skin within the receptive field of this reflex. This is called the spatial summation.

Process of stimulation of excitatory postsynaptic potentials form the basis of summation of the excitation in nerve centers. The portion of mediator thrown out by eachnerve terminal in response to the single impulse is not sufficient to cause the critical depolarization of the postsynaptic membrane. Such depolarization is possible when series of nerve impulses enter the same synapse or several synapses situated on the body or dendrites of the motor neuron, are stimulated simultaneously.

The central nervous system is made up of thousands of separate neuronal pools (populations), some of which contain very few neurons and others - vast numbers. Each imput fiber divides hundreds to thousands of times, providing an average of a thousand or more terminal fibrils that, spread over a large area in the pool to synapse with the dendrites or cell bodies of the neurons in the pool. The neuronal area stimulated by each incoming nerve fiber is called its stimulatory field. Large numbers of the terminals from each input fiber lie on the centermost neuron in its field, but progressively fewer terminals lie on the neurons farther from the center of the field.

Some input fibers has more than enough terminals to cause neuron to discharge. The stimulus from input fiber to such neuron is called an excitatory or a suprathreshold stimulus.

The same input fiber also contributes terminals to other neurons, but not enough to cause excitation. Nevertheless, discharge of these terminals makes both these neurons more excitable to signals arriving through other incoming nerve fiber. Therefore, the stimulus to these neurons is called a subthreshold stimulus, and the neurons are said to be facilitated.

In the central portion of the distribution field of each input nerve fiber almost all the neurons are stimulated by incoming fiber. This is called the discharge zone (excited zone) of the incoming fiber or liminal zone. To either sidethe neurons are facilitated but not excited, and these areas are called the facilitated zone or subliminal (subthreshold) zone.

So, in central facilitation the reflex reaction during simultaneous stimulation of two nerve fiber is more powerful than the sum of reactions caused by separate stimulation of these fibers.

Opposite of facilitation is occlusion. In this case the reflex reaction during simultaneous stimulation of two nerve fibers is weaker than the sum of reactions caused by separate stimulation of these fibers. Because the neurons to either side of the discharge zone of the incoming fiber in the pool are also supplied by sufficient amount of terminals to cause an excitation.

Some incoming fibers inhibit neurons, which is opposite of facilitation, and the entire field of the inhibitory branches is called the inhibitory zone. Degree of inhibition in the center of this zone is very great because of large numbers of endings in the center; it becomes progressively less toward its edges.

Response of nerve center depends not only on the stimuli acting at present, but also on the precedeng stimulation. For instance, the preceding frequent rhythmical (tetanizing) stimuli strengthen the reflex reaction. This is called posttetanic potentiation.

To demonstrate the posttetanic potentiation a monosynaptic reflex is caused by the single stimulation of an afferent nerve. Then thge nerve is irritated by the frequent stimuli (300-600 stimuli in 1 second) during 2-3 seconds. After the rhythmical stimulation is over, once again the single stimuli of the same power that was before the tetanization, is applied, but they cause considerably increased reflex responses.

The posttetanic potentiation of the reflex responses is connected with increasing of the excitatory postsynaptic potentials. Because under the rhythmical stimulation the presynaptic terminal acquires the ability to secrete larger portions of the mediator in response to every action potential.

In many instances, a signal entering a pool causes a prolonged output discharge, called afterdischarge, even after the incoming signal is over. This after - action period lasts from a few milliseconds to as long as many minutes. The two most important mechanisms by which after discharge occurs, are the following:

1. The afterdischarge of short duration is of synaptic character; it is connected with the afterpotential (depolarization of the neuron’s membrane). As a result of the synaptic afterdischarge mechanism alone, it is possible for a single instantaneous input to cause a sustained signal output (a series of repetitive discharges) lasting for many milliseconds.
2. The protracted afterdischarge is connected with reverberatory circuit. The reverberatory or oscillatory circuits are caused by positive feedback within the neuronal network. The output of the neuronal circuit feeds back to re-excite the input of the same circuit. Consequently, once stimulated, the circuit discharges repetitevily for a long time.

In the simplest reverberatory circuit the output neuron simply sends a collateral nerve fiber back to its own dendrites or soma to restimulate itself: once the neuron is discharged, the feedback stimuli could help keep neuron discharging for a long time thereafter.

In complex systems of feedback circuits additional neurons exist, which give a longer period of time between the initial discharge and the feedback signal. In still more complex systems both facilitatory and inhibitory fibers impinge on the reverberating circuit. A facilitatory signal enchances intensity and frequency of reverberation, whereas an inhibitory signal depressses or stops the reverberation. Most reverberating pathways are constituted of many parallel fibers.

In a typical reverberatory circuit the input stimulus may last only 1 millisecond or so, yet the output can last for many minutes. Intensity of the output signal increases to a high value early in the reverberation, then decreases to a critical point, at which it suddenly ceases entirely. The cause of this sudden cessation of reverberation is fatigue of one or more of the synaptic junctions in the circuit, for fatigue beyond a certain critical level lowers the stimulation of the next newron in the circuit below threshold level so that the circuit is suddenly broken.

During the transmission of impulses through nerve centers transformation of the frequency and rhythm of the impulses may occur. Because the central synapses can change the parameters of impulses and therefore, the frequency and rhythm of input impulses may not coincide with those of output impulses.

So, the frequency of the impulses generated in the neuron is relatively independent of that of impulses coming from other neurons. In response to single stimulation of the afferent nerve, the motor neuron can send a series of impulses. Figuratively speaking, to the single rifle-shot the neuron responses by the machine-gun fire.

In most cases the transformation of the frequency and rhythm of the excitations happens when the excitatory postsynaptic potential caused by the single afferent stimulation, is of long duartion. Then on the ridge of this potential the discharge of impulses occurs.

The discharges of nerve impulses from nerve centers to the periphery (to the proper organs and tissues) occur not only at the time when reflexes are realized, but even in the relatively resting state. These continuous (though of low frequency) impulses maintain the muscular tension, neuromuscular tonicity, vascular tension.

Such a constant excitation of nerve centers is called the nerve centers tonicity. It is maintained by the continuous afferent impulses entering from the peripheral receptors to the central nervous system and different humoral stimuli (hormones, carbon dioxide etc).

To demonstrate the role of the afferent impulses in the origin of the nerve centers tonicity, in the spinal frog the posterior (sensory) roots innervating the hind limb, are cut. This causes the fall of muscular tension of the limb, as if the motor nerve was cut.

So, the circular interaction exists between the nerve centers and periphery: the efferent impulses from the nerve centers maintain the muscular tension, and the tonicity of nerve centers themselves is maintained by the afferent impulses from the proprioreceptors and cutaneous ceptors.

The tonic influence of medulla oblongata, midbrain and diencephalon is more important. Decerebration, that is, dissection of the brain between anterior and posterior tubera of lamina testi of midbrain, causes sharp increase of the muscular tension of all extensor muscles.

Unlike the nerve fibers, which are relatively indefatigable, the fatigue of nerve centers occurs in the first place. It becomes apparent by the gradual decrease and then complete cessation of the reflex response of the muscle, though stimulation of the afferent nerve fibers is continued. If the efferent (motor) nerve fibers are stimulated, the muscle contracts once again. This proves that the fatigue is occurred not in the muscle, but just in the nerve center.

Not all of reflexes cause the fatigue in the same degree. For instance, the proprioceptive tonic reflexes that maintain the muscular tension may go on during a long time, not being accompained by the fatigue.

The nerve centers fatigue is connected with disturbance of the transmission of the excitation is resulted in by the decrease of reserves of the mediators in nerve terminals, decrease of sensibility of postsynaptic membrane to the mediator, decrease of power resources of the neuron.

One of the peculiarities of nerve centers is the intensive metabolism in neuronsand intensive consumption of oxygen by them. For instance, 100g cerebral tissue of dog consume 22 times more oxygen than 100g of muscle tissue in resting state and 10times more than 100 g of liver. The human brain consumes about 40-50 ml oxygen per minute and this is approximately 1/6 - 1/8 the oxygen consumed by all the body in the resting state.

Nerve cells are also very sensitive to the oxygen deficiency. Therefore cessation of brain blood supply rapidly leads to disturbance of the central nervous system functions and destruction of nerve elements. The cerebral cortex neurons perish 5-6 minutes after cessation of the blood supply. But functions of brain stem centers may be recovered 15-20 minutes later and that of spinal cord centers - after 20-30 minutes later after the blood supply is ceased. Since hypothermia decreases the metabolism, in this state the central nervous system endures the hypoxia during a longer time.

Neurons and synapses have a selective sensibility to different poisons which are called neurotoxins (strychnine, morphine, phenamine, cardiazol, ether, chloroform, barbiturates, alcohol, etc.). The selective sensibility of the neurons and synapses localized in different parts of the central nervous system to some poisons points out that the chemical processes, going in them, are peculiar. Practically it is very important that some substances influence mainly certain nerve centers.

For instance, apomorphine excites the vomiting center and causes vomiting; lobeline excites the respiratory center and increases the respiratory movements.

Some substances, called ganglioblocators, suppress the transmission of the excitation in ganglia of the vegetative nervous system. Strychnine blocks up the function of certain inhibitory synapses, and therefore, increases the excitability of the central nervous system (especially that of the spinal cord).

Some poisons influence certain areas of cerebral hemispheres. For instance, cardiazol selectively effects the motor zone of hemispheres and causes epileptoid convulsions. Mescaline (peyote), that is, the alkaloid from the Mexican cactus, influences the visual center of the brain and causes hallucinations.

The substances which exercise specific influence on the higher nervous activity, are studied by the psychopharmacology.

**Coordination of Reflex Processes. Principles of Coordination. Trophic Functions of Nervous System**

Each reflex is the reaction of entire central nervous system and depends on the state of the central nervous system and the totality of the intercentral correlations and interactions. The interaction of the neurons and hence, of the nervous processes in the central nervous system, providing its concerted activity, is called coordination.

The coordination occurs in all parts of the central nervous system, in any nerve center and during realization of any reflex. It provides the exact performance of the muscular movements, creates reflex acts adapted to different external situations which include motor, secretory vascular components. There are some general regularities or principles of the coordination.

Each neuron in central nervous system has a large number of contacts with different other neurons. For instance, in one Purkinje cell of the cerebellar cortex about 200000 synapses are counted. Ability of neurons to set numerous synaptic contacts with different nerve cell is called divergence. For example, the central endings of axons of the primary afferent neuron form synapses on many motor neurons-synergists, on intercalary neurons realizing inhibition of motor neurons-antagonists and on the cells originating the dorsal (ascending) spinocerebellar tract.

Thanks to the divergence one and the same nerve can take part in different nerve reactions, control a large number of other neurons, and each neuron can provide a wide redistribution of impulses which leads to irradiation of excitation.

The impulses entering the central nervous system during powerful and prolonged stimulation cause excitation of the neurons not only in this reflex center, but also in other nerve centers. This spreading of excitation in the central nervous system is called irradiation.

To demonstrate the irradiation the brain stem of cat is dissected. Weak irritation of the sole of the hind leg causes flexion of only this paw in the ankle joint. The stronger stimulus causes flexion also in the knee joint, and still more stronger stimulus- besides, flexion in the hip joint. More powerful stimulations cause simultaneous extension in other hind leg, then - extension in the anterior limb on the same side, and at last - flexion of the symmetrical anterior limb.

So, stronger stimulation - wider is irradiation of excitation in the central nervous system.

A large number of branchings of axons and dendrites of the neurons and intercalary neurons uniting different nerve centers promote irradiation of excitation in wide areas of the central nervous system. The reticular formation plays a special role in the mechanism of irradiation of excitation.

Irradiation is prevented by a large number of inhibitory neurons and synapses in different reflex centers. Role of inhibition in limitation of irradiation is demonstrated in experiments with strychnine which blocks up the inhibitory synapses and eliminates postsynaptic inhibition. The same effect is observed under the influence of the tetanic toxin.

One of the conditions providing coordination is that the impulses coming into central nervous system along different afferent fibers may converge to the same intercalary and effector nurons. So, convergence means signals from multiple inputs converging to excite a single neuron.

Principle of convergence was established by Sherrington. Convergence can result from input signals from a single source or from multiple sources (the signals may be excitatory or inhibitory). For instance, the interneurons of the spinal cord receive converging signals from:

1. peripheral nerve fibers entering the cord,
2. propriospinal fibers passing from one segment of the cord to another,
3. corticospinal fibers from the cerebral cortex,
4. several other long pathways descending from the brain into spinal cord.

Then the signals from the interneurons converge on the anterior motor neurons to control muscle function.

In spinal cord and medulla oblongata convergence is of relatively limited character. In intercalary and motor neurons converge mainly the afferent impulses from different areas of the receptive field of one and the same reflex. But in higher parts of the central nervous system (basal ganglia and cerebral cortex) the convergence of the impulses from different receptive zones is observed, that is, one and the same neuron may be excited by the impulses, originated during the stimulation of the auricular, visual and cutaneous ceptors.

Convergence allows summation of information from different sources and resulting response is a summated effect of all different types of information. So, convergence is one of the important means by which the central nervous system correlates, summates and sorts different types of information.

The convergence explains the spatial summation of excitations, occlusion and some other phenomena.

Thanks to the convergence the principle of the final common path is possible. One and the same reflex movement may be caused by a number of stimulations, effecting different receptors. For instance, the reflex contraction of flexor muscles of cat’s extremity may be caused by following ways:

1. stimulation of the skin on the side;
2. during the scratch reflex;
3. stretch of the muscles as a result of stimulation of proprioceptors;
4. stimulation of the receptive field of flexion of this extremity; **5)** stimulation of the receptive field of extension of opposite extremity; **6)** sound or photic stimuli (conditioned reflexes).

So, one and the same motor neuron enters the arches of many reflexes. Effector neurons form the final common path of different reflexes and may be connected with any receptors.

Because the number of receptor neurons is several times more than that of effector neurons. Reflexes, the arches of which have a final common path are divided into two groups: **1)** the allied reflexes;

**2)** the antagonistic reflexes.

**The allied reflexes** support and strengthen one another, whereas the antagonistic reflexes exert to one another inhibitory influences. They are competing with one another in seizing the common end pathway. This is called the fight for the common end pathway.

For instance, the scratch reflex and the flexor reflex have the same common end pathway (the motor neurons that innervate the flexor muscles), but afferent and intercalary neurons are different. If during the scratch reflex the strong painful stimulation is applied on the same area of the skin, the extremity is flexed, that is, the scratch reflex gives up its place to flexor reflex. Because when the impulses from painful receptors enter the intercalary neurons, taking part in the scratch reflex, they become inhibited.

Outcome of the fight among the antagonistic reflexes for the common end pathway depends on the strength of the stimulation, functional state of the nerve centers. Some stimulations causing pain, hunger, sexual act, etc. which are of particular physiological significance, easily get into the common end pathway and cause the reaction.

The principle of **dominant** was formulated by Ukhtomsky as the main principle of the nerve centers activity. According to this principle, for the activity of nervous system as a whole existence of the dominant, that is, prevailing foci of excitation, is characteristic. This dominant nerve center subjugates the activity of all other nerve centers. Since the dominant center’s excitability is very high, stimulation of different receptive fields cause the reflex response which is characteristic of this dominant center.

For instance, if at the moment preceding defecation, the motor zone of the brain cortex is stimulated, which in ordinary conditions cause flexion of the extremity, in this situation the flexion does not occur, and instead, the defecation is speeded up and intensified. When the same zone is stimulated during the swallowing reflex, it strengthens the swallowing, but does not cause flexion of the extremity.

The phenomenon of the dominant may be observed also in the clinical practice. For instance, the burning pain in the wounded extremity (causalgia) is increased during different incidental stimulations (touching to any parts of the body, the loud sound, etc.).

The dominant focus of the excitation is characterized by increased excitability, stability of the excitation, ability of summation of excitations and inertia, that is, the ability of holding the excitation for a long time after the stimulation has been ended.

Usually the centers connected with the satisfaction of the vital needs of the organism at present, become dominant. In the origin of the dominant center the humoral and hormonal factors are significant (the “hungry” composition of the blood, increase of the sexual hormones blood content, etc.).

Mechanism of the dominant phenomenon is connected with the wide irradiation of any excitation in the central nervous system. When the excitability of any center is increased, the spreading excitations become of threshold level for this dominant center and can cause or strengthen its reflexes.

An incoming impulse to a neuronal pool may cause an output excitatory signal going in one direction and at the same time an inhibitory signal going in other direction. For example, an excitatory signal is transmitted by one set of neurons in the spinal cord to cause forward movement of leg; simultaneously an inhibitory signal is transmitted through a separate set of neurons to inhibit the muscles on the back of the leg so that they will not oppose the forward movement. This type of circuit is called the reciprocal inhibition circuit.

The reciprocal innervation is characteristic of control of all antagonistic pairs of muscles. This type of circuit is also important in preventing overactivity in many parts of the brain.

The reciprocal inhibition is achieved by the following way. The input fiber directly excites the excitatory output pathway, but it stimulates an intermediate inhibitory neuron which then inhibits the second output pathway from the pool.

The similar mechanism causes the reciprocal inhibition of more complex reflexes. For instance, during the realization of food, sexual, defence reflexes, other reflexes are weakened.

Every motor act caused by any different stimulation is accompanied by the excitation of proprioceptors of muscles, tendons, joints from which the nerve impulses enter the central nervous system. If the movement is controlled visually or results in any sound (playing the piano), then besides the proprioceptive impulses the visual and acoustic signals also enter the central nervous system.

As distinct from the afferent impulses primarily causing the reflex act, these afferent impulses, occuring as a result of the activity of organs and tissues, is called the secondary afferent impulses (way back afferentation) or feedback.

The way back afferentation informs the central nervous system about the result of the reflex after it was performed. Without this information control of movements, as well as any functions of organism, is impossible. So, the feedback principle plays a great role in the mechanisms of the coordination. For instance, in patients with affected proprioceptive sensibility the central nervous system cannot control movements; walking of such persons loses its gracefulness and exactness. Their movements become abrupt and jerky. If such a person closes his eyes, he falls immediately.

In experiments after deafferentation (dissection of all sensory nerves) of the limb it begins to perform the rhythmical movements coinciding with the respiratory movements. Because absence of secondary afferent impulses causes weakening of the inhibitory process and intensifies irradiation of the excitation in the central nervous system.

The feedback principle is extremely significant also for regulation of the vegetative functions (heart rate, blood pressure, respiration rate, etc.).

In connection with the mechanisms of the coordination of reflex acts frequently the contrasting changes in the state of the central nervous system are noted: after the inhibition in the same area the powerful exciation occurs and after the excitation inhibition is observed.

The same phenomena were observed by I. P. Pavlov in the investigations of the conditioned reflex activity, and he called them succesive cortical positive (excitation after inhibition) and negative (inhibition after excitation) induction.

With the induction phenomenon, obviously, the rebound (recoil) phenomenon is connected. This is the rapid replacement of one reflex by another reflex of opposite significance. For instance, after cessation of the stimulation causing the powerful flexion reflex, the extremity is sharply extended. Because when the extremity is flexed, the center of the extension is in the state of reciprocal inhibition, though the continuous weak impulses from the relaxed muscles enter it. Therefore, as soon as the flexion is over, the inhibition in the extension center is replaced by excitation.

Owing to such mechanism one reflex can cause another one of opposite signifycance, this reflex - the third one and so forth. The complex reflex acts where the end of one reflex causes the origin of other reflex, are called the chain reflexes.

Often in chain reflexes (walking, scratching) one and the same simple reflex acts are repeated in certain sequence. These are called the rhythmical reflexes.

Adaptability of the nerve centers and changeability of their functional significance is called the plasticity of nerve centers.

The plasticity of nerve centers is observed in the surgical operations with the crossed suture of nerve trunks. Two different nerve trunks are dissected and the central end of one nerve is sewn to the peripheral end of another one.

If the vagus nerve is connected with the skeletal muscle nerve in above-mentioned way, it forms nerve terminals which are characteristic of any motor nerve, and the same vagus nerve when connected with the sympathetic nerve trunk, forms the terminals characteristic of sympathetic nerve. Several months later the nerve centers are radically reconstructed and acquire the new functions. For instance, after the central end of the hypoglossal nerve is connected with the phrenic nerve’s peripheral end, the neurons in the nucleus of hypoglossal nerve functionally join in the respiratory system and send rhythmical impulses to the diaphragm.To treat the facial nerve paralysis, to its peripheral end the central end of one of the neighbouring nerves was sewn. As a result of this operation the normal innervation of the muscles of the face was recovered.

Thanks to the plasticity of nerve centers, after destruction or removal of some areas of the central nervous system compensation of disturbed functions is observed several months later.

Great is the role of the cerebral cortex in the compensatory adaptability of nerve centers to the damage and their functional reconstruction. If the brain cortex is removed, all the operations with connecting of different nerves are unsuccessful.

The nervous system performs also the trophic functions, that is, it regulates the metabolism in tissues.

For instance, the nerve fibers conducting impulses to the muscles, simultaneously regulate the metabolic processes in the muscular tissue.

Dissection or damage of nerves or nerve centers cause different pathological changes in the denervated organs (skin, bones, internal organs).

I. P. Pavlov explained the strengthening and weakening influence of nerves on the heart muscle contractions by their effect on the metabolism. These nerve fibers were called by him the trophic nerves of the heart. Later Pavlov suggested that all other organs and tissues are also supplied by the trophic nerves, influencing the “chemism of life”.

However, at present it is considered that the specific trophic nerves do not exist, and every nerve fiber exerts the trophic influence on the tissues that are innervated by this fiber. Not only the motor nerves, but also the afferent nerves, as well as the vegetative nerves perform the trophic function.

In the experiments with dissection of motor nerves it was established that less the distance between the muscle and point of dissection of the nerve, earlier the degenerative changes in the muscle begin. This fact permits to assume that some “trophic agents” are moving through the nerve fibers in the direction from the proximal to the distal areas and are secreted by nerve endings.

Each area of the central nervous system takes part in the realization of the trophic function of the nervous system, but the role of hypothalamus and cerebral cortex. is particular.

In the experiment by the way of surgical operation the small glass ball was put on the Turkish saddle. Such chronic irritation of the hypothalamus nuclei caused the chronic trophic ulcers in the skin and digestive tract.

The trophic disturbances were observed also after the removal of the brain cortex and even in the difficult situations for higher nervous activity.

**LECTURE 5**

**Functions of Spinal Cord and Medulla Oblongata**

Spinal cord performs two main functions.

1. The white substances of the spinal cord consists of many afferent and efferent conductions tracts, that is, the spinal cord performs conductive function. It is a conduit for sensory signals to the brain and for motor signals from the brain back to the periphery.
2. In the gray substance of the spinal cord many nerve centers are situated, where arcs of many reflexes close, that is, the spinal cord performs regulatory function.

The spinal cord takes part in realization of all complex motor reactions of organism. Even the most fundamental motor systems of the brain cannot cause any purposeful muscle movement without the special neuronal circuits of the spinal cord. For instance, there is no neuronal circuit anywhere in the brain that causes the specific to - and -fro movement of the legs that is required in walking. These circuits are in the spinal cord, and the brain simply sends command signals to set into motion the walking process. The brain gives the sequential directions to the spinal cord activities, to promote turning movements when they are required, to lean the body forward during acceleration, to change the movements from walking to jumping, to monitor continuously and control equilibrium.

The spinal cord rceives impulses from exteroceptors of cutaneous surface, proprioceptors and visceroceptors of the trunk and extremities (except the visceroceptive impulses entering the central nervous system by the vagus nerves).

The information entering the spinal cord from receptors is conducted by the numerous afferent conduction tracts situated in the posterior and lateral columns to the centers of brain stem, then they reach cerebellar and cerebral cortex.

In its turn the spinal cord receives impulses from higher parts of the central nervous system by a number of efferent conduction tracts situated in the anterior and lateral columns.

The spinal cord innervates all the skeletal musculature except the muscles of the head that are innervated by cranial nerves.

Two types of experimental preparations are useful in studying spinal cord function:

1. the spinal animal in which the spinal cord is transected, frequently in the neck so that most of the spinal cord still remains functional (a few hours after preparing in low animals and after a few days to weeks in monkeys),
2. the decerebrate animal in which the brain stem is transected in the lower part of the mesencephalon.

In the decerebrate animal the normal inhibitory signals from the higher control centers of the brain to the pontile reticular and vestibular nuclei are blocked. These nuclei become tonically active transmitting facilitatory signals to most of the spinal cord motor control circuits. The result is that these become easy to activate by even the slightest sensory input signals to the spinal cord. Using this preparation, it is easy to study the intrinsic motor functions of the spinal cord itself.

Connection of the spinal cord with the periphery is realized by the nerve fibers passing in the spinal cord roots. The functions of the spinal cord roots were ascertained by the methods of dissection and stimulation, and then the results were confirmed by the way of recording of the bioelectrical potentials.

The posterior roots consist of afferent (centripetal, sensory) fibers, and the anterior roots consist of efferent (centrifugal, motor) fibers. This law of the distribution of the afferent and efferent fibers in the spinal cord roots is called the law of Bell and Magendie.

The anterior roots contain not only the motor nerves of the skeletal muscles, but also the fibers innervating the smooth muscles as well as the secretory and vasomotor fibers. All of these are the efferent fibers.

After dissection of the anterior roota on one side of the body the reflex movements on that side disappear, but the sensibility remains. Dissection of the posterior roots does not cause loss of ability to move, but since sensibility in the corresponding areas disappear, the exactness of coordination of the movements in these parts of the body are lost.

In the following experiment the functional role of the spinal cord roots is deminstrated visually. On one side of the frog’s spinal cord the posterior roots are dissected and on another side - anterior roots. As a result of dissection of the posterior roots the limb loses its sensibility completely and does not response when it is stimulated. But its ability to move is not lost, and therefore, the limb moves in response to the stimulation of other parts of the body.

Another limb (where the anterior roots were dissected) hangs immovab;le as lash, but its sensibility is preserved. Therefore, when this limb is stimulated, other parts of the body (in particular, the opposite limb) are moved.

The fibers that form the posterior roots are the processes of the neurons of intervertebral spinal ganglia. The anterior roots include axons of the motor neurons of the anterior horns and of the cells situated in the lateral horns of the thoracal and lumber segments of the spinal cord that belong to the vegetative nervous system.

Each segment of the spinal cord from each side of which one posterior from each side of which one posterior root originates, innervates three metameres (transversal segments) of the body, that is, not only the metamere that corresponds to the spinal cord segment, but also one situated on it and another under it. Therefore, dissection of one posterior root does not cause the complete loss of sensibility in the corresponding metamere. the segmental distribution of the anterior root fibers is clearly revealed in the intercostal muscle.

In spinal cord roots there are nerve fibers of different thickness in which the velocity of conduction of the impulses is also different.

The posterior roots include all groups of A type nerve fibers. The thick Aα type fibers conduct impulses from the nuclear bags of muscle spindles and Golgi tendon organs which cause the myotatic reflexes in response to the stretch of the muscle. Aβ and Aγ fibers originate from the tactile ceptors, receptors of muscle spindles situated to the periphery from the nuclear bag; receptors of the hollow organs (stomach, intestines, urinary bladder), mechanoreceptors. The thinnest fibers of Aβ type conduct impulses from thermoreceptors and pain receptors. The impulses from pain receptors are conducted to the spinal cord also by thin unmyelinated c type fibers.

In anterior roots there are efferent nerve fibers of different types: the thick Aα type fibers conduct impulses to the skeletal muscles. Aγ type fibers innervate the contractile elements of muscle spindles. Preganglionic sympathetic fiber are of B type.

After dissection of the posterior roota besides disappearance of the sensibility, disturbance of the movements is alo observed, though the anterior roots are intact. Because absence of feedback (cessation of afferent impulses to the brain, first of all, from the proprioceptors and exteroceptors of the skin) causes disturbance of the coordination of the movements. Therefore, the ovements become jerky and absurt, the extremities excessively bend or straighten. This is called the spinal ataxia.

The conductive tracts of the spinal cord conduct information from receptors (the afferent tracts) and higher brain structures (the efferent tracts) to the spinal cord.

With the exception of a few very small fibers of questionable importance that enter the ventral roots, the sensory information from the somatic segments of the body enters the spinal nerves. But from the entry point of the spinal cord and then to the brain the sensory signals are carried through one of two alternate sensory pathways: 1) the dorsal-column-lemniscal system, 2) the anterolateral system. These two systems again come together partially at the level of the thalamus.

The dorsal-column-lemniscal system carries signals mainly in the dorsal columns of the cord and then, after crossing to the opposite side in the medulla, upward through the brain stem to th thalamus by the way of the medial lemniscus. Signals of the anterolateral system, after originating in the dorsal horns of the spinal gray mather, cross to the of the spinal gray matter, cross to the opposite side of the spinal cord and ascend through the anterior and lateral white columns to terminate at all levels of the brain stem and also in the thalamus.

The dorsal column - lemniscal system is composed of large myelinated nerve fibers that transmit signals to the brain rapidly (30-110 m/sec), whereas the anterolateral system is composed of much smaller myelinated fibers that transmit signals slowly (from a few meters per second up to 40 m/sec). Also, the dorsal column - lemniscal system has a very high degree of spatial orientation of the nerve fibers with respect to their origin on the surface of the body, whereas the anterolateral system has a much smaller degree of spatial orientation.

Therefore, sensory information that must be transmitted rapidly and with temporal and spatial fidelity is transmitted in the dorsal column - lemniscal system, while that which does not need these qualities is transmitted mainly in the anterolateral system. But the anterolateral system has a special capability that te dorsal system does not have: the ability to transmit a broad spectrum of sensory modalities - pain, warmth, cold and crude tactile sensations, the dorsal system is limited to more discrete types of mechanoreceptive sensations alone.

So, the types of sensations transmitted in the two systems are the following.

The dorsal column - lemniscal system:

1. touch sensations required a high degree of localization of the stimulus;
2. touch sensations requiring transmission of fine gradations of intensity;
3. phasic sensations, such as vibratory sensation;
4. sensations that signals movement against the skin;
5. position sensations;
6. pressure sensations having to do with fine degrees of judgement of pressure intensity.

the anterolateral system: 1) pain; 2) thermal sensations, including both Warm and cold sensations; 3) crude touch and pressure sensations capable of only crude localizing ability on the surface of the body; 4) tickle and itch sensations; 5) sexual sensations.

The main afferent (ascending) tracts of the spinal cord are the following.

Impulses from the proprioceptors of muscles, tendons and ligaments are conveyed to the higher parts of the central nervous system partly by Goll’s (the fasciculus gracilis) and Burdach’s (the fasciculus cuneatus) bundles (within the posterior columns of the spinal cord) and partly by Gowers’ and Flechsig’s spinocerebellar tracts (in the lateral columns).

Goll’s and Burdach’s bundles end in the medulla oblongata. All the other ascending pathways begin from the neurons of the grey matter of the spinal cord.

The fibers of Gowers’ and Flechsig’s bundles begin at the columnar (Clarke’s) cells of the posterior horn and partly from the commissural cells of the spinal cord.

Disturbance of transmission of the afferent impulses along the spinocerebellar tracts leads to derangement of complex muscular acts with disorders of the muscular tone and symptoms of ataxia, just as in lesions of the cerebellum.

Impulses from pain and temperature receptors are carried to the cells of the posterior horns, where the second neuron of the afferent tract begins. The processes of this neuron extend to the opposite side, enter the white matter of the lateral columns and ascend in the lateral spinothalamic tract to the thalamus where the third neuron, conducting impulses to the cortex, begins.

In certain lesions of the spinal cord only sensation of pain or temperature may be impaired; even heat or cold sensitivity may be exclusively disturbed. This is evidence that impulses from the corresponding receptors are conveyed by different fibers.

Impulses from the tactile and pressure receptors of the skin are also partly conveyed by Goll’s and Burdach’s bundles.

The efferent (descending) pathways of the spinal cord are arranged in the anterior and lateral funiculi (columni) of the white matter. The corticospinal or pyramidal tract is the most important among the descending tracts. Its neurons lie in motor cortex. The endings of corticospinal fibers are found mainly on the spinal interneurons.

The typical symptom of lesion of the pyramidal tracts is the pathological reflex called Babinsky’s reflex or toe phenomenon.

The axons of the pyramidal cells forming the corticospinal tract give off collaterals which end in the nuclei of the corpus striatum, the hypothalamus, the red nucleu, the cerebellum and the reticular formation of the brain stem. From all of these nuclei impulses are conveyed through the descending pathways known as the extracorticospinal or extrapyramidal tracts, to the internuncial neurons of the spinal cord.

The most important of these tracts are the reticulospinal, rubrospinal, tectospinal and vestibulospinal. the rubrospinal tract (Mo kow’s bundle) conveys impulses to the spinal cord from the cerebellum, the corpora guadrigemina and the subcortical centers. The impulses passing by this tract are important for coordination of movements and regulation of the muscle tone.

The vestibulospinal tract extends from the vestibular nuclei in the medulla oblongata to the cells of the anterior horn. Impulses arriving by this tract bring about tonic reflexes of the position of the body. The reticulospinal tracts transmit activating and inhibitory influence of the reticular formation to the neurons of the spinal cord.

More than half of all ascending and descending nerve fibers of the spinal cord are propriospinal fibers, that is, the short tracts connecting the higher and lower segments of the spinal cord. Besides, the secondary fibers, as they enter the spinal cord, branch up and down it and some of the branches transmit signals only a segment or two in each direction, others - many segements. These short fibers provide pathways for the multisegmental reflexes, including reflexes that coordinate simultaneous movements in the forelimbs and hindlimbs.

The grey matter of the spinal cord is the integrative area for the spinal cord reflexes and other motor functions.

In the transversal section of the spinal cord the grey matter has the posterior and anterior horns with the intermediate zone between them. In addition, there are lateral projections of the grey matter in the thoracic segment, the lateral horns.

The dorsal part of the posterior horns lodges a typical accumulation of nerve cells which form thick bundles. This zone is known as Rolando’s fasciculus (or substance).

A layer-by-layer separation of the grey matter of the spinal cord into laminae provides the most correct idea on the topography of its nerve cells. Each lamina contains neuron groupings of the same type.

The grey matter can be divided into ten layers or plates.

All the neuronal elements of the spinal cord are classified into the four principal groups: efferent neurons, interneurons (intercalary or internuncial neurons), ascending tract neurons and intraspinal fibers of sensory afferent neurons.

In the human spinal cord there are more than 10 millions of neurons. Only 3% of these neurons are motor neurons and the rest 97% - interneurons.

The motor neurons located in each segment of the anterior horns of the spinal cord (anterior motor neurons) are 50 to 100% larger than most of the others. These neurons are of two types: the alpha motor neurons and the gamma motor neurons.

The alpha motor neurons give rise to large type Aα nerve fibers that innervate the skeletal muscle fibers. Stimulation of a single nerve fiber excites from as few as three to as many as several hunderd skeletal muscle fibers forming the motor unit.

The gamma motor neurons are much smaler. They transmit impulses through A γ type fibers to very small, special skeletal muscle fibers called intrafusal fibers. These are part of the muscle spindle.

The interneurons are present in all areas of the spinal cord grey matter - in the posterior and anterior horns and in the intermediate areas between them. These are small and highly excitable cells, ften exhibiting sponteneous activivty and capable of firing as rapidly as 1500 times per second. The interneurons have many interconnections one with another, and many of the directly innervate the anterior motor neurons.

The interconnections among the interneurons and anterior motor neurons are responsible for many integrative functions of the spinal cord. All the different types of neuronal circuits, including the divering, convering, repetitive-discharge circuits, are found in the interneuron pool of cells in the spinal cord. These different circuits take part in the performance of many specific reflexes acts by the spinal cord.

Only a few incoming sensory impulses from the spinal nerves or from the barin terminate directly on the anterior motor neurons - most of them are transmitted through processed. For instance, the corticospinal tract terminates almost entirely on interneurons. The signals from this tract finally impinge on the anterior motor neurons to control muscular functions only after they have been integrated in the interneurons pool with the signals from other spinal tracts or from the spinal nerves. Interaction of spinal cord neurons and strictly coordinated activity of motor neurons is realized thanks to the interneurons which set wide connections between different neurons.

Role of the peripheral and intraspinal recurrent facilitatory and inhibitory influence are of great significance in the mechanism of coordinati0on of the motoneurons activity, and consequently, in the motor reactions.

During the realization of any voluntary and involuntary motor act the motor neurons are subjected, besides the primary influence of starting impulses, to the secondary influence of the proprioceptive impulses from the muscles tendons and joints performing the movement. Impulses from muscle spindlers activate the alpha motor neurons by reflex way (through interneurons), and their excitation causes the muscle contraction.

When a muscle is contracted, afferent impulses from the muscle spindless become rare or cease, and this leads to the weakening of the activity of alpha motor neurons. Besides, the muscle contraction causes excitation of Golgi tendon organs, the afferent impulses from which exercise the direct inhibitory effect on the excited motor neuron and activates its antagonist.

Intraspinal recurrent inhibition is realized by small intrneurons called Renshaw cells, which are located also in the anterior horns of the spinal cord. Before going out of the spinal cord, axons of motor neurons form recurrent collaterals which end on the Renshaw cells. The axons of these cells are branched and form contacts by several motor neurons. The action potential spreading along the axon of motor neuron simultaneously by the collaterals reaches the Renshaw cell and axcites it. This cell, in its turn, sends frequent inhibitory impulses to the motor neurons. The Renshaw cells inhibit also the interneurons which are immediately connected with notor neurons.

Besides the recurrent inhibition, in the spinal cord exists also the mechanism of recurrent facilitation. This is also realized with the participation of the renshaw cells. But this time they inhibit the inhibitory Wilson cells and the motor neurons become free from the inhibition. So, inhibition of the inhibition causes facilitation.

A large number of reflex arcs end in the spinal cord. The tendon reflexes as well as the stretch reflexes are the simplest. The muscle stretch reflex (myotatic reflex) is also the simplest manifetation of muscle spindle function-whenever a muscle is streched, excitation of the spindle causes reflex contraction of the large skeletal muscle fibers that lie around the spindles. The arc of stretch reflexes may have a monosynaptic character.

The tendon reflexes, which can be easily elicited with the help of a light tap upon the tendon, are important for the diagnosis of nervous diseases. The knee-jerk reflex is manifested by extension of the leg at the knee-joint when the tendon of the quadriceps muscle is lightly struck. The Achilles - tendon reflex is manifested by extension at the talocrural joint when the Achilles tendon is sharply struck.

The flexion reflexes arise in response to stimulation of nociceptors (pain receptors) and are aimed at avaiding various injurious influences. Therefore, the receptive fied of the flexion reflex is rather complicated. Excitation of motor neurons which innervate flexor muscles are attended with simultaneous reciprocal inhibition of extensor motor neurons.

The flexion reflexes differe from mmyotatic and tendon reflexes by a greater number of synaptic relay stations on the way to the motor neurons and thanks to the polysynaptic pattern of these reflexes, their central time rather long.

More complex are the rhythmic and postural reflexes. The scratch reflex in mammals and the rubbing reflex in reptiles are examples of the rhythmic reflexes.

The postural reflexes (reflexes of body position) include many reflexes that control maintenance of a definite posture of the body.

When a spinal dog is suspended by the trunk, pressure applied to one of its paws elecits reflex movements of a walking type in all four legs. This is called Philippson’s reflex.

The spinal cord also plays a major role in the reflex regulation of the internal organs and is the center of numerous visceral reflex (th vasomotor and prespiration centers, the centers regulating the functions of the urogenital organs and rectum etc.). The preganglionic neurons of the vegetative nervous system (in the lateral and anterior horns of the grey matter) take part in these reflexes.

The normal activity of the spinal cord neurons depends to a great extent on continual tonic discharges of nerve fibers entering the spinal cord from higher centers (particularly those transmitted through the corticospinal tract, reticulospinal tract, vestibulespinal tract). Therefore, when the spinal cord is transectd, all of its functions (including spinal cord reflexes) immediately become depressed to the point of total silence. This state is called the spinal shock.

The maximum hight of spinal section in mammals at which an animal can survive for any length of time, is at the level of the IV-V cervical segments. A section performed above these segments causes death through stoppage of respiration, because the spinal nuclei of the diaphragmmatic nerves do not then receive impulses from the respiratory center.

So, the **spinal shock** is observed only when the complete transection of the spinal cord is performed not higher than the IV-V cervical segments.

The spinal shock is manifested by a sharp decline of excitability and depression of the reflex functions of all nerve centers situated below the section. But the centers lying above it continue to function.

During or following spinal shock the arterial blood pressure falls immediately, all skeletal muscle reflexes integrated in the spinal cord are completely blocked. In low animals a few hours to a few days are required for the reflexes to return to normal. But in human beings the return is often delayed for several weeks or several months and occasionally it is never complete.

Sometimes the recovery is excessive, with resultant hyperexcitability of some or all spinal cord functions (hyperreflexia). For instance, a patient with spinal injury exhibited so-called mass reflexes: stimulation of the feet caused a jerking back of both legs, perspiration, urination and defecation.

Hyperreflexia is due to cessation of inhibitory influences from the brain, in particular, from the reticular formation.

Medulla oblongata and pons Varolii form the hindbrain. Together with the midbrain they make up the brain stem. The brain stem is closely connected with the spinal cord, cerebellum, cerebral hemispheres. The arcs of many complex coordinated motor reflexes close in brain stem. Besides, here are located the centers resulting vitally important functions. The reticular formation of brain stem is of great functional importance.

Role of analogous to brain stem divisions of the brain varies in different species of animals. That is why the varied pictures of functional disorders follow its section in animals. This is a substantial difficulty in experimental study of the physiology of the brain stem.Therefore, clinical observation of functional dissorders in various diseases involving lesions of the nuclei or conducting pathways of the brain stem are important for understanding its physiology in man.

The hindbrain also, like the spinal cord, performs two main functions:

1. The white matter of the hindbrain consists of conducting (ascending and descending) tracts passing from the spinal cord and various higher - located formations. The hindbrain receives afferent fibers from the vestibular and auditory receptors, skin and head muscles, internal organs.
2. The hindbrain contains accumulations of nerve cells that form nuclear structures. In hindbrain the nuclei of the last 8 pairs (V-{II) of cranial nerves are situated - that of V- VIII pairs in the pons Varolii and that of IX – XII pairs in the medulla oblongata.

All nerve impulses coming from the spinal cord to the brain and from the brain to the spinal cord pass through the medulla oblongata and the pons. Here some of them (for instance, the impulses passing through to another neuron which transmits them to the higher divisions of the central nervous system. A number of conducting tracts (the lateral corticospinal tract, the ascending tracts coming from Goll’s and Burdach’s nuclei) decussate in the hindbrain, the fibers of some tracts (corticobular tract) end here, forming synapses in the interneurons or motor neurons. And some descending tracts (the reticulospinal tract and the vestibulospinal bundle) transmitting impulses to the spinal cord, begin in hindbrain.

The spinal tracts decussate either in the spinal cord itself or in the hindbrain, whereas the cranial nerves do not cross here. Such facts help to form an idea of the mechanisms by which functional disorders develop after damage to its different parts. For instance, a characteristic sign of unilateral lesion of the hindbrain is alternating paralysis: motor paralysis of one or more cranial nerves on the affected side and disorders of motor function and sensation on the opposite side of the body.

Afferent impulses transmitted by the fifth to twelfth cranial nerves are switched over in hindbrain to the interneurons and motor neurons.

The neuronal organization of the hindbrain has more comples structure than that of spinal cord. Similar to the spinal cord, the hindbrain has efferent neurons (including motor neurons), interneurons, neurons of ascending and descnding tracts, primary sensory fibers, fibers of conducting tracts passing through the hindbrain in the ascending (rostral) and descending (caudal directions.

Resembling the spinal cord neuron centers, nuclei of the crnial nerves receive afferent impulses from the periphery and send efferent impulses to the muscles, organs and tissues.

The trigeminal nerve (V pairs) is mixed. Its sensory nucleus arises in the caudal part of the medulla oblongata and is projected through the pons to the rostral end of the midbrain. The cells of this nucleus receive signals from the receptors of the facial skin, parietal and temporal regions, nasal mucosa, periosteum of the bones of skull, dura mater, the teeth, the tongue. The motor nucleus of this nerve has cells which supply the masticatory muscles, the tensor palatini and tensor tympani muscles.

The abducent nerve (VI) is motor nerve. Its motor neurons are located in the floor of the fourth ventricle in the posterior part of the pons. They innervate the external rectus muscle of the orbit. The facial nerve (VII) is mixed. Its afferent fibers transmit signals from the taste receptors of the anterior part of the tonque. The effernt fibers supply the muscles of facial expression.

The vestibulocochlear nerve VIII is sensory nerve and consists of two branches. A considerable part of the vestibular nerve is formed by the afferent fibers running from the receptors of the semicircular canals. Some of them pass to the cerebellum the vestibular nucleus neurons give rise to the vestibulocerebellar and vestibulospinal tracts. The cochlear nerve is formed by the afferent fibers running from the spiral organ of Corti.

The viscerosensory nucleus of the mixed glossopharyngeal (IX) and vagus (X) nerves (nucleus of the fasciculus solitarius) receives impulses through sensory fibers from the receptors of the tongue larynx, trachea, ocsophagus, thoracic and abdominal viscera. It is connected with the visceromotor nuclei of these nerves by interneurons. The effernt neurons located in these nuclei innervate the parotid gland, the glandular and smooth muscles cells of the trachea, bronchi, stomach, intestine and also heart and vessels. The somatomotor and vegetative nuclei of the tenth - ninth pairs of the cranial nerves are formed by accumulations of nerve cells with a less pronounced differentiation of separate nuclear structures. Axons of neurons of the motor nuclei pass as part of the glossopharyngeal and vagus nerve branches to innervate the muscles of the pharynx and larynx.

The nuclei of the accessory (XI) and hypoglossal (XII) nerves are purely motor. The axons of their motor neurons innervate the muscles of the tongue and those responsible for movement of the head.

The reticular formation is situated in the medial part of the medulla oblongata cells of the reticular formation give rise to the ascending and descending tracts which form numerous collaterals whose endings make synaptic contacts with various nuclei of the central nervous system. the reticular cell fibers passing to the spinal cord form the reticulospinal tract.

The reticular formation neutons also receive numerous collaterals arising from the fibers of the ascending tracts originating in the spinal cord (spinoreticular fibers) and from the neurons of the higher-lying brain parts (cerebellum, brain cortex).

The nuclei of the pons Varolii reticular formation are the continuation of the bulbar reticular formation nuclei. The medial nuclei of the reticular formation of the pons give rise to the ascending fibers extending to the midbrain and dencephalon.

The hindbrain is responsible for numerous functions many of which are vitally important for the body. The reflex somatic reactions mediate the maintenance of body posture, the perception, swallowing and digestion of food. The vegotative reflexes regulating secretion of salivary and other alimentary glands are also involved in the processes associated with digestion.

The postural reflexes (static and stato-kinetic reflexes) are related to the receptors of the vestibular apparatus and semicircular canals. they involve almost all body musculature.

Along with motor reflexes, activation of the vestibular apparatus causes excitation of the vegetative centers, including vagus nuclei. The arising vestibulo-vegetative reflexes cause changes in respiration, heart rate, gastrointestinal activity.

Many motor reflexes that involve the hindbrain nuclei are associated with food intake, chewing and swallowing. They are interconnected so that one reflex stimul;ates the next one, that is, they are in the nature of chain reflexes. the motor nuclei of the trigeminal, glossopharyngeal vagus, accesory and hypoglossal nerves take part in the performance of the motor feeding reflex. The trigeminal nerve motor neurons mediate the chewing reflex. Swallowing of food and its movement to the ascophagus is ensured by a chain reflex with gradual involvement of neurons of the glossopharyngeal, vagus accesory and hypoglossal nerve nuclei. The receptive field ofthese reflexes is made up of the receptors of the oral mucosa and root of the tongue.

The vegetative (automatic) nuclei of the hindbrain are related to the parasympathetic part of the nervous system. the main vegetative nuclei of the medulla oblongata belong to the vagus nerve. Activation of neurons of these nuclei and also of the vegetative nuclei neurons of the facial and glossopharyngeal nerves ensures the reflex control of respiration, cardiac activity, vascular tone, functioning of the digestive glands, sweating.

The medulla oblongata contains centers of both relatively simple and more complex reflexes, though in general the bulbar reflexes are more complicated, perfect and more complexly coordinate than the spinal reflexes. Since in bulbar animal all the principal vital functions are unified by a more perfect system of control and are better coordinated, it is capable of more complex reactions to external stimuli than a spinal animal.

Reflexes of medulla oblongata are excited by impulses arriving from the spinal cord as well as from the receptor systems of the trigeminal, acoustic, vestibular, glossopharyngeal and vagus nerves. Various muscle groups, vessels, many internal organs take part in these reflexes.

The reflex and centers of the medulla oblongata connected mainly with the activity of the skeletal musculature are the following.

The respiratory center is a single functional system consisting of several groups of neurons in different parts of the medulla oblongata and in the pons. Most important parts of the respiratory center are the inspiratory, expiratory and pneumotaxic centers. Impulses from the center are conveyed to the spinal cord motor neurons innervating the diaphragm and the intercostal musculature.

Association of the respiratory center with the center regulating cardiac activity is responsible for the reguar, periodic deceleration of cardiac activity at the end of expiration before the next inspiration begins. This respiratory orrhythmia is called also the respiratory- cardiac reflex.

The association between the respiratorycenter and the spinal cord centers was demonstrated in the following experiment. After deafferentation of dog’s leg (dissection of the dorsal roots through which impulses from the leg are conveged to the spinal cord) the leg begins to perform rhythmic movements coinciding with the rhythm of respiration. Because deafferentation disturbs the inhibitory precosses in the corresponding parts of the spinal cord, and its motor from the respiratory center by reticulospinal tract.

Afferent impulses reaching the respiratory center from the receptors of the lungs, respiratory passages and respiratory muscles are important not only for regulation of respiration, but also for regulation of respiration, but also for maintaining the activity of the reticular formation and consequently, they are important for the activity of the whole nervous system through the activating influence of the reticular formation.

The bulbar reflexes such as chewing, sucking, swallowing, vomiting, sneezing, coughing, blinking etc. are observed even in babies born without the greater part of the brain.

**Sucking** movements are caused by touching the lips of new-born baby. This reflex is the response to stimulation of the sensory endings of the trigeminal nerve from which excitation is switched to the motor nuclei of the facial and hypoglossal nerves in the facial and hypoglossal nerves in the medulla oblongata.

Chewing (mastication) is a motor act which is elicited in response to stimulation of the receptors of the oral cavity and consists in movement of the lower jaw in relation to the upper jaw.

**Swallowing (deglutition)** is a complex coordinated reflex act in which the afferent systems of the trigeminal, glossopharyngeal and vagus nerves are involved and many muscles of the oral cavity, pharynx, the beginning of the ocsophagus take place. There are two phases of the act of swallowing the first of which is regulated volitionally and the second - involuntarily by an unconditioned reflex:

1. formation of a food bolus and its delivery to the pharyngeal cavity;
2. the act of swallowing in which simultaneously the muscles of the pharynx contract, the soft palate is raised and the epiglottis is lowered.

**Vomiting** is also a complex coordinated reflex act evoked by stimulation of the receptrs of the pharyn[ and stomach, vestibuloceptors. Impulses from the receptors conveyed by afferent fibers to the medulla in the medulla oblongata and spinal cord. During the act of vemiting the entrance to the stomach is opened, the muscles of the intestine and the gastric walls, the abdominal muscles and the diaphragm, the pharynx, larynx, tongue and oral cavity contract; salivation and lacrimation occur.

Thanks to involvement of the reticular formation of the brain stem, during the act of vomiting the condition of many centers of the central nervous system is changed.

Vomiting can be triggered also by direct stimulation of definite areas of the medfulla oblongata by a growing tumour, an inflammatory process or increased intracranial pressure. The vomiting center can be excited also by the action of humoral factors (microbial toxins and certain medicines dissolved in the blood) as well as by the conditioned reflex way.

Sneezing and coughing are defensive respiratory reflexes.

Sneezing is a complex expiratory reflex caused by stimulation of the receptors of the trigeminal nerve in the nasal cavity. The effrent fibers of the glossopharyngeal, vagus, hypoglossal and certain spinal nerves are involved. The soft palate is elevated and closes the internal nasal orifice. Then contraction of the expiratory muscles produces an increase of pressire in the thoracic cavity, after which the nasal orifice is suddenly opened, and a flow of air is forcibly expelled through the nose, removing the particles irritating the nasal mucosa. Coughing is excited by stimulation of the mucous membrane of the larynx, trachea or bronchi. The rima dlottis is closed and suddenly opens when the air pressure in the lungs has risen to a definite level, and lets out a strong stream of air removing the cause of irritation. The afferent impulses are transmitted by fibers of the vagus nerve. The efferent fibers are the same that take part in sneezing.

Winking is also defensive reflex. It is caused by stimulation of the cornea and conjunctiva of the eye. The impulses conveyed by the afferent fibers of the trigeminal nerve to the medulla oblongata are switched to the motor nucleus of the facial nerve whose fibers innervate the orbicularis oculi muscle; as a result, the eyelids are closed.

Medulla oblongata in involved also in the reflex mechanisms of spatial orientation and regulation of the muscular tone. The afferent impulses evoning corresponding reflexes are trasmitted along the V - XII (in particular the vestibular) cranial nerves and also along the spinal nerves conveying impulses from receptors of the muscles of the face neck, extremities, trunk.

**Midbrain. Tonic Reflexes of the Brain Stem. Brain Stem Reticular Formation**

The midbrain (mesencephalon) anatomically consists of two main portions: the dorsal part (the tegmentum of the midbrain) and the ventral part (the cerebral peduncles). The midbrain contains also the nuclei of the corpora quadrigemina, that is, quadrigeminal bodies (under the Sylvian aqueduct in the region of the roof or tectum), substantia nigra, the red nuscleus (nucleus ruber), the nuclei of cranial nerves (third and fourth pairs) and the neurons of the reticular formation.

All the ascending tracts carrying impulses to the cerebellum, thalamus, cerebral hemispheres as well as the descending tracts transmitting impulses from the cerebral hemispheres, corpus striatum, hypothalamus to the medulla oblongata and spinal cord, pass through the midbrain.

The nuclei of the midbrain perform a number of important reflex functions.

The motor neuron axons of the oculomotor nerve (III) supply the oblique muscles of the orbit and the levator palpebrae superioris muscle. Efferent fibers of preganglionic parasympathetic neurons which innervate the ciliary muscle and sphincter of the pupil also pass in attendance to the oculomotor nerve.

The neurons of the trochlear nerve (IV) nucleus supply the oblique muscle of the orbit.

The anterior quadrigeminal bodies are the primary optic centers and the posterior quadrigeminal bodies are the primary auditory centers. They are involved in the perfomance of visual and auditory orientation reflexes accordingly. That is, even an animal with no cerebral hemispheres, but possessing a midbrain, reacts to a light stimulus by moving its eyes and body to the light and to the sound stimulus by pricking up the ears and turning the head and body towards a new sound.

Reflex movements of eyes are induced by impulses conveyed to the eye muscles from the oculomotor and trochlear nerves nuclei. The anterior quadrigeminal bodies also take part in the pupillary reflex, accomodation and convergence reflexes.

The motor reactions accompanying orientation reflexes in animals with an intact midbrain are concurrent with certain vegetative reflexes (changes in the heart rate, blood pressure).

The nuclei of the quadrigeminal bodies are responsible for the guarding reflex, whose function is to keep the organism in a state of readiness to respond to any new, sudden stimulation. An essential component of this complex reflex is a redistribution of muscular tone, increased tone of the flexor muscles, which enables the animal to escape or attack its prey. A person with derangements in this region is unable to react quickly to an unexpected stimulus.

The substantia nigra is directly related to the coordination of the complex acts of mastication and deglutition. It is a collection of nerve cells containing the pigment melanin which imparts the typical dark colour to this nucleus. Its electrical stimulation causes swallowing movements and corresponding changes in respiration. The substantia nigra also takes part in regulation of plastic and performance of delicate movements of the fingers requiring great accuracy and consequently, fine regulation of tone. That is why the human substantia nigra is better developed.

Damage to the substantia nigra causes hypertone (increased muscular tone). This is connected not only with the role of the substantia nigra but also with disturbance of its connections with the red nucleus and reticular formation.

The substantia nigra lodges the dopamine-containing neurons many of which send axons to the forebrain. They take part in the regulation of emotional behaviour. The other part of the dopaminergic neurons of the substantia nigra sends axons to the nuclei of the corpus striatum, where the role of dopamine consists in the control of complicated motor acts. Damage to the substantia nigra leads to degeneration of dopaminergic fibers running to the corpus striatum, cause derangement of fine movements of fingers and development of muscular rigidity and tremor (Parkinson’s disease).

The red nucleus and the midbrain reticular formation are closely connected with regulation of muscular tone.

The thickest and having higher conduction velocity axons of the rubrospinal tract arise from the large neurons of the red nucleus which receive excitatory signals from the nerve cells of the substantia nigra, cerebellum and motor area of the cerebral cortex.

Unlike the bulbar animal, the mesencephalic animal has a normal distribution of muscular tone and is able to recover and maintain its normal posture.

Transection of the brain stem below the red nucleus (decerebration) in animals causes a state called decerebrate rigidity. This state is characterized by sharply increased tone of the extensor muscles. The animal’s extremities are greatly extended, the head is tilted back and the tail is raised.

Development of decerebrate rigidity is associated with interruption of signal transmission to the spinal cord through the corticospinal and rubrospinal tracts activating primarily the motor neurons of the flexor muscles. As a result, activity of the vestibulospinal system which intensifies the tone of the motor neurons of the extensor muscles, becomes dominating.

Dissection of the dorsal roots innervating a hind leg eliminates rigidity of its muscles. This proves that the tonic tension of the musculature resulting from decerebration is of reflex origin.

In man rigidity is often due to injuries to the higher parts of the brain stem and the basal ganglia while the middle brain remains intact. Rigidity of the upper extremities in man is manifested in increased tone of the flexor muscles rather than the extensors as in cats and dogs.

A most important function of the brain stem is redistribution of muscular tone according to the posture of the body. This is performed by reflex way and ensures maintenance of balance.

The entire variety of tonic reflexes were divided into two major groups by Magnus:

**1.** Static reflexes - are responsible for maintaining a definite position of the body in space. These are subdivided into two groups:

1. reflexes of position or postural-tonic reflexes-ensure maintenance of a definite stance or

posture of the body;

1. righting reflexes - ensure return of the body from an unnatural position to a normal one.

**2.** Stato-kinetic reflexes - are evoked by movement of the body.

Postural reflexes involve redistribution of tone in one extremity or the other (decrease in the tone of the extensor muscles and increase in the flexors and so forth). They are governed by centers of the medulla oblongata and are elicited mainly by afferent impulses arriving from the receptors of the vestibular apparatus and the proprioceptors of the cervical muscles.

According to the principle of the leading role of the head discovered by Magnus, movements of the body are more easily made, if they are preceded by an appropriate movement of the head, which ensures the most advantageous redistribution of muscular tone in the trunk and extremities for performance of a particular movement. This principle is particularly important in sport physiology. For instance, a speed-skater taking a turn on the track first must turn his head to the corresponding side. With a physiologically wrong position of the head, certain physical exercises are difficult or even impossible to perform.

The tonic reflexes and the principle of the leading role of the head may be demonstrated in simple way. If a piece of meat is held above a cat’s head, it will raise its head, straighten its front legs, bend hind legs, assuming a position convenient for a jump. If a saucer with milk is set before the cat, it will bend its head, which causes flexion of the front legs and a slight extension of the hind legs; the redistribution of tone enables it to lap the milk.

Role of proprioceptors of the cervical muscles in tonic reflexes is well demonstrated in an animal with a destroyed labyrinth. When the head of such animal is tilted back, the tone of the extensor muscles is increased in the front extremities and decreased in the hind ones. The opposite happens when the head is inclined to the thoracic cage.These reflexes depend on the proprioceptors of the cervical muscles and after dissection of posterior roots of the spinal cord cervical segments redistribution of tone does not occur.

To demonstrate the role of the labyrinth in tonic reflexes a plaster-of-Paris was applied to the neck of a decerebrate animal so that the head was kept in a constant position in relation to the trunk, and hence, the proprioceptors of the cervical muscles could not be stimulated. The animal was then rotated about an axis passing through both it temples.

When the animal was on its back, the tone of the extensor muscles was at its maximum and vice versa. If the same experiment is carried out on the animal with preliminarily destroyed labyrinth, no change in the distribution of tone is discovered during rotation.

Tonic righting (or uprise) reflexes are performed by the midbrain and consequently they are absent in bulbar animals. Some time after dissection of the brain above the quadrigeminal bodies, the test animal raises its head, then its trunk and stands up, that is, assumes a natural posture.

In righting reflexes the receptors of the labyrinths, cervical muscles and skin are involved.

Stato-kinetic reflexes are evoked by rotation of the body or by relative displacement of its individual members. During the rotation of the body two types of nystagmus are observed:

1. head nystagmus - first the head turns slowly as far as possible to the side opposite to the direction of rotation, then is reversed by a quick motion to a normal position in relation to the trunk;
2. nystagmus of the eye - the eyes react to rotation by turning slowly against the direction of rotation followed by a quick reversal to the initial position.

For the realization of stato-kinetic reflexes the midbrain nuclei are indispensable.

In the latter half of the last century Deiters described an anatomical formation in the central part of the brain stem consisting of diffuse aggregations of neurons of various size and shape thickly interlaced by numerous fibers running in different directions. Since the outward appearance of the nerve tissue in this region resembles a net under the microscope, he called it the reticular formation. Ramon y Cajal described the structure of the reticular formation in detail. In the thalamus also exist nuclei close in structure to the reticular formation.

As distinct from the well-known (specific) tracts, the patways formed by the nerve fibers passing from the reticular formation (non-specific) nuclei are called non-specific tracts.

However, the physiological functions of the reticular formation were studied only at the middle of the twentieth century.

Thanks to the researches of H. Magoun and G.Moruzzi the physiological importance of the reticular formation was revealed. In the experiments with accurately localized destruction and stimulation of different parts of the reticular formation and dissection of the nerve tracts extending from it, changes in the electrical activity of the cerebral hemispheres and the spinal cord were studied. Various areas of the reticular formation were stimulated with very fine electrodes introduced by the help of stereotaxic technique.

As a result of these experiments, it has been established that the reticular formation was of the highest importance for regulating the excitability and tone of all divisions of the central nervous system. Through the ascending (reticulocortical) tracts it produces an activating influence on the cerebral cortex. Impulses from the reticular formation and the non-specific nuclei of the thalamus maintain the cortex in a wakeful state; under its influence reflex reactions become stronger and more accurate.

Through the descending (reticulospinal) tracts the reticular formation is capable of exerting both activating and inhibitory influences on the reflex activity of the spinal cord.

In its turn, activity of the reticular formation is sustained by impulses arriving through collaterals of various afferent pathways, that is, the most varied stimulation of the receptors affect its condition. The reticular formation also receives impulses from the effector centers of the cerebellum and the brain hemispheres. Its neurons are extremely sensitive to various chemical agents, hormones, certain metabolites.

Both afferent and efferent impulses interact in the region of the reticular formation. Circulation of impulses through its closed circular neuronal chains maintain excitation of the reticular formation neurons at a constant level.

This ensures the tone and a definite degree of readinesss for activity of various parts of the central nervous system.

Notwithstanding the importance of the reticular formation, impulses arriving from the cerebral cortex are capable of governing its activity, and the cortex regulates how far it is excited.

The reticular nuclei are divided into two major groups: 1) the pontine reticular nuclei (bulboreticular facilitory area) which are located mainly in the pons but extend into the mesencephalon and lie more laterally in the brain stem; 2) the medullary reticular nuclei (reticular inhibitory area) which lie ventrally and medially near the midline and extend the entire extent of the medulla oblongata.

These two sets of nuclei function mainly antagonistically to each other, that is, the pontine nuclei excite the antigravity muscles and the medullary nuclei inhibit them.

The pontine reticular nuclei transmit excitatory signals downward into the cord through pontine (medial) reticulospinal tract. Fibers of this pathway terminate on the medial anterior motor neurons which excite the muscles that support the body against gravity, i.e., the muscles of the limbs. The pontine reticular nuclei have a high degree of natural excitability. Besides, they receive excitatory signals from local circuits within the brain stem and especially strong excitatory signals from the vestibular nuclei and also the deep nuclei of the cerebellum.

The medullary nuclei transmit inhibitory signals to the same antigravity anterior motor neurons by way of the medullary (lateral) reticulospinal tract. The medullary reticular nuclei receive strong input collaterals from the corticospinal tract, rubrospinal tract and other motor pathways. These normally activate the medullary reticular inhibitory system to counterbalance excitatory signals from the pontine reticular system. Other signals from the cerebral, red nucleus and cerebellar pathways “disinhibit” the medullary system when the brain wishes for excitation by the pontine system to cause standing. Or at other times, excitation of the medullary reticular system can inhibit the antigravity muscles in certain portions of the body to allow those portions to perform other motor activities, which would be impossible if the antigravity muscles opposed the necessary movements.

So, excitatory and inhibitory reticular nuclei form a controllable system that is manipulated by motor signals from the cortex and elsewhere to provide the necessary muscle contractions for standing against gravity and yet to inhibit appropriate groups of muscles as needed so that other functions can be performed as required.

Electrical stimulation of corresponding parts of the reticular formation inhibits spinal reflexes in animals and reduces rigidity of the muscles in decerebrate animals. Weak stimulation of the reticular formation on one side causes inhibition of spinal cord neurons on the same side, but when the stimulation is stronger, the neurons of both halves are inhibited. Inhibition was observed in research into both flexor and extensor reflexes.

To trace the course of the fibers transmitting impulses from the neurons of the reticular formation inhibiting spinal reflexes, section of the spinal tracts was performed. It was ascertained that these fibers act on Renshaw’s cells and intensify their inhibitory effect on the motor neurons. Besides, direct impulses from the reticular formation may also inhibit activity of motor neurons.

The reticular formation neurons, activating the spinal cord reflex function were found, besides the medulla oblongata (to the periphery of those parts that have an inhibitory influence), in the grey matter tegmentum of the midbrain and pons, in the diencephalon (in the hypothalamus). Stimulation of these parts intensifies the spinal reflexes and the contractions of skeletal muscles evoked by stimulation of the cortex. Tracing of the pathways of the impulses activating the neurons of the spinal cord has shown them to be fibers of the reticulospinal tract.

The activating fibers of the reticular formation end in the interneurons of the reflex arcs. It may be assumed that activation of spinal reflexes under the influence of the reticular formation results from the suppression of inhibitory discharges from Renshaw’s cells. So, inhibition of the inhibition leads to increase in the excitability of the motor neurons.

The reticular formation influences not only phasic reflexes (reflex motor acts) but also tonic reflexes (tone of the skeletal musculature). Elimination of the activating and inhibitory influences of the reticular formation after dissection of the spinal cord is apparately one of the causes of spinal shock and the hyperreflexia developing later. Contributory role of the reticular formation in decerebrate rigidity has been demonstrated experimentally.

The mechanism of the reticular formation’s influence on the muscular tone has been made clear by Granit’s experiments which have proved that it changes the activity of the gamma-motor neurons of the spinal cord innervating the muscle fibers of the peripheral parts of the muscle spindles. The axons of those gamma motor neurons known as gamma-efferents are A-gamma type thin nerve fibers.

The gamma efferent fibers condition the tension of the muscular elements of the spindles which result in an intensified flow of afferent impulses from the receptors of the nuclear sac to spinal cord. These afferent impulses excite the motor alpha neurons and maintain muscular tone. The flow of afferent impulses from the spindles is regulated in turn by the motor gamma neurons.

These intricate interrelations and feedback connections between the neurons of the spinal cord and the skeletal muscles are regulated by the reticular formation which, by influencing the motor gamma-neurons, changes the flow of afferent impulses from the spindles and in this way affects the tone. Muscular tone is regulated by the midbrain tegmentum through two reticulospinal tracts.

The reticulospinal mechanisms are controlled by the cerebellum and the cerebral cortex.

To study the reticulocortical interconnections Magoun and Moruzzi stimulated the reticular formation in different parts of the brain stem by the help of implanted microelectrodes and found that stimulation of the reticular formation caused changes in the electrical activity of the cortex characteristic of wakening and of the natural waking state. The similar reaction can be caused by stimulation of the non-specific nuclei of the thalamus and the dorsal part of the hypothalamus.

After destruction of the reticular formation in the upper parts of the brain stem the animal lapses into a deep sleep, although afferent impulses continue to enter the sensory areas of cerebral cortex through the specific pathways.

These experiments indicate that the normal activity of the hemispheres of the brain and cerebral cortex depends greatly on the tonic, activating influences of the reticular formation of the brain stem and the non-specific nuclei of the thalamus.

There is evidence that different afferent stimuli activate different groups of cells of the reticular system, so that its activating influence on the cortex is variable. For example, Anokhin established that the electrical reactions of the reticular system and cerebral cortex during the nutritional reflexes differ from those observed during defensive reactions of the animal.

Different fibers carrying impulses to the thalamus give off numerous collaterals to the reticular formation. So, activity of the ascending activating reticular formation is sustained by impulses from all the receptors of the body. Besides, the reticular formation receives impulses from the cerebellum, basal ganglia, limbic system, cerebral cortex.

While exerting a great influence on the cerebral cortex and maintaining its activity at a definite level, the reticular formation itself is under the constant regulating influence of impulses from the cortex.

The reticular formation is closely connected with the basal ganglia and hypothalamus. Stimulation of certain parts of the midbrain reticular formation produces effects directly related to animal’s bahaviour that are identifical to those produced from stimulating of the hypothalamus, basal ganglia or limbic system.

In Olds’ experiments electrodes were permanently implanted in different parts of rat’s brain (the region of the hippocampus, the posterior hypothalamus, the mesencephalon) and connected to a stimulator which the rat could switch on by pressing a lever with its leg. A rat that had accidentally pressed the lever, thereby stimulating the brain structures, began to press the lever more and more frequently stimulating its brain centers. When the electrodes had been successfully implanted in the midbrain reticular formation or the posterior hypothalamus, the rat lost all interest in its surroundings and food, and kept pressing the lever up to 8000 times in hour. So, stimulation of definite brain structures excited certain positive reactions in the animals which were called “reactions of pleasure” or “enjoyment”.

When the electrodes were in the medial part of the hypothalamus, the frequency of selfstimulation depended on whether the animal was hungry or had been fed before the experiment (in the latter case the frequency of self-stimulation was lower). But when the electrodes had been implanted in lateral parts, the frequency of self-stimulation was increased by injection of sex hormones and reduced by castration.

These facts indicate that the reactions aroused in self-stimulation experiments are associated with unconditioned nutritional or sexual reflexes in which the limbic system of the hemispheres, the subcortical ganglia, the reticular formation, hypothalamus are involved.

When electrodes were implanted in the dorsal part of the diencephalon and the ventromedial nucleus of the hypothalamus, after a single self-stimulation the animal avoided touching the lever: apparently this stimulation evoked negative emotions. Stimulation of this region in a cat may arouse a ferocious reactions (it attacks other animals in the vicinity).

So, together with the centers in the diencephalon, basal ganglia and limbic system the reticular formation is involved in exciting unconditioned reflex and instinctive behavioural reactions, fulfilment of which satisfies vital needs of the organism, and which have the significance of drive (motivation) in animal behaviour. But they must not be regarded as proof of the decisive role of the basal ganglia or brain stem in behaviour, because the reactions of the lower sections of the central nervous system are controlled by the cerebral cortex.

Owing to corticalization, that is, to the transfer of complex nervous functions to cerebral cortex in man, activity of sub cortical formations, diencephalon and reticular formation is subordinated to the cerebral cortex in a much larger degree than in animal.

Deep knowledge of the reticular formation functions forced the physiologists to revise some key ideas and helped to form a true notion about the mechanisms of the irradiation of the excitation in the central nervous system, origin of the sleep, closing of the conditioned reflex arc etc.

Stimulation of any receptor causes the afferent impulses reaching by specific pathways the certain nerve center, and from there the excitation is irradiated to other parts of the central nervous system. This was regarded as the only way of the irradiation. But now it is known that this horizontal way of the irradiation is insignificant, and the decisive way of irradiation is vertical - through the reticular formation. That is, the same afferent impulses, through collaterals excite the reticular formation which produces an activating influence on the cerebral cortex, causing irradiation of the excitation in wide areas of the central nervous system.

In the light of our knowledge of reticular formation functions, impulses from the reticular formation maintain the cortex in a wakeful state, and sleep is the result of cessation of these activating influences.

It is well known that the building of a conditioned reflex is based on the formation of temporary connections between two groups of cortical cells-those receiving conditioned stimulation and those receiving unconditioned stimulation. At present it is clear that the excitation is transmitted between these cells not directly-by horizontal way, but by vertical way, that is, through the reticular formation (cortico-subcortico-cortical pathways).

**Cerebellum. Diencephalon. The Basal Ganglia**

Cerebellum takes part in the coordination of all complex motor acts of the organism incuding voluntary movements. It is very old in terms of evolution.

The cerebellum is especially vital to the control of rapid muscular activities such as runnig, typing, playing the piano and even talking. Loss of the cerebellum results in almost total incoordination of these activities even though not causing paralysis of any muscles.

 The cerebellum helps sequence the motor activities and also monitors and makes corrective adjustments in the motor activities elicited by other parts of the brain.

It receives continuously information from the motor control areas of the other parts of the brain and from the peripheral parts of the body. The cerebellum compares the actual movements as depicted by the peripheral sensory feedback information with the movements intended by the motor system. It helpes the cerebral cortex in plannig the next sequental movement a fraction of a second in advance while the present movement is still being executed, aiding to progress smoothly from one movement to the next.

If a movement does not occur exactly as intended, the cerebellar circuit learns to make a stronger or weaker movement next time, thus learning by its mistakes.

Like the sensory and motor cortex, basal ganglia, red nucleus and reticular formation, the vermis and intermediate zones of the cerebellum also have topographical representations of the different parts of the body. The axial portions of the body lie in the vermal part of the cerebellum, the limbs and facial regions-in the intermediate zones. These topographical representations receive afferent nerve signals from all the respective parts of the body as well as from the corresponding topographical areas of the motor cortex and brain stem motor areas. In turn, they send motor signals into the same respective topographical areas of the motor cortex, the red nucleus and the reticular formation.

The large lateral portions of the cerebellar hemispheres have not topographical representations of the body, they connect mainly with corresponding assotiation areas of the cerebral cortex and play important roles in planning and coordinating the sequential muscular activities.

The human cerebellar cortex is actually a large folded sheet (17x120cm) with the folds (called folium)lying crosswise.

The cerebellar cortex has about 30 millions almost identical functional units.The output from the functional unit is from a deep nuclear cell which is continually under the influence of both excitatory and inhibitory influences. The excitatory influences arise from direct connections with the afferent fibers that enter the cerebellum from the brain or the periphery. The inhibitory influences arise entirely from the cerebellar cortex Purkinje cell.

Afferent inputs to the cerebellum are mainly of two types: the climbing fiber type and the mossy fiber type. The climbing fibers all originate from the inferior olivary complex of the medulla oblongata. The mossy fibers enter the cerebellum from multiple sources (the higher brain, brain stem, spinal cord).

Direct stimulation of the deep nuclear cells by both the climbing and the mossy fibers excites them. But the signals arriving from the Purkinje cells inhibit them.

Three other types of neurons are located in the cerebellar cortex, all of which are inhibitory cells with very short axons:basket cells, stellate cells and Golgi cells.

All these cells and interactions among them promote perfomance of complicated coordinating functions of the cerebellum. The cerebellum is especially important in controlling the balance between agonist and antogonist muscle contractions during rapid changes in body positions as dictated by the vestibular apparatus. Its typical function is to help provide rapid turn- on signals for agonist muscles and simultaneous reciprocal turn-off signals for the antagonist muscles at the onset of a movement. But at the termination of the movement the cerebellum is mainly responsible for timing and executing the turn-off signals to the agonists and turn-on signals to the antagonists.

Under stimulation of the proprioreceptors of muscles, tendons and ligaments, exteroceptors of the skin, eyes and ears, interoreceptors of certain visceral organs, induced potentials are recorded in various areas of the cerebellar cortex.

Besides the feedback circuitry between the body periphery and cerebellum, the circuitry exists between the motor cortex of the cerebrum and the cerebellum. When the electrical potentials from the surface of the cerebellum are recorded, oscillations of varying frequensy-150-200 cycles per second and 8-12 cycles per second –are registrated. The high frequensy oscillations continue even after a complete isolation of the cerebellum, but the slow ones cease after the tracts connecting the cerebellum to the cerebral cortex are severed.

Consequently, the slow rhythms of the electrical waves in the cerebellum are conditioned by the influence of the cerebral cortex.

The circuitry between the motor cortex of the cerebrum and the cerebellum affects only slightly if at all the control of equilibrium and other postural movements of the axial and girdle muscles of the body. It serves two other principal functions:1)it helps the cerebral cortex to coordinate patterns of movement involving mostly the distal parts of the limbs, especially the hands, fingers and feet(intermediate zone of the cerebellar cortex and its associated nucleus interpositus); 2)it helps the cerebral cortex to plan the timing and sequencing of the next successive movement that will be performed after the present movement is completed (lateral zone of the cerebellar hemisphere, along with its associated dentate nucleus).

Electrical stimulation of different parts of the cerebellum causes a change in the electrical activity of neurons in definite areas of the certebral cortex, in the nuclei of the diencephalon, mesencephalon, medulla oblongata, reticular formation. Sufficiently strong stimulation of the cerebellum surfase or its individual nuclei causes movement of the eyes, head, extremities. As distinct from the movement evoked by stimulation of the cerebral cortex, those evoked by the stimulation of the cerebellum are slow and have a tonic character, the effect of stimulation persists for a long time. There are bilateral connections between definite areas of the cerebellar cortex and cerebral cortex. For instance, the zone of representation of the front extremities in the cerebellar cortex is linked with that in the cerebral cortex, the visual and auditory areas of the cerebellum has bilateral connections with the visual and auditory zones in the cerebral cortex, etc. These connections ensure most accurate correlation of control mechanism of the motor system of the organism.

Removal of the cerebellum or damage to it causes disturbances in the static and statokinetic reflexes (voluntary motor acts are affected most)

Excision of one half of the cerebellum is followed by strong extension of the extremities on the dependent side. It perfoms manege movements, that is, moves in a circle to the side operated. When the initial severe symptoms have passed, the animal can stand up and walk, but elements of awkwardness and a motor disturbance on the side operated remain forever.

Luciani (1893)made the first detailed discription of disorders of the motor apparatus of animals following excision of cerebellum. He observed the appearance of the three symptoms (atony, astasia, asthenia). Later, other symptoms were described (ataxia, dysmetria, disequilibration, etc.)

Atony is loss of muscular tone. But the tone of certain muscle groups may be increased. Therefore, it would be more correct to describe the sequels of extirpation of the cerebellum as dystonia(disturbed regulation of the muscular tone.) The anterior part of the posterior lobe of the cerebellum and the dentate nucleus are particularly important in the control of muscular tone.

Astasia consists in loss of the ability of the muscles for hormonious contraction which results in continuous trembling or swaying of the animal’s head, trunk, extremities. The tremor is particularly distinct after any voluntary movement.

Asthenia - quick fatiguability in consequence of intensified metabolism is due to movements being performed uneconomically, with use of a large number of muscles.

Ataxia is disturbance of locomotion, that is, inadequate coordination of movements is manifested by incertain and overshooting gait.

Dysmetria is disorders in the intensity, scope, speed and direction of movements. Disequilibration is disturbance of balance. Adiadochokinesis is inability to perform quick movements with groups of antagonist muscles (to bend and extend an arm several times in succession).

A person with a cerebellar disorder staggers greatly when standing up with his eyes open, falls when his eyes are closed and walks in a zigzag fasion. His movements are incoordinate.

In the absence of the cerebellum a person moves the hand or some other part of the body considerably beyond the point of intention. This is called past pointing and is a manifestation of dysmetria.

Almost all movements of the body are pendular, and all pendular movements have a tendency to overshoot. If the cerebellum is intact, appropriate learned, subconscious signals stop the movement precisely at the intended point, thereby preventing the overshoot and also the tremor. This is the basic characteristic of a damping system. In the motor control mechanism of the central nervous system the cerebellum provides most of this damping function.

A tremor of the eyeballs that occur when one attempts to fixate the eyes on a scene to one side of the head is called cerebellar nystagmus.

Loss of the cerebellar component of the stretch reflex results in so-called rebound. For instance, if a person with cerebellar disease is asked to pull upward strongly with his arm while the physician holds it back at first and then lets go, the arm will fly back until it strikes the face instead of being automically stopped.

Many rapid movements of the body, such as the movements of the fingers in typing, occur so rapidly that it is not possible to receive feedback information either from the periphery to the cerebellum or from the cerebellum to the motor cortex before the movements are over-such movements are called ballistic movements (meaning that the entire movement is preplanned and is set into motion to go a specific distance and then to stop). Another important example is the saccadic movements of the eyes, in which the eyes jump from one position to the next when reading or looking at successive points along a road as a person is moving in a car. In the absence of the cerebellar circuit the automatism of ballistic movements is lost.

Since formation of words depends on rapid and orderly succesion of individual muscular movements in the larynx, mouth, respiratory system, lack of coordination between these and inability to predict either the intensity of the sound or the duration of each successive sound cause jumbled vocalisation, with some syllables loud, some weak, some held long, some for short intervals. This is called dysarthria.

Comparison of the effects of the stimulation and destruction of the cerebellum and the data of modern electrophysiological researches have made it possible to form a definite idea of its significance for the organism.

Removal of the cerebellum does not cause reflex reactions to disappear; in particular the tonic reflexes of the brain stem are retained. At the same time certain changes occur in muscular tone, while the accuracy and coordination of reflex reactions are impaired.

The cerebellum receives afferent impulses conveyed to the central nervous system through feedback pathways from all receptors excited by movements of the body. Obtaining information in this way about the condition of the motor apparatus, the cerebellum exercises an influence on the red nucleus and the reticular formation of the brain stem, which directly regulates tone. Cerebellar influence on the reticular formation is manifested, for instance, by the fact that stimulation of the anterior lobe reduces decebrate rigidity of the extensor muscles.

Influence of the cerebellum on the reticular formation may be opposite to that of the cerebral cortex. For instance, stimulation of the cerebellum produces an inhibitory influence on the discharges of individual neurons of the reticular formation, whereas electrical stimulation of the motor area of the cerebral cortex accelerates them.

A definite role in the mechanism whereby the cerebellum influences muscular tone is played by changes in the discharges of the motor gamma-neurons of the spinal cord. Efferent impulses issuing from the cerebellar nuclei exert an inhibitory influence on proprioceptive (myotatic) reflexes. Owing to this inhibitory mechanism, conversion of a simple reflex into a complex chain reflex does not occur. The muscular tremor, swaying and staggering characteristic of astasia, of served after removal of the cerebellum, are probably due to inihibited proprioceptive reflexes.

The cerebellum corrects the motor reactions of the organism, that is, adjusts them to the required level, and ensures their accuracy. This role is manifested with particular clarity in the perfomance of voluntary movements. The chief function of the cerebellum is to coordinate the quick (phasic) and slow (tonic) components of motor acts.

Stimulation of certain parts of the cerebellum inhibits the effects of cerebrocortical excitations, while stimulation of other parts has an activating influence on them. Impulses emanating from the cerebellum and conveyed to the cerebral cortex through the thalamus may directly influence the cerebrocortical neurons. Cerebellar impulses also influence the cerebral cortex by causing a change in the condition of the reticular formation. Thus, stimulation or destruction of the cerebellum changes the character of the impulses sent by the cerebral cortex through the corticospinal tracts. After removal of the cerebellum or damage to it the cortical mechanism cannot adjust voluntary movements to the required scope. That is also the cause of the ataxia and dysmetria. A characteristic symptom of a deranged cerebellar control is the slow beginning of voluntary motor acts and their marked intensification towards the end.

The diencephalon (interbrain - between - brain) is anatomically a division of the brain stem, but unlike the medulla oblongata and midbrain, in the process of embryogenesis the diencephalon and cerebral hemispheres develop from the anterior cerebral vesicle.

The diencephalon forms the walls of the third ventricle. Its chief formations are the thalami and hypothalamus. Nuclei of the thalami are located in the region of the lateral walls of the third ventricle; nuclei of the hypothalamus form its inferior and inferolateral walls.

In the diencephalon tissue depths nuclei of the medial and lateral geniculate bodies are located. The outer border of the diencephalon passes lateral to the geniculate bodies. It is made up of the white matter of the internal capsule which separates the diencephalon from the basal ganglia of the endbrain.

The thalamus is a switchboard where all the afferent (sensory) tracts leading to the cerebral hemispheres meet, that is, all sensory signals, except those arising in the olfactory tract, reach the cerebral cortex only through the thalamocortical projections. It is a kind of gate on the way to the cerebral cortex, through which passes all information from the receptors perceiving stimuli from the external and internal environments of the organism. The local damage to certain nuclei of thalamus deprives the cerebral cortex of information of a particular kind (visual, auditory, gustatoty, etc.)

The name "optic thalamus" is due to the ancient idea that only the optic tract pass through thalamus. It would be more correct to call it "sensory thalamus".

The thalamus is divided by layers of white matter into regions. Each of them is an aggregation of nuclei, of which about forty have now been distinguished. They are classified topographically into the following main groups: anterior, lateral, intralaminar, medial and posterior.

All thalamic nuclei were divided by function into two major groups by Lorento de No: specific and non-specific. This division is based on the morphological characteristics of the endings of the fibers passing from the nuclei to the cerebral cortex and on the electrophysiological characteristics of the changes occurring in the cortical electrical activity when they are stimulated.

The fibers from the specific nuclei, the specific thalamic tracts, terminate in the third and fourth layers of the cerebral cortex and form synapses with a limited number of cells in the sensory and associative areas.

The non-specific nuclei are a continuation of the reticular formation of the midbrain and are the reticular formation of the thalamus. Phylogenetically they are older and include the medial and intralaminar nuclei, the medial part of the anterior nucleus. Neurons of these nuclei first transmit signals into the subcortical structures from where impulses pass to different cortical areas.

The fibers from the non-specific nuclei, non-specific thalamic tracts, give of many arborizations in various areas of the cerebral cortex and involve a large number of cortical neurons in the excitatory process.

So, the specific nuclei are directly connected with definite areas in the cerebral cortex, but the non-specific nuclei send signals to the subcortical nuclei from which impulses are conveyed simultaneously to different parts of the cerebral cortex.

Stimulation of specific nuclei causes changes in the electrical activity (primary responses) only in circumscribed areas of the cerebral cortex, whereas stimulation of non-specific nuclei affects the electrical activity in wide areas of the cerebral cortex, causing an "activation reaction".

The latent period of an evoked potential in the cerebral cortex from the moment of stimulation of specific nuclei is 1-6 milliseconds only, whereas that of from stimulation of the non-specific nuclei - 10-50 msec. This is a weighty argument in the latter case in favour of the existence of a large number of neurons and synapses connected in series on the route from the non-specific nuclei to the cerebral cortex.

The specific thalamic nuclei are subdivided into two groups: relay nuclei (thalamic or cortical relays) and associative nuclei. Each cortical relay nucleus receives impulses coming from a definite sensory tract (optic, auditory, lemniscus, spinothalamic, etc.), whereas the associative nuclei receive impulses from the thalamic relay nuclei. So, associative nuclei are supplied with information processed in the thalamus itself.

The principal relay nuclei are the lateral and medial geniculate bodies, the anterior, ventrolateral, posterior ventral nuclei.

The lateral geniculate bodies are the relay nuclei for visual signals. Their neurons receive impulses from the primary visual centers of the anterior quadrigeminal bodies, and their processes extend to the visual area of the cerebral cortex. The medial geniculate bodies are the relay nuclei for the auditory tract. Their neurons receive impulses from the primary auditory centers in the posterior quadrigeminal body, and give off processes to the auditory area of the cerebral cortex.

Information from the receptors of the skin, face, trunk, extremities and from the proprioceptors are transmitted to the thalamus along fibers coming from Goll’s and Burdach’s nuclei in the medulla oblongata (lemniscus tracts), along the spinothalamic tract and along fibers from the nuclei of the trigeminal nerve. This information is supplied to the posterior ventral nucleus of the thalamus and passed by its neurons to the posterior central convolution of the cerebral cortex, that is, to the somatosensory area. The posterior ventral nucleus also receives impulses from the taste receptors. Impulses from visceroreceptors are transmitted to the posterior medial nucleus.

The ventromedial nucleus receives impulses from cerebellum which are passed to the anterior central convolution, that is, to the motor area of the cerebral cortex.

The anterior thalamic nuclei also receive impulses from the visceroreceptors and a part of impulses from the olfactory receptors. Impulses from these nuclei are transmitted to the cerebral cortex limbic region.

Dusset de Barenne injected a strychnine solution into separate parts of the monkey thalamic nuclei by the help of very thin needle and studied changes in skin, sensitivity in various parts of the body. Hyperesthesia (increase in sensitivity) varying with the site of injection and appearing either in the facial region or in the extremities (particularly marked on the opposite side of the body) was discovered. Recording induced potentials in different parts of the posterior ventral nucleus upon stimulation of various parts of the body, Mountcastle and Hennemann found that impulses from receptors in different areas of the body arrived at different parts of the nucleus. The thalamic receiving area for the facial part of the head and front extremities, particularly that of their distal parts, is considerably larger than the number supplied with information by the receptors of the trunk and hind extremities. The areas receiving impulses from the visceroreceptors are situated in the same parts of the nucleus as the neurons receiving signals from the exteroreceptors of the corresponding part of the body. Interaction of these impulses is the cause of referred pain, that is, during a morbid process in a definite visceral organ the flow of impulses from visceroceptors produces a disturbance of sensitivity in the skin above it.

Impulses from the thalamic neurons perceiving signals about stimulation of various parts of the body pass to different parts of the somatosensory zone of the cerebral cortex where the representation of the skin and musculo-articular receptors also has a definite spatial distribution.

The associative nuclei of the thalamus are located chiefly in its anterior part and receive impulses from the relay nuclei and send them to the associative areas of the cerebral cortex. They comprise lateral, dorsomedial and pulvinar nuclei. The associative nuclei (particularly the associative areas of the cerebral cortex) are especially well developed in man.

The feedback connections exist between the associative areas of the cortex and the thalamic nuclei, and between the sensory areas of the cortex and the relay nuclei through which a circular interaction of the impulses is realized.

The non-specific system of the thalamus takes part in a quick and short – lived activation of the cortex in contrast to the slow and long – time activation effected by the reticular formation of the brain stem.

The brain stem reticular formation maintains the tone of the whole cortex, whereas the non-specific thalamic nuclei activate only those of its structures that take part in concrete reflex acts. In particular, the non-specific system takes part in organizing the attention process in the waking organism.

The afferent impulses transmitted to the cortex through the reticular formation do not cause any definite sensations in man, but increase cortical reactions to impulses arriving along the specific sensory pathways.

The non – specific nuclei have wide reciprocal connections with the relay and associative nuclei and subcortical formations, the anterior ventral and reticular nuclei send fibers directly to various areas of the cerebral cortex.

Role of the thalamus in the origin of sensation is significant. The information received from various receptors is processed in thalamic nuclei, with the result that the character of sensation is changed. Then thalamus sends the impulses into cerebral cortex.

The thalamus is the highest pain center. Direct stimulation of different areas of the cerebral cortex during neurosurgical operations very seldom causes a sensation of pain, whereas the application of stimulating electrodes to the thalamus produces marked pain reactions and disagreable sensation. Also, certain lesions of the thalamus cause agonising pain (the slightest stimulation, touching of the skin, a light pin-prick, even a sound or light provoke attacks of excruciating pain)

The typical reactions of the organism usually attended with a feeling of pain can be induced in thalamic animals after extirpation of the cerebral cortex. But some types of damage to thalamus block the perception of painful sensations and give rise to a state of analgesia in which painful stimuli are not appreciated as such.

The reticular formation plays an important role in the origin of painful reactions. Deadening of this system by the injection of certain narcotics (barbiturates) which ceases its ascending activating influence on the cerebral cortex, leads to suppression of painful reactions.

But the role of cerebral cortex in the sensation of pain cannot be denied. Evoked potentials are recorded in the sensory areas during painful stimulation. Consequently, impulses from pain receptors reach the cortex. Besides, painful sensations can be suppressed by hypnotic suggestion (for instance, in painless child birth). Damage to the sensory areas of the cortex impairs the accuracy of locating the paint of painful stimulation.

The hypothalamus is situated under the thalamus and is formed by 32 pairs of nuclei.these are the higher subcortical centers of the vegetative nervous system and governing all vitally important body functions.

The neuron accumulations of the hypothalamus form the following groups of nuclei: preoptic (medial and lateral preoptic nuclei), anterior (supraoptic, suprachiasmatic, paraventricular nuclei), medical (ventromedial and dorsomedial nuclei), lateral (lateral hypothalamic nucleus and nuclei of the tuber cinereum), posterior (posterior hypothalamic nucleus and a large group of mamillary nuclei).

The neuronal organisation of the hypothalamus is marked by extensive and highly complicated afferent and efferent connections. Afferent signals are supplied from the cerebral cortex, thalamic structures and basal ganglia. Main efferent pathways include the paraventricular system and the mamillotegmental tract. Fibers of this tract are directed caudally along the walls of the midbrain (Sylvius) aqueduct giving off numerous branchings to the midbrain structures.

Axons of the hypothalamic nuclei form numerous short efferent pathways which pass to the thalamic and subthalamic areas and other subcortical formations.

There are extensive nervous and vascular connections between the hypothalamus and the hypophysis (pituitary body); the two are often taken together as a single hypothalamo-pituitary system. The supraoptic and paraventricular nuclei (anterior hypothalamus) are connected with the hypophysis by a special system of fibers serving as conducting pathway and as transport routes for the neurohormones secreted by the neurons of these nuclei.

The hypothalamo-pituitary system ensures integration of the nervous and hormonal regulation of the functioning of many organs.

Effects of stimulation of the hypothalamus are due partly to its connections with the reticular formation and the sympathetic and parasympathetic centers and partly to intensified secretion of pituitary hormones acting directly or through other endocrine glands on many functions of the organism. So, stimulation of the hypothalamus causes complex reactions where nervous component is supplemented with a hormonal one.

The results of the stimulation and destruction of the hypothalamic nuclei show that they influence the cardiovascular system, digestive organs, thermal regulation, water-salt balance, carbohydrate, fat and protein metabolism, urination, the functioning of the endocrine glands.

The hypothalamic nuclei are abundantly supplied with blood. The permeability of the hypothalamic capillaries is higher than those of in other parts of the central nervous system. Therefore, the nerve cells of the hypothalamus can be influenced by some large molecular compounds which are unable to penetrate the hemato – encephalic barrier in other parts of the brain.

Some of hypothalamic nuclei are excited by impulses coming from the thalamus and other parts of the brain and as a result of the selective sensitivity to physico-chemical influences possessed by certain of its cells.

In the posterior hypothalamic nuclei the higher centers of the sympathetic nervous system are situated, and in the anterior nuclei – those of the parasympathetic nervous system. Accordingly, stimulation of the posterior nuclei causes increase in the adrenalin and noradrenalin content of the blood and its glucose concentration, pulse rate, constricttion of blood vessels and increase of blood pressure, dilation of the pupils and palpebral fissures, inhibition of gastrointestinal tract functions. Stimulation of the anterior nuclei causes, on the contrary, rise in the secretion of insulin with a resulting reduction of blood glucose content, decrease of pulse rate, fall in arterial tone and arterial pressure, narrowing of the pupils and palpebral fissures, intensified secretory and motor activity of the gastrointestinal tract.

In experiments with stimulation and destruction of the middle nuclei (the region known as tuber cinereum) various disturbances were observed. Damage to this area can give rise to general obesity and sexual infantilism, its chronic stimulation caused increase in the lipid content of the blood and atherosclerotic changes in the aorta. Chronic stimulation of certain hypothalamic nuclei in monkeys caused ulceration of the stomach and duodenum. These experiments indicate to the role of the hypothalamus in the regulation of trophic functions.

The hypothalamus plays a significant role in thermoregulation (anterior, middle and posterior nuclei). When the hypothalamus is destroyed an animal loses its ability to maintain body temperature at a constant level and becomes poikilothermic. On the other hand, stimulation of the posterior nuclei causes hyperthermia as a result of increased heat production (intensification of metabolic processes and tremor of the skeletal muscles).

In the cells of the supraoptic nucleus the hormones of the posterior pituitary gland (neurohypophysis) are produced and transported into neurohypophysis. This process is similar to the release of a neurotransmitter by the endings of axons of ordinary nerve cells under the effect of arriving action potentials. The hypothalamus regulates also the production of anterior pituitary gland (adenohypophysis) hormones by the neurohumoral way, that is, secreting liberins and statins.

Electrical stimulation of the hypothalamic nuclei leads to complex hormonal changes resulting in increased secretion of the adrenocorticotropic, thyrotropic and gonadotropic hormones of the adenohypophysis. The influence of the hypothalamus on the hormonal secretion of the pituitary gland is regulated on the feedback principle.

The nuclei of hypothalamus are involved in many general behavioural reactions of the organism. The hypothalamus takes part in nutritional behaviour. There are the centers of hunger (lateral nucleus) and satiety (ventromedial nucleus) in hypothalamus. Their activity is stimulated by changes in the chemical composition of the inflowing blood.

Lack of water in the body causes the adaptational behavioural reactions, the sensation of thirst arises consequent upon activation of the hypothalamic areas located dorsolaterally of the supraoptic nucleus. The intake of water sharply increases (polydipsia). Destruction of these hypothalamic centers causes the absence of thirst and refusal of water (adipsia).

The hypothalamus has centers associated with the regulation of sexual behaviour. It has been established that the pleasure centers are components of the neuronal system participating in the regulation of emotional sphere of sexual behaviour.

The hypothalamus plays an important role in regulation of the sleeping – waking rhythm.

The hypothalamus is also involved in aggressive –defensive reactions. Punctate stimulation of the ventromedial nucleus (in cat) produces sharply expressed aggressive reflex (sham rage).

So, regulating the functions of the sympathetic and parasympathetic nervous systems and secretory functions of the endocrine glands, hypothalamus provides a vegetative component in all complex reactions of the organism.

In turn the activity of the hypothalamus is controlled by the higher divisions of the central nervous system (basal ganglia, cerebellum and the cerebral cortex).

With the cerebral cortex the hypothalamus is connected both by direct pathways and through the reticular formation of the brain stem.

The forebrain (prosencephalon), that is, the most rostral part of the central nervous system, is formed by the basal ganglia (subcortical nuclei) and the cerebral cortex.

The basal ganglia are located within the cerebral hemispheres between the frontal lobe and diencephalon, mainly lateral to the thalamus.

Anatomists consider the motor portions of the basal ganglia to be the caudate nucleus and lentiform nucleus, which consists of putamen and globus pallidus. But physiologically the subthalamus and substantia nigra also are intimately involved.

The caudate nucleus and the putamen make up the striate body (corpus striatum) in which accumulations of nerve cells forming the grey matter alternate with layers of the white matter (hence the name "striate"). Together with the globus pallidus they form the striopallidal system of subcortical nuclei.

The caudate nucleus and the putamen are phylogenetically younger formations (neostriatum) than the globus pallidus (paleostriatum).

The basal ganglia are another accessory motor system (like the cerebellum) that functions not by itself but in close association with the cerebral cortex and corticospinal system. As a component of the extrapyramidal system, the nuclei of the striopallidal complex take part in the coordination of the motor activity.

Almost all of the motor and sensory nerve fibers connecting the cerebral cortex and spinal cord pass between the two major masses of the basal ganglia (the caudate nucleus and the putamen). The mass of nerve fibers is called the internal capsule of the brain. So, there is intimate association between the basal ganglia and the corticospinal system for motor control.

There are very complex anatomical connections between the basal ganglia and the other elements of motor control (motor cortex, thalamus, corticospinal pathways, brain stem, cerebellum) as well as the tremendous number of interconnections among the basal ganglia themselves.

Two major circuits of basal gandlia are the putamen circuit and the caudate circuit.

The putamen circuit controls complex patterns of motor activity, that is, of any skilled movements (writing of letters of the alphabet, cutting paper with scissor, hammering nails, shooting basketballs through a hoop, shoveling dirt, some aspects of vocalization). When there is serious damage to the basal ganglia, the cortical system of motor control can no longer provide these patterns. For instance, one’s writing becomes crude as if one was learning for the first time how to write.

The principal pathways through the basal ganglia for executing learned patterns of movement begin mainly in the premotor and supplemetal motor areas of the motor cortex and also in the primary somatic sensory area of sensory cortex. So, the putamen circuit has its imputs mainly from the parts of the brain adjacent to the primary motor cortex, but not much from the primary motor cortex itself. Then its outputs go mainly back to the primary motor cortex.

When any portion of the putamen circuit is damaged or blocked, certain patterns of movement become severely abnormal. Lesions of the globus pallidus often cause athetosis, that is, spotaneous writhing movements of a hand, an arm, the neck or the face.

A lesion in the subthalamus frequently leads to sudden flailing movements of an entire limb-hemiballismus.

Multiple small lesions in the putamen cause chorea-flicking movements in the hands, face and other parts of the body (St. Vitus’ dance). Lesions of the substantia nigra cause Parkinson's disease-the common and extremely severe disease of rigidity and tremors.

The caudate circuit plays a major role in the cognitive control of motor activity. Cognition means the thinking processes of the brain, utilizing both the sensory input to the brain as well as information already stored in memory. Most of our motor actions occur as a consequence of thoughts generated in the mind, and this process is called the cognitive control of motor activity.

Unlike the putamen circuit, the caudate circuit extends into all lobes of the cerebrum. Furthermore, the caudate nucleus receives large amounts of its input from the associative areas of the cerebral cortex (the areas that integrate the different types of sensory and motor information into usable thought patterns).

The signals passing from the cerebral cortex to the caudate nucleus are transmitted to the globus pallidus, then to the relay nuclei of the thalamus, and finally back to the prefrontal, premotor and supplemental motor areas of the cerebral cortex, but almost none of the returning signals pass directly to the primary motor cortex. So, the returning signals go to those accessory motor regions that are concerned with patterns of movement instead of individual muscle movements.

Cognitive control of motor activity determines which patterns of movement will be used together and in what sequence to achieve a complex goal. Without cognitive functions the person might not have the instinctive knowledge, without thinking far too long a time, to respond quickly and appropriately.

For instance, a person that sees an approaching tiger responds instantaneously and automatically by attacking the tiger (if he has a weapon), beginning to run or attempting to climb a tree.

Three main concepts constitute the basis of all hypotheses on the functions of the neostriatum: 1) its important role in the motor control, 2) its sensory mechanisms, 3) its involvement in complex forms of behaviour. The corpus striatum is part of the system taking part in the analysis and interpretation of the multifarious inputs in the sensory and effector spheres. It plays a critical role in the motor learning processes. This structure is responsible for the complex organization of the motor behaviour with consideration of all the environmental factors.

Evidently, the corpus striatum is an effector nucleus lacking independent motor functions but controlling the functions of the globus pallidus, regulating and partly inhibiting its unconditioned reflex activity, that is, the corpus striatum has a similar action on the globus pallidus that the latter has on the red nucleus.

Low-frequency electrical stimulation of the caudate nucleus causes a change in the bahaviour of animals (a longer reaction time in the cerebrocortical neurons, an onset of drowsiness and sleep) which is connected with the influence of the caudate nucleus on the nonspecific thalamic nuclei that activate the cortex.

Lesions of the corpus striatum in man cause athetosis and chorea which result from suppression of the inhibitory influence exerted by the corpus striatum on the globus pallidus. Besides, strengthening of the unconditioned reflexes and hyperkinesia (intensifycation of the auxiliary movements accompanying any principal motor act) are observed. But as a result of uninhibition of the globus pallidus the muscular tone is disturbed- usually decreased (hypotonus).

The corpus striatum is the principal subcortical center which regulates and coordinates the motor apparatus. It also contains the higher vegetative coordination centers which regulate metabolism, heat generation and emission, vascular reactions. Evidently, the corpus striatum contains centers intergrating and unifying unconditioned motor and vegetative reflexes into a single, coordinated behavioural act. Influences of the corpus striatum on the organs which are supplied by the vegetative nervous system are performed by the way of its connections with the hypothalamus.

The globus pallidus receives afferent impulses through fibers coming from the thalamus and closing the thalamopallidal reflex arc. It has effector connections with the centers of the mesencephalon and metencephalon, regulates and coordinates their activity. Obviously, it inhibits the lower nuclei, mainly the red nucleus. That is why damage to the globus pallidus causes hypertonus (increase in the tone) of the skeletal musculature: the red nucleus is freed from its inhibitory influence. Electrical stimulation of the globus pallidus, on the contrary, inhibits the contractions of the skeletal muscles caused by stimulation of the motor area of the cerebral cortex.

In the higher animals and man the thalamo-hypothalamo-pallidal system takes part in complex unconditioned reflexes (defensive, orientation, feeding, sexual), which exist in a pallidal animal.

Many complex reflexes are missing in patients with an injured globus pallidus (for instanse, defensive reactions to sudden intense sound or light stimuli).

When making any movement, a person uses in addition to the muscles performing it, a number of others so that the principal movement is better coordinated and smoother. For instance, swinging of the arms when walking, or a number of auxiliary movements when the position of the body is changed. The reflex arches governing these auxiliary movements that accompany any complex motor act, pass through the pallidal system. With lesions of the globus pallidus movements become awkward and monotonous, and motor acts lack auxiliary movements (hypokinesia).

So, the lesions of the globus pallidus cause the phenomena (hypertonus and hypokinesia), which are direct opposite of those caused by lesions of the corpus striatum (hypotonus and hyperkinesia).

The pallidal patients have mimic immobility of the face (a mask-like face). By this symptom they are recognized at first glance.

In controlling movements two important abilities of the brain are distinguished: 1) to determine how rapidly the movement must be performed; 2) to control how large the movement must be.

These timing and scaling functions are performed by basal ganglia in close association with the cerebral cortex.

For example, it is possible to write the letter “t” slowly or rapidly. A small “t” or a very large “t” on a chalk board may be written. But the proportional characteristics of the letter will remain the same.

In the absence of the basal ganglia these timing and scaling functions are very poor, in fact almost nonexistent.

The posterior parietal cortex is the locus of the spatial coordinates for all parts of the body as well as for the relationship of the body and its parts to all surroundigs. A person lacking a left posterior parietal cortex may draw the human face providing proper proportions for the right side of the face, but almost ignoring the left side (which is in his right field of vision) and will try always to avoid using his right parts of body (right arm, right hand) for performing of tasks. As if not knowing that these parts of his body even exist.

The timing and scaling of movements are functions of caudate cognitive motor control circuit that functions mainly with the associative areas of the cortex, such as the posterior parietal cortex.

Within the basal ganglia some specific neurotransmitters function.:

1. dopamine pathway from the substantia nigra to the caudate nucleus and putamen;
2. GABA pathway from the caudate nucleus and putamen to the globus pallidus and substantia nigra;
3. acetylcholine pathways from the cortex to the caudate nucleus and putamen;
4. multiple general pathways from the brain stem that secrete norepinephrine, serotonin, enkephalin and some other neurotransmitters in the basal ganglia and in other parts of the cerebrum.

GABA always functions as an inhibitory agent. Dopamine also functions as an inhibitory neurotransmitter in most parts of the brain.

Acetylcholine functions as an excitatory transmitter and therefore provides many of the positive features of motor action.

Two major diseases result from damage in the basal ganglia: Parkinson’s disease and Huntington’s chorea.

Widespread destruction of part of the substantia nigra sending dopamine- secreting nerve fibers to the caudate nucleus and putamen, cause Parkinson’s disease which is charecterized by: 1) rigidity of most of the musculature of the body; 2) involuntary tremor of the involved areas even when the person is resting (at a fixed rate of 3-6 cycles per second); 3) akinesia-a serious inability to initiate movement.

Theoretically destruction of the substantia nigra would allow the caudate nucleus and putamen (which are inhibited by substantia nigra) to become overly active and possibly cause continious output of excitatory signals to the corticospinal motor control system. These signals could overly excite many muscles of the body, leading to rigidity.

Because of high feedback gains after loss of inhibition, some of the feedback circuits might easily oscillate, leading to the tremor. Since this tremor occurs during all waking hours, it is called an involuntary tremor, unlike the cerebellar tremor which occurs only when the person performs intentionally initiated movements and is called intention tremor.

The akinesia might be connected with loss of dopamine secretion leading to loss of balance between the excitatory and inhibitory systems.

Huntington’s chorea is characterized at first by flicking movements at individual joints and then progressive severe distortional movements of the entire body. Besides, severe dementia develops. This is a hereditary disorder, and its symptoms are usually manifested in the third or fourth decades of life.

The abnormal movements of Huntington’s chorea are caused, probably, by loss of most of the cell bodies of the GABA-secreting neurons in the caudate nucleus and putamen. Normally the axon terminals of these neurons cause inhibition in the globus pallidus and substantia nigra. Loss of inhibition allows spontaneous outbursts of these structures’ activity that cause the distortional movements. The dementia results, evidently, from simultaneous loss of many acetylcholine-secreting neurons not only in the basal ganglia but also in much of the cerebral cortex. This could block much of the thinking process.

**Cerebral Cortex. Cortical Control of Motor Reactions. Hematoencephalic Barrier. Brain Electric Activity**

The cerebral cortex (the cortex of the cerebral hemispheres) is the highest section of the central nervous system and as phylogenetically the youngest formation of the brain, it is the most complicated in structure and functions. The cerebral cortex is a thin layer of grey matter (neurons) 2-5 millimeters in thickness, that covers the whole surface of the cerebral hemispheres (all the convolutions). The folding of the cortex provides a large surface area, 0.25 square meter for human being, whose total cerebral cortex contains about 100 billion neurons.

In terms of developmental history the cerebral cortex is subdivided into the archicortex (olfactory bulbs, olfactory tracts, olfactory tubercles), paleocortex (gyrus cinguly, hippocampal gyrus, amygdala) and neocortex (all other regions). In mammals the neocortex is evolved at a higher rate.

The functions of the cerebral hemispheres and those of he cerebral cortex were studied in experiments with their extirpation and surgical removal (to find out which functions are lost and which are retained after such operation).

The first extirpation of the cerebral hemispheres was performed at the first quarter of the XIX century by Flourens in birds. Since then many researchers have excised the cerebral hemispheres or cortex of mammals.

 After removal of the cerebral hemispheres birds sit motionless for hours. But they are capable of flying when thrown up into the air and of moving about the cage if prodded slightly. They react normally to changes of the body's spatial position and do not lose the ability to react to auditory and visual stimuli, avoiding obstacles that throw intense shadows. But the decerebrated birds lose the capacity for training, disorders in the complex behavioural acts associated with their individual life experience occur; they cannot find or take food without assistance.

Much more severe behavioral disorders follow extirpation in mammals.

After removal of the cerebral cortex a dog seems blinded and partially deaf. The dog runs into obstacles, fails to recognize its master, does not respond to its name or approach a food set before it. Decrease in the dexterity, smoothness and accuracy of its movements are observed. The period of sleep becomes rather longer. The sex instinct is sharply reduced. But a décorticated dog retains some visual and auditory perceptions. It can turn its head away from a very bright light and retains the papillary reflex. If something bitter is added to its food the animal will split it out and wrinkle its nose. To keep such a dog alive food and water must be put into its mouth. The swallowing of food causes a normal reflex secretion of gastric juice.

Extirpation of the cerebral cortex in rhesus monkeys causes even more marked derangements. Their individually acquired reactions to stimuli disappear, movements elicited by external stimuli are weak and slow, the motor acts are clearly deranged, no voluntary movements occur, mimicry and gesticulation are absent. When not under stimulation the monkey is motionless and sleeps most of the time. It does not endure the operation well and soon does.

In human monsters lacking cerebral cortex at birth (anencephali) severe abnormalities of behaviour occur. They do not live longer than a few days. But in 1913 an exceptional case of the survival of an anencephalic infant for three years and nine months was reported. At autopsy in place of the hemispheres two thin - walled bladders were found, the pyramidal tracts were underdeveloped, the quadrigeminal bodies and cerebellum were unchanged.The child slept throughout its first year of life. Nursing at the breast or putting a soother in its mouth elicited regular sucking movements. No conscious reaction to light or sound was observed, but certain reflexes were noted (closing the eyelids in response to bright light.)

So, removal (or absence) of the cerebral hemispheres or their cortex in higher animals are followed by sharper and deeper disturbances than in lower animals. This is due to corticalization of functions, that is, displacement of complex nervous functions to the cerebral cortex which is the hignest and phylogenetically last-developed sector of the nervous system.

After extirpation of the hemispheres of a frog or a tortoise conditioned reflexes can be formed (by the diencephalon and mesencephalon), but in dogs removal of the cortex alone wipes out all old conditioned reflexes and makes it impossible to form new ones.

Disorders caused by lesions of the cerebral cortex are especially severe in man. Very effective coordination of nervous processes required in connection with the vertical posture and perfomance of complex movements, depends on the cerebral cortex. In the course of development cortical control over the motor sphere (striated musculature) and vegetative processes is created.

Structure of the human cerebral cortex is very complicated.There are different types of cells arranged in layers.

The granule cells having short axons function mainly as intracortical interneurons. Some are excitatory, releasing glutamate, others are inhibitory, releasing JABA. The sensory areas of the cortex, as well as the association areas (between sensory and motor), have large concentrations of these cells, suggesting a high degree of intracortical processing of incoming sensory signals and of the cognitive analytical signals.

The pyramidal and fusiform cells give rise to almost all of the output fibers from the cortex. The pyramidal cells are larger and more numerous, being the source of the long, large nerve fibers that go all the way to the spinal cord. They also give rise to most of the large subcortical associative fiber bundles that pass from one major part of the brain to the other.

Within the different layers of the cortex there are numerous horizontal fibers extending between adjacent areas and vertical fibers extending to and from the cortex to lower areas of the brain and to the spinal cord or to distant regions of the cerebral cortex through the long associative bundles of the cerebral cortex.

The cerebral cortex contains six separate layers of neurons beginning with layer I next to the surface and extending progressively deeper to the layer VI.

1. molecular (plexiform) layer contains few neurons and is mainly formed by interlacing nerve fibers;
2. external granular layer contains closely packed small neurons whose bodies have oval, triangular or polygonal shape;
3. external pyramidal layer contains pyramidal neurons of varying size;
4. internal granular layer contains small neurons like the external granular layer ;
5. internal pyramidal layer contains large pyramidal cells (giant cells of Betz), apical dendrites of which form multiple arborization in the superficial layers, the basilar dendrites

spread laterally, while the axons project to various cerebral and spinal nuclei;

1. fusiform cell (polymorphous) layer contains spindle- shaped and triangular neurons.

Development of these layers varies widely in different regions of the cortex.

Most incoming specific sensory signals terminate in cortical layer IV. Most of the output signals leave the cortex from neurons located in the layers V (to the brain and spinal cord) and VI (to the thalamus). Layers I-III perform most of the intracortical associative functions.

So, the cerebral cortex neurons can be divided into three basic groups:

1. sensory neurons in which the axons of the third neurons of the specific afferent pathways terminate. This function is performed mainly by the stellate neurons which are particularly numerous in the III and IV layers of the sensory areas of the cortex;
2. motor or effector neurons which send impulses to the lower divisions of the brain: giant pyramidal neurons concentrated mainly in the fifth layer of the motor area and also certain spindle -shaper cells;
3. contact neurons (interneurons) providing communication between the different neurons of the same or of different cortical areas. These include small and medium- sized pyramidal and spindle -shaped cells.

According to the features of the composition and structure of the cerebral cortex, it is divided into a number of sectors called cortical areas. In the map of the human cerebral cortex drawn up by Borden 52 cellular areas are described.

A specific features of the neuronal organization of the cerebral cortex is its columnar arrangement, that is, the neurons form the “elementary functional units” or cortical columns which are arranged perpendicular to the cortical surface and incorporate all the cortical layers.

The cortical columns exhibit a well defined functional specialization. Each somatosensory column inervates only one spinal motor nucleus and receives strictly defined topographically isolated cutaneous and proprioceptive signals from the limb innervated by this nucleus.

The cortical areas to which primarily afferent impulses are conveyed are called the central divisions or cortical representations of analyzers (Pavlov). The direct transmitters of impulses to the cortex (except those coming from the olfactory receptors) are the nuclei of the thalamus and the adjoining formations (where the third neurons of the afferent pathways are located).

Cortical representations of many analyzers coincide in space and partly overlap. The cortical regions in which they are situated are called sensory areas. So, the sensory areas are the cortical projections of the peripheral receptive fields.

In each cerebral hemisphere there are two areas of representation of somatic (cutaneous and musculo-articular) and visceral sensitivity - somatic sensory area I (S-I area) and somatic sensory area II(S-II area). S-I area is larger and much more important than S-II area, and in popular usage the term “somatic sensory cortex” most often means somatic area I.

Somatic sensory area I lies in the postcentral gyrus of the cerebral cortex. It receives afferent impulses from the posterior ventral nucleus of the thalamus supplying information received by skin (tactile and temperature), muscular - articular and visceral receptors on the opposite side of the body (with exception of a small amount of sensory information from the same side of the face).

Some areas of the body are represented by large areas in the somatic cortex (the lips - the greatest of all, followed by face and thumb), whereas the entire trunk and lower part of the body are represented by relatively small areas. The sizes of these areas are directly proportional to the number of specialized sensory receptors in each respective peripheral area of the body (a great number of specialized nerve endings are present in the lips and thumb, and only a few - in the skin of the trunk). Also, the head is represented in the most lateral portion of somatic sensory area I, and the lower part of the body- medially.

Somatic sensory area II lies posterior and inferior to the lateral end of somatic sensory area I (below Rolando's fissure) and also receives afferent impulses from the posterior ventral nucleus of the thalamus. The degree of localization of the different parts of the body is very poor in this area, compared with somatic sensory area I (the face is represented anteriorly, the arms centrally and the legs posteriorly). Signals enter this area from both sides of the body, from S-II area and also from other sensory areas of the brain (such as visual and auditory signals).

Visual areas are localized on the medial surface of both hemispheres around of calcarine sulcus and the adjoining gyri. Auditory areas are situated in the first temporal and transverse temporal gyri of Heschl. Taste areas are localized near the Sylvian and circular fissures.

Olfactory areas are situated in the anterior part of the pyriform lobe. The olfactory tracts are the only afferent pathways that do not pass through the nuclei of the thalami. Their first neurons (the olfactory cells) are localized in the nasal mucous, the second - in the olfactory bulb.

Stimulation of human sensory areas (during the operations that are performed under local anesthesia) cause elementary sensation. For instance, during stimulation of the visual area sensations of flash of light, darkness and various colours are observed, but no complex visual hallucinations are noted. Or electrical stimulation of the auditory area gives rise to sensation of various sounds, but a patient never has a sensation of speech sounds. Stimulation of the olfactory or gustatory area causes various sensations of smell or taste (mainly unpleasant). Stimulation of the somatosensory area gives rise to sensations of touch, pricking, numbness and less frequently a weak sensation of temperature or pain (severe pain is almost never felt).

Destruction of human sensory areas cause severe disorders of the given type of sensitivity on the side of the body opposite to the focus of the lesion (bilateral lesion of the visual areas causes total blindness and that of the auditory areas - total deafness). In the cortical end of each analyzer Pavlov distinguished a central part or nucleus and scattered elements. Thanks to these elements, the functional compensation is realized when the analyzer nucleus is destroyed. In man the nerve cell of the cortical ends of the analyzer are mainly concentrated in the sensory areas, and therefore this compensation is less marked.

After the widespread excision of somatic sensory area I the person is unable to localize discretely the different sensations in different parts of the body, to judge critical degrees of pressure against his body, the weights and shapes of objects (astereognosis), texture of materials. The appreciation of pain and temperature sense modalities may be altered either in quality or in intensity, and these sensations are poorly localized.

Ablation of somatic sensory area II in lower animals makes it difficult to learn to discriminate shapes of objects.

Afferent impulses from the thalamic nuclei are conveyed not only to the sensory areas but also to the regions adjoining them. These regions are called somatic associative areas or secondary sensory areas. They lie along the margins of the primary sensory areas, extending from 1 to 5 centimeters on all sides of them.

Cells of associative areas are able to respond to stimulation of various peripheral receptors. For instance, not only sounds but also light or electrical stimuli applied to the skin can evoke potentials in the secondary auditory area in cats. This means that afferent pathways carrying impulses from the various receptor systems converge in these areas. So, somatic associative areas combine information from multiple points in the somatic sensory areas to decipher its meaning. Electrical stimulation in the somatic associative area can occasionally cause a person to experience a complex somatic sensation sometimes even the “feeling” of the concrete object (a knife or a ball).

Extirpation of associative areas does not cause loss of the given type of sensitivity, but the ability to interpret the significance of the acting stimulus correctly, is disturbed. For example, stimulation of the secondary visual area does not cause blindness, but the patient becomes unable to appreciate his visual sensations (does not understand the meaning of words he reads). Destruction of the secondary auditory area leads to loss of ability to understand the meaning of spoken words.

When the somatic associative area is removed, the person loses the ability to recognize complex objects and complex forms by the process of feeling them. He loses even most of the sense of form of his own body, and is mainly oblivious to the opposite side of the body (forgets that it is there). When feeling objects he tends to feel only its one side and forgets that the other side even exists. This complex sensory deficit is called amorphosynthesis.

Thus, the associative areas play an important role in the analysis and synthesis of stimuli in the cortex. The area occupied by them is the largest in man.

Destruction of associative areas in man leads only to a temporary derangement of a particular function, because the remaining parts of the cortex take over the functions of the destroyed areas and compensate for the damage.

Most of the neurons whose axons extend to the lower divisions of the central nervous system, are concentrated in the precentral gyrus anteriorly to Rolando's fissure. This region is called the motor area. The motor area's cellular structure is characterized by the presence of giant Betz cells. Long processes of these cells reach the interneurons and motor neurons of the spinal cord within the pyramidal tract.

Localization of the motor points, that is, the points on the cerebral cortex, stimulation of which causes movement of definite muscles, corresponds to the sequence of sensory representtation in the postsentral gyrus (the largest zone is occupied by the representation of the muscles of the hands, face, lips and tongue, and the smallest by the representation of the trunk and lower extremities).The motor points of the lower extremities are located above all the others, below them are those of thrunk muscles, further down those of the upper extremities and still lower of the musculature of the head. Stimulation of all these points causes muscular contraction on the opposite side of the body (the descending motor tracts decussate).

The extent of the cortical motor representation of any given part of the body determines fineness of control of its movements.

By the way of electrical stimulation of the human motor zone around the motor points of the fingers, it is possible to cause contraction of individual muscles or even of separate motor units, but stimulation of trunk musculature motor points cause simultaneous contraction of 30-50 synergetic muscles.

The boundary between the motor and sensory areas (Rolando's fissure) is conventional, because the motor area contains a large number of sensory cells, and giant pyramidal cells are found in the sensory area. Therefore, in 25 % of cases electrical stimulation of the human precentral convolution causes sensation instead of movement or together with movement, and in 20% of cases stimulation of the postcentral convolution causes movement instead of sensation or together with sensation. Taking into account the functional proximity of these two areas, they are taken together under the common name of sensomotor area. Pavlov considered it the cortical end of the kinesthetic (motor) analyzer.

Injuries to the motor area (or circulatory disturbances in this region) cause hemiplegia, that is, total or partial paralyses of the musculature on the opposite side of the body.

The motor area of the cerebral cortex regulates the activity of the organism's motor apparatus through impulses sent along the descending tracts to the lower parts of the central nervous system. Some of the processes of the pyramidal cells form corticospinal tract. Other fibers extend to the subcortical structures. Some of these connect motor area cells with the corpus striatum, the red nucleus and the substantial nigra, and other cross the pons and connect the motor area with cerebellum, forming the ponto - cerebellar tract.

Vascular reaction in response to stimulation of the motor area are to the descending fibers extending directly to the cells of the reticular formation and hypothalamus.

In front of the motor area lies premotor area. The topographical organization of the premotor cortex is roughly the same as that of the primary motor cortex, with the face area located most laterally and then the upwards direction the arm, trunk and leg areas. Since the premotor area occupies a large share of the area 6 in the Brodmann classification of brain topology, it is often called simply motor area 6.

Most nerve signals generated in the premotor area cause patterns of movement involving groups of muscles that perform specific tasks. For example, to achieve such position of shoulders and arms that the hands become properly oriented to perform specific tasks the premotor area sends its signals either directly into the primary motor cortex to excite multiple groups of muscles or (more likely) by way of the basal ganglia and then back through the thalamus to the primary motor cortex. So, the premotor cortex, basal ganglia, thalamus and primary motor cortex form complex system controlling many more complex patterns of body's coordinated muscle activity.

Removal of small parts of the human premotor area during neurosurgery leads to disturbance of motor habits, although fine movements of the hand are retained.

Removal of the region representing the muscles of the leg in the motor or premotor cortex in adults causes Babinsky's reflex,

The supplemental (accessory) motor area lies on the medial surface of the cerebral hemispheres immediately superior and anterior to the premotor area. The muscles of all parts of the body are represented here (the leg area lies most posteriorly and the face anteriorly).

To elicit muscle contraction considerably stronger electrical stimuli must be applied to the supplemental area than in the other motor areas. But if contractions are caused, they are frequently bilateral rather than unilateral and stimulation often leads to movements such as unilateral grasping of a hand or bilateral grasping of both the hands (perhaps rudiments of the hand functions for climbing). Also, various vegetative reactions, changes in the diameter of the pupils, vocalization or yawning may occur.

It is supposed that the supplemental motor area plays an auxiliary role in controlling posture which is governed by the primary motor and premotor areas. It provides attitudinal movements, fixation movements of the different segments of the body, positional movements of the head and eyes as background for the finer motor control of the hands and feet by premotor and primary motor cortex.

Stimulation of different points of the cerebral cortex is attended with coordinated movements of both eyes. Some cortical areas (in occipital lobe) are responsible for fixation of the eyes on the object seen, others (in frontal lobe)- for voluntary movements of the eyes.

In higher animals and human beings all motor acts of the organism are controlled by the cerebral cortex. Thanks to the corticalization of functions, in monkeys and especially in man such movements as walking and running are impossible without cortical control.

A circular interaction between the cortex and the motor apparatus ensures accurate adjustment of the movement to the varying conditions of its performance and reconstruction of the motor act according to the results obtained. For the motor reactions governed by the cortex their formation as a result of individual life experience (in the course of training) is characteristic.

Training is the repeated performance of a definite complex of movements which leads to their automation. As a result they become more accurate, rapid and even strong according to the task to be achieved. In the process of training superfluous movements are eliminated. The human motor acts that have become automatic are walking, running, standing and many work movements.

The reciprocal movements of human body's individual parts during walking, running, jumping and various work movements are so rapid that their detailed examination is impossible without the use of snapshot photography or motion picture.

The method of cyclography is used to record movements: the successive positions of a person in motion are recorded on one photographic plate. Mechanograms are obtained by conversion of the non-electrical values to electrical ones by the help of various transducers. For simultaneous recording of movement together with speed and acceleration electronic differentiators are used. Electromyography, that is, recording of the action potentials arising on muscle excitation, permits to analyze the muscular work in the performance of the motor act.

The anatomical classification of muscles (flexors and extensors, synergists and antagonists) not always reflects muscle function in movements. For example, certain biarticular muscles perform flexion in one joint and extension in the other. An antagonistic muscle may be excited together with agonistic to ensure precise movements. Therefore, it would be appropriate to separate the prime mover (the main motive power), accessory muscles (synergists and others that help motor tasks performance) and stabilizers (muscles that fixate joints but do not take part in movement).

The most common form of human locomotion is walking. Walking belongs to the syclic motor acts in which movement phases follow in succession and are regularly repeated. Each walking cycle is divided into periods:

1. twin - support (double - support) period - both legs rest on the support;
2. single - support period for the right leg (swing period for the left leg); **3)** twin support period;

**4)** single - support period for the left leg (swing period for the right leg).

Walking is performed with the participation of the muscles of the foot, shin, thigh, pelvic girdle. During various phases of a step different patterns of the muscle contraction are observed: concentric, eccentric, isometric and even ballistic (shifting of the leg parts by inertia).

The kinematics of walking results from the interaction of the muscular and nonvascular forces. For instance, heel jerk (pushing the foot away from the support caused by the plantar flexure) occurs as a result of contraction of the posterior group of leg muscles, while foot is lowered under gravity.

The principal difference between walking and running is the existence of a period without the support (a moment of flight) during running that is, the leg which is behind is pushed against the support before the other has touched the support. Thanks to a higher speed of movements, ballistic components are more essential in running.

Working movements include a broad spectrum of various goal - directed movements, especially those of the arm, as the major working organ of human being. High extent of freedom of the upper limb enables the hand to get to a needed point by the different trajectories and at various relationship between angles in the shoulder, elbow and wrist joints.

The posture is maintained by the same mechanism of muscle contraction that provides the movement. But in postural activity the muscular contraction force is not great, the mode of contraction is nearly isometric and the duration of contraction is long. In postural activity low threshold, slow, fatigue - resistant motor units take part.

A typical example of human posture is standing. To keep balance in standing the projection of the body's center of gravity must be located within the area of contact between the feet and the ground.

Maintenance of posture is an active process and is accomplished with participation of the feedback mechanism. Muscles of the leg counteract shifting of the body and bring it back into the vertical position. The preceding redistribution of muscular activity provides steadiness of posture during movements.

Great extent of freedom in the locomotion apparatus, the influence of gravity and inertia make performance of any motor act difficult, particularly that of new movements. The motor apparatus opposes obstacles by developing supplementary muscle contraction, ensures solid fixation of the joints which do not take part in movements and actively breaks the inertia of quick movements. This way is disadvantageous and tiresome. Besides, use of the feedback is still inadequate. The electromyograms show simultaneous activation of antagonistic simultaneous muscles and almost no relaxation of muscles taking part in cyclic movements. Excitation of many muscles not directly related to a given motor act is observed.

As a result of learning excess muscular tension disappears and movements become more resistant to obstacles, the non- muscular forces become involved in the dynamics of the motor act and become its composite part. The electromyograms show concentration of muscular excitation in time and space. Periods of activity of the working muscles shorten and the number of muscles involved in excitation decreases. This leads to saving muscular activity, pattern of movements becomes more smooth, precise and free.

Feedback serve for the correction of the program of the next movements proceeding from the errors of the preceding one.

Fatigue, resulting from the prolonged physical exertion, causes changes of muscular activity coordination, and the pattern of muscular activity closely resembles that of new uncommon movement performance.

The main condition for the normal cerebral activity is an uninterrupted supply of blood to the brain. Because demand of brain for oxygen and nutrients (in particular for glucose) is great. No other cells cease to act as quickly as do the nerve cells when their blood supply is stopped or sharply reduced.

Filling the cerebral ventricles, the central canal of spinal cord and the subarachnoid spaces, the cerebrospinal fluid (CSF) plays a role of the internal environment of the brain. It maintains cerebral saline composition and osmotic pressure, serves as a hydraulic buffer of the brain and ensures reliable mechanical protection of the nerve cells.

The cerebrospinal fluid is a nutrient medium of the brain: in the ventricles where it is produced the sugar content is higher than in the subarachnoid space where it is absorbed. The cerebrospinal fluid is important transport medium by which the products of cerebral metabolism are eliminated from the brain and into the blood stream.

The capillary walls separating the blood and cerebrospinal fluid, and certain neuroglial cells (astrocytes) form hemato - encephalic (blood - brain) barrier (BBB). The composition of the cerebrospinal fluid largely depends on the properties of this barrier.

A number of facts confirm the existence of the hemato - encephalic barrier. For instance, many substances containing in the blood or introduced into it are completely absent in the cerebrospinal fluid. But the membranes separating the blood and cerebrospinal fluid possess selective permeability. Therefore, other substances are contained both in the blood and the fluid in equal concentrations.

Iodine compounds, nitrates, salicylates, methylene blue, all colloids, immune bodies, antibiotics (penicillin, streptomycin) do not pass from the blood to the cerebrospinal fluid through the barrier.

Alcohol, chloroform, strychnine, morphine, tetanus toxin readily pass through the barrier and enter the cerebrospinal fluid. That is why they act on the nervous system quickly after introduction into the blood.

The drugs and biologically active substances that do not pass through the hemato - encephalic barrier, are administered directly into the cerebrospinal fluid by the way of the suboccipital or lumbar puncture. In this case the action of these substances may be quite different. For instance, administration of ATP into the blood causes drop of the arterial pressure owing to the dilatation of the arteries and arterioles, but when it is injected directly into the cerebrospinal fluid by suboccipital puncture, the arterial pressure is increased thanks to stimulation of the vasomotor center (in the medulla oblongata).

Natural regulation of the cerebral function by changing the composition of the cerebrospinal fluid is also possible. The biologically active substances that influence the nerve and glial cells of the central nervous system can be secreted by the nerve cells themselves (neurosecretion). The cerebral function may be regulated by changing selectively the permeability of the hemato- encephalic barrier to certain substances. Since the permeability of the barrier is regulated by the central nervous system, this is the case of the cerebral functional self - control.

As a result of generation of synaptic potentials and impulses in individual nerve cells the cerebral cortex maintains continuous electric activity which can be recorded from the surface of the brain or from the outer surface of the head. This method is called electroencephalography (Gr.encephalon-brain), the entire record is an electroencephalogram (EEG) and the undulations in the recorded electrical potentials are called brain waves. The intensity and patterns of the brain electrical activity (the character of the brain waves) are determined to a great extent by the overall level of excitation of the brain resulting from wakefulness, sleep, brain diseases (epilepsy, psychoses).

In the electrophysiological investigation of the brain its background electrical activity and changes in it due to various afferent stimuli are recorded. Since the background electrical activity is observed in all parts of the central nervous system in the apparent absence of any stimuli acting from the outside, it is called also spontaneous activity.

In 1929 Berger, using electronic amplifiers, demonstrated the possibility of recording electroencephalograms from the human scalp through the intact skin covering the head. This method has since been widely applied in experimental and clinic researches.

There are two methods of recording of electroencephalograms:

1. bipolar lead - two recording electrodes are applied to the cortex or to corresponding areas of scalp, the electroencephalograph records the potential differences of the cortical areas beneath the electrodes;
2. monopolar lead - one electrode is applied to the cortical region (active electrode) and the other (indifferent) electrode is applied to the ear - lobe (in man) or the nasal bone (in animal); the waves under the active electrode are recorded.

The amplitude of human brain waves from the scalp varies from 5-10 to 200-300 microvolts, and their frequency - from once every few seconds to 50 or more per second.

To study the relationships between the changes of electrical potentials in different areas of the cortex and subcortical formations multichannel electroencephalographs are used which allow to record the electrical activity at four to thirty two points in the brain simultaneously. Possibilities of electroencephaloscope are greater: it records the activity of 50-100 cortical areas (in the form of points of light of continuously changing brightness). The changes of electrical potentials are analyzed with the help of the computer.

Much of the time no general pattern can be distinguished in the EEG (the brain waves are irregular), but at other times distinct patterns appear. According to the frequency, amplitude and physiological characteristics of the electrical waves in normal persons four basic types of electroencephalogram waves or rhythms are distinguished: alpha, beta, delta and theta waves.

Alpha waves (rhythmic waves of almost sinusoidal form with a frequency of 8-13 per second and an amplitude up to 50 microvolts) are distinctly expressed in the electroencephalograms of almost all normal adult persons at physical and mental rest (without any external stimuli), lying in a comfortable way, with their muscles relaxed and eyes closed. Alpha rhythm is recorded in the occipital (more intensely) parietal and frontal cortical regions.

The occipital alpha rhythm is recorded in the visual area of the cortex and is absent or faint in the blind persons. The parietal (Rolandic) alpha rhythm is associated with the activity of the Rolandic area where the cortical end of the proprioceptive analyzer is localized.

Under similar conditions in animals alpha-like rhythms are recorded.

During deep sleep the alpha waves are replaced by more slow theta and delta waves and under different stimulations- by more rapid (beta) waves.

Beta waves (frequency - above 13 per second and amplitude - up to 20-25 microvolts) are rapid waves. They are most distinct in the frontal region and rather less - in the parietal. In the occipital region alpha waves are quickly replaced by beta waves under various kinds of stimulation (especially by light), during mental work (solving arithmetic problems), emotional excitement and so on. The Rolandic rhythm is rapidly replaced by beta rhythm particularly under the influence of proprioceptive stimuli caused by movements of the extremities.

Theta waves and delta waves are slow waves.

Theta waves (frequency - 4-8 per second and amplitude - 100-150 microvolts) are recorded during sleep and narcosis, also in different pathological conditions (hypoxia, disappointment and frustration) and many cerebral disorders. In children theta waves are recorded mainly in the parietal and temporal regions.

Delta waves (frequency- 0.5- 3.5 per second amplitude- up to 250-300 microvolts) are recorded during deep sleep, deep narcosis, hypoxia, various pathological processes in cortex. In animals these waves may be recorded even after separation of the cerebral cortex from the thalamus by subcortical transaction. This means that they can occur strictly in cortex independent of activities in lower regions of the brain, whereas alpha waves, for instance, will not occur in the cortex without connections with the thalamus.

Narcosis (general anesthesia) causes characteristic changes in the EEG, corresponding to its phases. In the first phase of narcosis which is characterized by motor and verbal excitement, beta waves are recorded. As the narcosis deepens, the beta waves are replaced by theta waves. These are soon replaced by delta waves, followed by periods of silence (absence of electrical oscillations). Finally, complete inhibition of electrical activity is observed. During recovery from narcosis changes occur in the reverse order.

In the hypoxia also initially beta waves appear which then are replaced by delta waves (this coincides with loss of consciousness). Continued hypoxia causes cessation of electrical activity, but it oxygen supply is restored, changes occur in the reverse order.

During convulsive (epileptic) seizures caused by the action of convulsing or pathological focus (scar, tumor) in the cortex or subcortical structures, typical changes in the EEG are revealed. That is, complexes made up of a high - amplitude peak of short duration followed by a slower wave of a considerably smaller amplitude and longer duration, are recorded. Less frequently isolated high - amplitude waves (convulsive peaks) are recorded which often are accompanied by convulsions of skeletal musculature.

The problem of the origin of electroencephalogram is still not fully clear. The suggestion that the slow EEG waves are the algebraic sum of the action potentials of a multitude of asynchronously operating individual neurons, has now been abandoned. Because it has been shown that there is no connection between the impulse activity of individual neurons and EEG waves, and even they may be completely different under certain influences. For instance, under ether anesthesia the cortical cells are incapable of generating action potentials, but slow EEG waves continue to be recorded.

Most investigators connect the origin of EEG waves with algebraic summation of postsynaptic potentials. High- amplitude, slow alpha - like or delta - like brain waves are recorded as a result of summation of postsynaptic potentials during synchronous excitation of a large group of cortical cells. This occurs when the supply of afferent impulses to the cortex are limited (closing the eyes, confinement in a darkened and quiet room), and also during sleep and narcosis.

When afferent impulses are supplied to the cortex, postsynaptic potentials do not arise simultaneously in the different cells and frequent low - amplitude beta - type waves are recorded (upon waking from sleep and in a wakeful state).

Stimulation of the brain stem reticular formation causes a transition from slow rhythms to rapid rhythms (replacement of alpha rhythm by beta rhythm when a person opens his eyes). This phenomenon is called the desynchronization or activation reaction.

The experiments with undercutting of cortex prove the leading role of afferent impulses in the origin of EEG waves. If all the nerve fibers entering a small area of the cortex from the basal ganglia are dissected, while preserving its connections with the vascular bed (preparation of an “isolated strip of cortex”), electrical activity in that area ceases completely. But when electrical stimuli are applied directly to this area, a series of gradually fading waves will be generated in it.

Direct stimulation of afferent nerve fibers or stimulation of the receptors of any receptive field causes the appearance in the EEG of characteristic evoked (induced) potentials in the form of primary or secondary responses.

In the nerve centers which receive afferent impulses from definite groups of recaptors, evoked potentials have their greatest amplitude and shortest latent periods. These are called the primary responses. A typical primary response is a biphasic potential with an amplitude between 400 and 600 microvolts. Initially a positive oscillation is recorded (10-12 milliseconds) which is followed by a negative oscillation (15-20 milliseconds). Primary potentials have a strictly defined spread, thanks to which the zone receiving definite sensory signals can be accurately located.

The first (positive) wave of the primary responses is associated with excitation of the pyramidal cells in the III and V cortical layers and the second (negative) wave reflects excitation of the I-II layers (due to synchronous depolarization of the apical dendrites in these layers).

Besides the primary responses, arising with the minimum latent period, a number of secondary responses are recorded in different areas of the cerebral cortex. As distinct from the primary responses, the secondary responses have more complex configuration and a long latent period.

**Limbic System.**

**Behavioural and Motivational Mechanisms of the Brain**

Control of behavioural is a function of the entire nervous system. But such functions as control of activity levels in the different parts of the brain, motivational drives, especially the motivational control of the learning process and the feelings of pleasure and punishment, are performed mainly by basal regions of the brain, which together are loosely called the limbic system.

Originally, the term “limbic” was used to describe the border structures (“limbic” means “border”) around the basal regions of the brain, including the cingulate gyrus, hippocampal gyrus, hippocampus, dentate gyrus, fornix and amygdala. But as limbic system functions were studied profoundly, this term had been expanded to mean the entire neuronal circuity that controls emotional behaviour and motivational drives. So, hypothalamus, located in the midst of all these structures, from physiological point of view is a major part of the limbic system. The epithalamus, anterior nucleus of thalamus, portions of basal ganglia also belong to this system.

Thus, on the medial and ventral surfaces of each cerebral hemisphere there is a ring mostly of palaeocortex that surrounds a group of deep structures intimately associated with overall behaviour and emotions.

Thanks to the numerous connections of all parts of the limbic system with the parietal, visual, temporal, auditory and other cortical regions, it plays an important role in the process of synthesizing afferent stimulation, participates directly in the emotional reactions by which an animal or human being displays its positive or negative attitude to a particular stimulus.

Certain areas of limbic system control many internal conditions of the body (body temperature, osmolality of the body fluids, the drive to eat and drink, control of body weight, etc.), which are collectively called vegetative functions of the brain and whose control is closely related to behaviour.

Many of the behavioural functions elicited from the hypothalamus and other limbic structures are mediated through the associated nuclei in the brain stem.

So, the limbic system governs the activities of the body concerned with homeostasis, selfpreservation and preservation of the species. Certain areas of palaeocortex play an important role in memory processes.

Besides the vegetative and endocrine functions of the hypothalamus, it concerns greatly the emotional behaviour. So, stimulation of lateral hypothalamus not only causes thirst and eating, but also increases the general level of activity of the animal, sometimes leading to overt rage and fighting.

Effects opposite to those caused by lateral hypothalamus are caused by stimulation of ventromedial nucleus and surrounding areas.

Stimulation of a thin zone of periventricular nucleus, located immediately adjacent to the third ventricle as well as of the central grey area of the mesencephalon leads to fear and punishment reaction.

Sexual drive is stimulated from several areas of hypothalamus (particularly most anterior and most posterior portions).

Lesions in the hypothalamus, in general cause the opposite effects. Bilateral lesion of the lateral hypothalamus decreases drinking and eating almost to zero, cause extreme passivity of the animal with loss of most of its overt drives. Bilateral lesion of the ventromedial areas cause (besides excessive drinking and eating) hyperactivity, continuous savagary along with frequent bouts of extreme rage on the slightest provocation.

Fascicles of fibers localized immediately in front of hypothalamus take part in the suppression of the rage reaction. When they are dissected, the violent fit of rage occurs, and the animal destroys everything on its way. It is interesting that the rabies virus (lyssin) is localized just in the areas of the limbic system which are connected with the aggressive behaviour of the animals.

So, several limbic structures are particularly concerned with the affective nature of sensations, which are called reward and punishment or satisfaction and aversion. That is, electrical stimulation of certain regions pleases or satisfies the animal, but that of other regions - causes pain, fair, terror, defence, escape reactions and other elements of punishment. These two oppositely responding systems greatly affect the behaviour of the animal.

Olds’ experiments were extremely demonstrative. Electrodes were permanently implanted in different parts of the rats’ brains and were connected to a stimulator which the rat could switch on by pressing a lever with its leg.

When the electrodes had been implanted in the posterior hypothalamus or the reticular formation of the midbrain, the rat that had accidentally pressed the lever, lost all interest in its surroundings and food, and kept pressing the lever up to 8000 times an hour. Thus, such positive reactions as reactions of “pleasure” or “enjoyment” cause self-stimulation.

When the electrodes had been implanted in the medial part of the hypothalamus, the frequency of self-stimulation changed according to whether the animal was hungry or had been fed (in the latter case the frequency of self-stimulation was lower). But when the electrodes were in lateral parts, the frequency of self-stimulation was increased by injection of sex hormones and reduced by castration.

These facts indicate that the reactions aroused in self-stimulation experiments are associated with unconditioned nutritional or sexual reflexes.

When the electrodes were localized in the dorsal part of the diencephalon and the ventromedial nucleus of the hypothalamus, reaction of a different character developed, that is, after a single self-stimulation the animal avoided touching the lever. Evidently, this stimulation caused negative emotions. Stimulation of this region in cats may arose a ferocious reaction when it attacks other animals in vicinity.

With the help of the self-stimulation method the major reward centers have been found along the course of the medial forebrain bundle, especially in the lateral and ventromedial nuclei of the hypothalamus.

Less potent reward centers are localized in the septum, amygdala, certain areas of the thalamus and basal ganglia. The most potent punishment areas were found in the aqueduct of Sylvius in the mesencephalon and extending upward into the periventricular zones of the hypothalamus and thalamus. Less potent punishment areas are located in the amygdala and hyppocampus.

Many areas give a sense of reward with weaker stimuli, and a sense of punishment with stronger ones. Besides, stimulation in the punishment centers can frequently inhibit the reward and pleasure centers completely.

The reward and punishment centers constitute one of the most important of all the controllers of the bodily activities, drives, aversions, motivations: if a person is doing something rewarding, he continues to do it, if it is punishing, he ceases to do it.

Administration of a tranquilizer (chlorpromazine) greatly decreases the affective reactivity of the animal by the way of inhibiting both the reward and punishment centers.

Strong stimulation of the punishment centers of the brain (periventricular zone of the hypothalamus or lateral hypothalamus) causes the animal to develop a defence posture, extend its claws, lift its tail, hiss, spit, growl, develop piloerection, wide - open eyes and dilated pupils. The slightest provocation causes an immediate savage attack. This behaviour is characteristic of an animal being severely punished. It is a pattern of behaviour called rage.

Stimulation of the more rostral areas of the punishment (in the midline preoptic areas) causes mainly fear and anxiety with a tendency to run away.

The rage phenomenon is held in check mainly by counterbalancing activity of the ventromedial nucleus of the hypothalamus. Besides, hippocampus, amygdala, anterior portions of the limbic cortex help suppress the rage phenomenon. If they are damaged or destroyed, the animal becomes far more susceptible to bouts of rage.

Stimulation of reward centers causes the opposite emotional behaviour patterns, that is, placidity and tameness.

The basolateral nuclei of the human amygdala has become more highly developed than olfactory portion and plays exceedingly important roles in many behavioural activities. Thanks to multiple connections of the amygdala (with all portions of the limbic cortex, neocortex of the temporal, parietal, occipital lobes, auditory and visual association areas) it has been called the “window” through which the limbic system sees tha place of the person in the world.

The amygdala is a behavioural awareness area which operates at a semiconscious level. It helps pattern the person’s behavioural response so that it is appropriate for each occasion.

Stimulation in the amygdala can cause almost all the same effects as those elicited by stimulation of the hypothalamus and still other effects, as well as different types of involuntary movement (raising the head, bending the body, circling movements, licking, chewing, swallowing).

Stimulation of certain amygdaloid nuclei can rarely cause a pattern of rage, escape, punishment and fear (similar to the rage pattern elicited from the hypothalamus). Stimulation of other nuclei can cause reward and pleasure reactions.

Sexual activities (erection, copulatory movements, ejaculation, ovulation, uterine activity, premature labour) may be caused by excitation of still other portions of the amygdala.

Destruction of the anterior portions of both temporal lobes in a monkey removes also the amygdalas lying deep in these parts of the temporal lobes. This causes a combination of changes in behviour called the Kluver-Bucy syndrome: excessive tendency to examine objects orally, loss of fear, decreased aggressiveness, tameness, changes in dietary habits (herbivorous animal becomes carnivorous), psychic blindness, excessive sex drive.

The hippocampus is an additional channel through which incoming sensory signals can lead to appropriate behavioural reactions. Stimulaion of its different areas causes different behavioural patterns (rage, passivity, excess sex drive). Very weak electrical stimuli can cause local epileptic seizures during which the person experiences various psychomotor effects (olfactory, visual, auditory, tactile hallucinations).

The limbic cortex occupies intermediate associative position between the function of the remainder of the cerebral cortex and that of the subcortical limbic structures for control of behavioural patterns. All above - mentioned behavioural patterns can be caused by stimulation of its different parts. Ablation of a few limbic cortical areas can cause persistent changes in behaviour (consummatory behaviour, intense sex drives, insomnia, fits of rage and so forth).

The local destruction of some limbic system areas in the animals causes the change of their “social behaviour”, that is, the behaviour in the association, herd (flock).

**Neural Regulation of Vegatative Functions**

Beginning from the early XIX century functions of the organism have been divided into animal (somatic) and vegetative (autonomic).The first include the perception of stimuli and the motor reactions carried out by skeletal musculature, the second-metabolism and the functions on which the perfomans of metabolism depends (digestion, secretion, respiration, blood circulation, etc.) as well as growth and reproduction.

In accordance with this distribution of functions the nervous system also is divided into somatic and vegetative (autonomic) parts:

1. the somatic nervous system-is responsible for the sensory and motor functions (skeletal musculature) of the organism;
2. the vegetative nervous system-provides efferent innervation of all the visceral organs, blood vessels, sweat glands, as well as trophic innervation of the skeletal musculature, receptors and the nervous system itself.

The vegetative nervous system regulates the metabolism, excitability and automatism of the peripheral organs and central nervous system. It controls changes in the physiological condition of tissues and organs, governs their adjusment to the current activity of the whole organism and environmental events. Depending on the conditions under which organs are functioning, the vegetative nervous system exerts a corrective (adjusting) or triggering (starting) influence on them:

1. corrective influence-if an organ possesses automaticity and functions continuosly (is already “launched into work”),then the impulses coming to it along the sympathetic or parasympathetic nerves only intensify or weaken its activity;
2. triggering influence-the organ does not operate continuously and is excited by impulses arriving along the sympathetic and parasympathetic nerves.

The triggering influences are often supplemented by the corrective ones.

The sensory, motor and vegetative components of the organism’s reactions as a whole are closely interconnected. But unlike the vegetative components, the somatic ones can be voluntarily evoked, intensified or inhibited; they are controlled by the cerebral hemispheres during their entire course. However, vegetative components are not, in general, under the direct voluntary control. That is why some investigators call this system the autonomic nervous system (Langley) and others-involuntary system (Gaskell). The concept of the “autonomy” of the vegetative nervous system, as unconnected with the higher divisions of the central nervous system is quite conventional. Because the cerebral cortex regulates the activity of all organs supplied by the vegetative nervous system and coordinates their activity.

The vegetative nervous system can change visceral functions very rapidly and intensively: within several seconds it can increase the heart rate and the arterial pressure to two times normal or decrease the pressure low enough to cause fainting, empty bladder or cause sweating. Just these extremely rapid changes are measured by the lie detector polygraph, reflecting the innermost feelings of a person.

The vegetative nervous system is distinguished from the somatic nervous system by the localization of its nuclei in the central nervous system, focal output of fibers from the brain, absense of their segmentary distribution at the periphery, small fiber diameter. Besides, in their way from the central nervous system to the internal organs vegetative nerve fibers are interrupted in the peripheral ganglia, forming synapses on the neurons located in these ganglia. The internal organs are influenced by axons of the ganglionic neurons. Centers of the vegetative nervous system are located mainly in the spinal cord, brain stem and hypothalamus. Portions of cerebral cortex (especially of the limbic cortex) also influence vegetative control by the way of transmitting impulses to the lower centers. The vegetative nervous system frequently operates also by means of visceral reflexes.

The vegetative nervous system has two parts: the sympathetic and parasympathetic systems.

Centers of the sympathetic nervous system are located only in the thoracic and lumbar (from the 1thoracic to the II-IV lumbar segments of the spinal cord (thoracolumbar part of the vegetative nervous system).Their fibers extent through the anterior roots of the corresponding spinal segments along with the processes of the motor neurons.

But the centers of the parasympathetic nervous system are scattered all over the central nervous sytem:

1. the sacral centers-their fibers form part of the pelvic splanchnic nerves;
2. the bulbar centers- their fibers form part of the facial, glossopharyngeal and vagus nerves; **3)** the mesencephalic centers- their fibers form part of the oculomotor nerve;

So, parasymathetic fibers leave the central nervous sytem through the III, VII, IX, X pairs of cranial nerves and sacral spinal nerves.But speaking of the parasympathetic nervous system we frequently think mainly of the vagus nerve, because about 75% of all parasympathetic nerve fibers are in two vagus nerves passing to the entire thoracic and abdominal regions of the body.

The sympathetic nerve fibers are more extensively distributed and supply actually all organs and tissues of the organism. But the parasympathetic nerves do not innervate central nervous system, skeletal muscles,sense organs, certain vessels of the abdominal cavity, skin vessels,uterus, etc.

All parts of the vegetative nervous sytem are subordinated to the higher vegetative centers (in the hypothalamus, corpus striatum) which in turn are subordinated to the cerebral cortex. Thanks to the cerebral cortex activity the organism reacts as a whole, unifying its somatic and vegetative functions into single acts of behaviour.

Unlike the somatic nerve fibers having only a single neuron (in the central nervous system),the bineuronal structure is the typical feature of the vegetative nerves.The body of the first neuron lies in the central nervous system.Its axon passes to the periphery and ends in the ganglion, forming a synapse with the body of the second neuron which is located in the ganglion. The second neuron's axon runs to the periphery and innervates the appropriate organ. The axon of the first neuron is called the preganglionic fiber and that of the second neuron-the postganglionic fiber.

On its way to the periphery the vegetative fiber may run successively through several ganglia, but it is interrupted, commonly,only in one of them, and there is only one synapse in the vegetative nerve after it exits from the central nervous system.

To determine in which of the ganglia the vegetative nerve is interrupted, that is, where the first neuron terminates and the second neuron begins,the morphological and the pharmacological methods are applied.

Using the morphological method the termination of the nerve fibers is determined by tracing the degeneration of the fibers after they are cut (when peripheral parts of the axons are separated from their cell bodies their endings degenerate within a week or two):

If the fiber that is cut, is preganglonic, then degeneration extents only from the place of dissection to the synapses connecting it with the postganglionic fiber. But if the fiber that is dissected,is postganglionic,then degeneration extends to the terminal arborizations of the vegetative nerves in a muscle or a gland.

The pharmacological method is based on the peculiarity of nicotine to paralyse the interneuronal synapses of the vegetative ganglia whereas it does not influence the conduction of impulses in nerve fibers.The portion of the vegetative pathway containing the ganglion under examination is painted with nicotine. The following stimulation of a preganglionic fiber passing through the painted ganglion without a break (having a synapse in another ganglion) produces the effect usual for a stimulated nerve, whereas stimulation of the preganglionic fiber interrupted at this ganglion ceases to affect the peripheral organ innervated by it.

There are some exceptions to the bineuronal structure rule. For instance,the postganglonic sympathetic fibers passing to the smooth muscles of the gastrointestinal tract terminate not on the muscle fibers,but mainly on the parasympathetic ganglionic cells in the wall of the stomach and intestine.Evidently they decrease the activity of these cells and in this way realize their inhibitory influence on the smooth muscles.In this case the peripheral vegetative pathway has a trineuronal structure.

Another exception concerns the efferent sympathetic pathway of mononeuronal structure:

the chromaffin cells of the adrenal medulla are supplied not by the postganglionic but by the preganglionic sympathetic fibers.

Preganglionic fibers belong to type B, and the postganglionic fibers-to type C.

Excitability of vegetative fibers(especially that of postganglionic fibers) is relatively low, the rate at which they conduct impulses is slow.The thinner the vegetative fiber-the larger its threshold and chronaxy,the longer the refractory period and the slower the rate of impulse conduction.

Duration of acting potentials in vegetative nerve fibers may be about 100 times longer (150 milliseconds) than that of in somatic fibers. They are also followed by protracted hyperpolarization (up to 0.5 second).

The one-way transmission of impulses in the interneuronal synapses, overlapping of the preganglonic fibers,convergence,occlusion, spatial and temporal summation in vegetative ganglia indicate that the properties of their ganglion neurons and synapses are similar to those of the neurons and synapses of the central nervous system. But also there are number of features specific to the generation of excitation in the neurons of the vegetative ganglia: long synaptic delay and long period of excitatory postsynaptic potential, clearly pronounced after hyperpolarization, transformation of the rhythm of nerve impulses.

The vegetative ganglia are assumed to be the peripheral reflex centers.A large number of local peripheral reflexes performed by the intramural ganglia partricipate in the regulation of cardiac activity, intestinal peristalsis and ensure the interrelation between different gastric portions and certain other organs. The reflex function is not performed by all the ganglia. For instance, the peripheral reflexes are mediated by the prevertebral gnaglia (celiac plexus) and they have not been observed in the cervical sympathetic ganglia.

Some axons of preganglonic or postganglionic neurons ramify in such a way that one branch supplies one organ or part of an organ,while the other innervates another organ or another part of the organ. Stimulation of one branch of axon causes excitation to spread through other branch and evoke a reaction in another organ. This is called axon reflex or pseudoreflex. Unlike the true reflexes,the axon reflex do not transmit excitation from a receptor neuron to an effector neuron.

The axon reflex was observed in studying the innervation of the urinary bladder.

Many of the vegetative centers have a constant tone, that is,they are in the state of tonic activity (resting activity) and continuously send excitatory or inhibitory impulses to the organs that they innervate. For instance, dissection of both vagus nerves in the neck of a dog causes increase of heart rate, because it eliminates the inhibitory influence continually exerted on the heart by the nuclei of these nerves, which have a definite tone. Unilateral dissection of the sympathetic nerve in the neck of a rabbit causes dilatation of the vessesls in the ear on the affected side since the vessels are deprived of vasoconstrictive tonic influence.

Tone of the vegetative centers is ensured and maintained by the afferents from the visceral receptors and partly from the exteroceptors and results from the action of various factors of the blood and cerebrospinal fluid on the centers.

The vegetative nerve fibers secreting acetylcholine as synaptic transmitter substance,are called cholinergic fibers,and those secreting norepinephrine (or adrenalin) are called adrenergic fibers. In both the sympathetic and parasympathetic nervous systems all preganglonic neurons are cholinergic.That is why acetylcholine(as well as acetylholine-like substances),when applied to the ganglia, excite both sympathetic and parasympathetic neurons.

The postganglionic neurons of the parasympathetic system are also all cholinergic.

Most of the postganglionic sympathetic neurons are adrenergic. But the postganglionic sympathetic nerve fibers to the sweat glands, to the piloerector muscles and to a few blood vessels are cholinergic.

So, acetylcholine and norepinephrine are called respectively, parasympathetic and sympathetic transmitters.

To stimulate the effector organ, the transmitter secreted at the sympathetic or parasympathetic nerve endings must first bind with highly specific receptors of the effector cells.This causes a conformational change in the structure of the receptor protein molecule, and the altered protein molecule excites or inhibits the cell mainly by two ways: **1)** changes the cell membrane permeability to one or more ions;

**2)** activites or inactivates an enzyme attached to the other end of the receptor protein where it protrudes into the interior of the cell.

So, whether the vegetative transmitter substance will cause excitation or inhibition in some or other organs is determined by the nature of the receptor protein in the cell membrane and the effect of receptor binding on its conformational state.

There are two different types of cholinergic receptors: muscarinic and nicotinic receptors. Muscarine (a poison from toadstools) activates only the muscarinic receptors but does not activate the nicotinic receptors, and nicotine activates only nicotinic receptors. However, acetycholine activates both of them.

The muscarinic receptors are found in all effector cells stimulated by the postganglonic neurons of the parasympathetic nervous system and the postganglionic cholinergic neurons of the sympathetic sytem.

The nicotinic receptors are found in the synapses between the preganglionic and postganglionic neurons of both the sympathetic and parasympathetic systems and also in the membranes of skeletal muscle fiber at the neuromuscular junction. The adrenergic receptors are also of two major types: alpha (α 1 and α 2) receptors and beta (β1 and β2) receptors.

Norepinephrine excites mainly alpha receptors and to a slight extent the beta receptors.

Epinephrine excites both alpha and beta receptors approximately equally.

Isopropyl norepineprine (a synthetic hormone chemically similar to epinephrine and norepinephrine) has an extremely strong action on beta receptors and no action on alpha receptors.

Alpha and beta receptors are not necessarily associated with excitation or inhibition. Because certain alpha or beta functions are excitatory while others are inhibitory. Alpha receptors cause vasoconstriction, and beta receptors vasodilatation.

Iris dilatation,intestinal sphincter and bladder sphincter contraction as well as pilomotor contraction are caused by alpha receptors,whereas beta receptors cause cardio-acceleration,increased myocardinal strength, bronchodilatation,bladder wall relaxation, etc.

Stimulation of sympathetic and parasympathetic fibers in most of the organs produces opposite effects,that is,when sympathetic stimulation excites a particular organ, parasympathetic stimulation inhibits it. So,the two systems act reciprocally to each other. But some organs are dominantly controlled by one or the other of the two systems.

The special feature of the sympathetic influences on the organs is that these influences are purposeful to mobilize the strengths of the body to overcome the powers which threaten the organism and are dangerous for the life.This is,the sympathetic nervous system makes the organism ready for the fight,ensures intensive activity of the organism under conditions reqiuring exertion. But the parasympathetic system helps to restore reserves of the organism expended during emotions.

Thus, sympathetic stimulation excites the functions that are necessary for the fighting organism and inhibits those that will prevent the organism to fight.That is why the sympathetic stimulation inhibits secretory and motor functions all over the gastrointestinal tract.But it increases the strength of skeletal muscles, heart rate and strength of heart muscle contraction, constricts most of blood vessels and increases blood pressure. But the bronchi are dilated, because the oxygen supply to the organism must be improved (blood glucose is also increased). The pupils are also dilated (to frighten the enemy). Blood coagulation is increased (organism becomes ready to prevent loss of blood if it would be wounded).

Parasympathetic stimulation,on the contrary, increases secretory and motor functions of the gastrointestinal tract,decreases heart rate, dilates most of blood vessels and decreases blood pressure, constricts bronchi and pupils, etc.

In all situations demanding urgent reactions from the organism the tone of the sympathetic system is heightened,while the tone of the parasympathetic system is heightened during sleep.

The functional antagonism between the sympathetic and parasympathetic systems is also expressed in one of them innervating an endocrine gland that produces a change in the state of organism in one direction,while the other innervates another gland changing this state in the opposite direction. For instance, the sympathetic nerves supply the adrenal medulla and increase the secretion of adrenalin which causes hyperglycemia,whereas the parasympathetic (vagus) nerves supply the insulae of the pancreas and increase the production of insulin which causes hypoglycemia.

Besides the antagonist effects certain functional synergy of sympathetic and parasympathetic systems was also noted (secretion of saliva is activated both by the sympathetic and parasympathetic nerves). Also, an increase in the tone of one system may cause an increase in the tone of other.

Reactions caused by the vegetative nervous system may alter considerably depending on the tone of the nerve centers and on the condition of the peripheral organ.Therefore, the effects of sympathetic and parasympathetic nerves and their antagonism is not absolutely constant or invariable.

The functional state of the organism and of the organs and tissues on which the character and intensity of their reaction depend,is known as their reactivity. For instance, under normal conditions the vagus nerve stimulates the movements of the stomach and small intestine.But when it is stimulated against the background of a marked increase of muscular tone of these organs their automatic contractions are inhibited rather than intensified.

Also,with an excess of potassium ions stimulation of the cardiac sympathetic nerves inhibits rather than intensifies cardiac activity,and with an excess of calcium ions this activity is increased rather than reduced by stimulation of the vagus nerve.

Such changes in the vegetative stimulation effects are called ''functional perversion'' or ''paradoxical action''.

Double innervation of the organs (by sympathetic and parasympathetic fibers) is very important. Because acting in the opposite directions (like whip and bridle),these systems provide the normal activity of the organ.That is,normal functioning of the organ can be ensured only in case when sympathetic influences are balanced by parasympathetic ones.Domination of the tone of one system causes diminution of the other.A continuous increase in the sympathetic or parasympathetic tone causes different disorders (sympathicotonia or vagotonia).

There are peculiarities in vegetative innervation of some organs. For instance,the sweat glands are supplied by sympathetic fibers only. But the endings of most of their postganglionic fibers produce acetylcholine rather than norepineprine.Therefore, injection of atropine completely arrests perspiration even at high ambient temperature. However, in some areas of the body (in the palms) sweating can be caused by adrenalin.

Evidently, there are two different types of perspiration:

1. thermal perspiration-is caused by the impulses transmitted across cholinergic endings of the sympathetic nerves;
2. emotional perspiration (''cold sweat'' of fright)-is caused by the impulses transmitted across adrenergic endings of the sympathetic nerves.

Stimulation of the sympathetic nerves of a fatigued skeletal muscle restores its working capacity. Sympathetic system acts also on the sense organs and the central nervous system, especially on the reflex function of the medulla oblongata and midbrain and on conditionedreflex activity of the cerebral cortex. Removal of the superior sympathetic ganglia in a dog causes disordes of conditioned reflex activity.

So, the sympathetic nervous sytem has unuversal adaptational-trophic function, that is, it controls metabolism, nutrition and excitability of all organs and tissues and ensures adjustment of the body to the current conditions of activity.

The main task of the parasympathetic system is to provide continuous correction of shifts evoked by the sympathetic influences, restoration and maintenance of homeostasis.

Acetylcholine released by the parasympathetic nerve endings may inhibit the secretion of norepinephrine by the sympathetic nerve endings. So, the parasympathetic system plays the role of the regulator of sympathetic influences and is the peculiar anti-stress factor.

The parasympathetic nerve fibers may exert the excitatory and inhibitory influences on the functions of the organs they control. Because impulses reaching organ through the preganglionic parasympathetic fibers interact in the intramural ganglia with impulses realizing reflex regulation within the organ. Also, among the intramural efferent neurons there are cholinergic, adrenergic, purinergic, serotoninergic, dopaminergic, histaminergic, peptidergic, GABA-ergic neurons. All this provides a possibility for a broad spectrum of regulatory influences.

Many of the visceral functions of the body are regulated by vegetative reflexes.These reflexes are evoked by stimulation of exteroreceptors or interoreceptors, neurons of the vegetative nervous system are involved in their perfomance and impulses are involved in their perfomance, and impulses are transmitted from the central nervous system to peripheral organs along sympathetic and parasympathetic nerves.

The number of vegetative reflexes is very great.In the cardiovascular system they help to control especially the heart rate and blood pressure (for instance, baroreceptor reflexes). The functions of the gastrointestinal tract are also controlled by vegetative reflexes (secretion of digestive juices, peristaltic contraction that empty the bowels, emptying of the bladder or rectum and so on). Other vegetative reflexes include sweating, excretion of urine, sexual reflexes, etc.

Some vegetative reflexes are used in the clinical practice (vegetative functional tests) to assess the state of the vegetative nervous system. For instance, the oculocardiac (Aschner's) reflex, the respiratory cardiac reflex (respiratory arrhythmia), the orthostatic reaction (tachycardia and increase in blood pressure in changing from a recumbent to an erect position) and so forth.

If electrodes connected to a galvanometer are applied to a portion of the skin containing many sweat glands, any stimulus producing emotional excitation (pricking with a needle, an electrical shock, exciting story) causes a deviation of the galvanometer needle.This phenomenon is called psychogalvanic (galvanic) skin reflex.

One of tests to examine vascular reactions is dermographism in which the skin is irritated mechanically by a blunt instrument.In many healthy subjects this causes the white dermographism,that is,a reflex constriction of arterioles manifested by a brief paleness of the irritated part of the skin.In more sensitive subjects the red dermographism is observed,that is, a red streak of dilated skin vessels appears fringed with the pale streaks of narrowed vessels.Similar irritation of the skin in hypersensitive subjects causes a streak of swollen skin (edema).

Histamine and adrenalin tests (intracutaneous injection of these substances) are also employed.The reactivity of skin vessels is judged from the size of red (histamine) or pale (adrenalin) spot at the site of the injection and by its duration. In the subjects with very high reactivity at the point of histamine injection not only a reddening but also edema appears. Three types of the vegetative reflexes are distinguished: the viscero-visceral, viscero-cutaneous and cutano-visceral reflexes.

The viscero-visceral reflexes are elicited by stimulation of visceroreceptors of the internal organs and terminate also by a change in the activity of the internal organs: reflex changes in cardiac activity and vascular tone due to increased or decreased pressure in aorta, carotid sinus or pulmonary vessels; reflex cardiac arrest on stimulation of the abdominal organs.

The viscero-cutaneous reflexes are also evoked by stimulation of visceral organs, but they are manifested by changes in perspiration,electric resistance (conductivity), sensitivity of the skin in the corresponding areas of the body surface. That is why lesions of the visceral organs cause increase in sensitivity and decrease in electrical resistance in certain areas of the skin.

Cutano-visceral reflexes are expressed in vascular reactions and changes in the activity of certain visceral organs caused by the stimulation of the definite areas of the skin. Certain therapeutic procedures are based on this effect (local heating or cooling of the skin for pains in the visceral organs, mud-treatment)

Vegetative reflex changes are constant components of all conditioned and unconditioned reflex reactions of the organism.That is, all the behavioural acts expressed in muscular activity and active movement are accompanied by changes in the functioning of the visceral organs (circulation, respiration, digestion, excretion, internal secretion).

The experiments with complete extirpation of the sympathetic system demonstrate its importance in adapting the organism to different life situations.Under various conditions involving stress in the organism (intensive muscular effort, overheating, chilling, blood loss,emotional excitement) such animals exhibited less endurance.

The immune extirpation causes similar effect.A protein in the salivary glands of mice promoting the growth of sympathetic nerve cells is injected into other animals. Obtained blood serun containing immune bodies that bind the substance promoting growth of sympathetic neurons, when injected into newborn animals, causes destruction of sympathetic nerve cells.

Some drugs act on vegetative nervous system. For instance, intravenous injection of norepinephrine causes essentially the same effects throughout the body which the sympathetic stimulation does.Therefore, norepinephrine, as well as epinephrine and methoxamine, are called adrenergic or sympathomimetic drugs.

The drugs that stimulate specific adrenergic receptors are phenylephrine (alpha receptors), isoproterenol (beta receptors), albuterol (beta2 receptors).

Some drugs (ephedrine, tyramine, amphetamine) have an indirect sympathomimetic action rather than directly exciting adrenergic effector organs. They release norepinephrine from its storage vesicles in the sympathetic nerve endings, and norepinephrine in turn causes the sympathetic effects.

Some drugs block adrenergic activity at different points in the stimulation process:

1. reserpine prevents the synthesis and storage of norepinephrine in the sympathetic nerve endings;
2. guanethidine blocks release of norepinephrine from the sympathetic endings;
3. phenoxybenzamine and phentolamine block the alpha receptors;
4. propranolol blocks all beta receptors, and metoprolol blocks only beta1 receptors;
5. hexamethonium causes blockade of both sympathetic and parasympathetic transmission through the ganglia.

Acetylcholine injected intravenously does not cause the same effects as parasympathetic stimulation.Because it is destroyed by cholinesterase in the blood and body fluids before it can reach all the effector organs. But some other drugs (parasympathomimetic drugs) that are not so rapidly destroyed can produce typical parasympathetic effects: pilocarpine and methacholine act directly on the muscarinic type of cholinergic receptors (muscarinic drugs).

Parasympathomimetic drugs act also on the effective organs of cholinergic sympathetic fibers,causing profuse sweating or vascular dilatation. Anticholinesterase drugs (neostigmine, pyridostigmine) inhibit acetylcholinesterase, thus preventing rapid destruction of the acetylcholine liberated by the parasympathetic nerve endings. Atropine, homatropine and scopolamine block the action of acetylcholine on the muscarinic type of cholinergic effector organs (antimuscarinic drugs). Since the preganglionic neurons of both the parasympathetic and sympathetic systems secrete acetylcholine at their endings which in turn stimulates the postganglionic neurons,the injected acetylcholine can stimulate the postganglionic neurons of both systems causing at the same time both sympathetic and parasympathetic effects. Nicotine can also stimulate postganglionic neurons in the same manner as acetylcholine. Because the membranes of these neurons all contain one nicotinic type of acetycholine receptors.Therefore, drugs that cause vegetative effects by stimulating postganglionic neurons are called nicotinic drugs. Acetylcholine and methacholine have both nicotinic and muscarinic actions, but pilocarpine has only muscarinic actions.

Nicotine excites both the sympathetic and parasympathetic postganglonic neurons at the same time, resulting in strong sympathetic vasoconstriction in the abdominal organs and limbs, but at the same time resulting in parasympathetic effects, such as increased gastrointestinal activity (sometimes also slowing of the heart activity).

Ganglionic blocking drugs (tetraethyl ammonium ion, hexamethonium ion, pentolinium) block impulse transmission from the preganglionic neurons to the postganglionic neurons.They inhibit impulse transmission in both the sympathetic and parasympathetic systems simultaneously.These drugs are frequently used for blocking sympathetic activity but rarely for that of parasympathetic activity. Because the sympathetic blockade usually far overshadows the effects of parasympathetic blockade.

The nervous mechanism underlying the vegetative control have a ''multi-storeyed'' hierarchial structure.The first (lowest) ''storey'' or level of this hierarchy are the peripheral intraorganic reflexes which are closed in the intramural vegetative ganglia. The second level are the reflex reactions closed in the extraorganic vegetative ganglia (mesenterial plexus,solar plexus,ganglia of the sympathetic trunk). The lower vegetative centers of the spinal cord and brain stem form the third level. The higer levels are represented respectively by the hypothalamus, brain stem reticular formation, basal ganglia, limbic system, neocortex.

The lower levels possess certain autonomity and can regulate the state of organs and tissues on a local level. Each higher level of regulation ensures a higher degree of integration of vegetative functions.For instance,the spinal sympathetic centers can change the vascular tone of certain organs and body regions, whereas the bulbar cardlovascular center regulates the general level of blood pressure.The centers of hypothalamus are concerned with involvement of the cardiovascular and other vegetative systems in general responses of organism.The limbic system (including hypothalamus) ensures adequate changes in vegetative functions at varying degrees of tension. Finally, the cerebral cortex maintains coordination of the vegetative and somatic functions in complex behavioural responses arising on the basis of personal experience. Of course, the concept of ''storeys'' is conventional,because in an integral organism neither of the levels is autonomous and the lower levels are subordinated to the higher ones.

At the level of the last cervical and two upper thoracic segments of the spinal cord the ciliospinal center of Budge is situated. Its neurons supply the three smooth muscles of the eye (the muscle dilating the pupil, the orbital part of the orbicular muscle of the eye and one of the muscles of the upper eyelid. Stimulation of the sympathetic fibers originating from this center causes dilation of the pupil (mydriasis),opening of the palpebral fissure and protrusion of the eyeball (exophthalmus).Transection of these fibers or lesion of the center leads to Horner's syndrome: constriction of the pupil (myosis), narrowing of the palpebral fissure and recession of the eyeball into the orbit (enophthalmos).

Five upper thoracic spinal cord segments contain sympathetic neurons supplying the heart and bronchi.Impulses from those neurons accelerate and intensify cardiac contraction and dilate bronchi.

All the thoracic and superior lumbar segment contain sympathetic neurons supplying vessels and sweat glands. Lesions in these segments cause disappearance of the vascular tone and vascular reaction to various stimuli and lead to cessation of perspiration in the corresponding parts of the body.

In the sacral segments there are spinal centers of the urination, defecation, erection and ejaculation. Damage to these centers causes sexual impotence – incontinence of urine and feces. Paralysis of the spihincters of the urinary bladder and rectum results in disorders in urination and defecation.

The medulla oblongata and midbrain contain centers regulating the activity of organs supplied by the parasympathetic fibers of the III,VII, IX and X pairs of the cranial nerves.

The nerve centers inhibiting heart activity,stimulating lacrimation, secretion of the salivary,gastric and pancreatic glands, secretion of bile from the gallbladder and bile ducts, contraction of the stomach and small intestine, are situated in the medulla oblonggata. Here (in the reticular formation) lies the vasomotor center. The cardioinhibiting centers are involved in various cardiac reflexes (Holtz' reflex, Aschner's reflex, respiratory-cardiac reflex, etc.). Owing to the connections between the neurons which regulate the cardiac activity and vascular tone, many reflex reactions of the heart are coupled with changes in the vascular tone.

In the midbrain (in the anterior corpora quadrigemina) the centers of the pupillary and eye accomodation reflexes are situated.

The hypothalamic nuclei influence the cardiovascular system, digestive organs, thermoregulation, water-salt balance, carbohydrate, fat, protein metabolism, urination, endocrine functions. They take part in many general responses (including the behavioural ones), for instance, in sexual and aggressive-defensive responses.

Exorting excitatory and inhibitory influences on the different divisions of the central nervous system,the reticular formation produces tonic effect on the vegetative centers.The activating function of the reticular formation and the adaptational-trophic function of the sympathetic system are similar in principle.Evidently the sympathetic nervous system forms a functional unity with the reticular formation and transmits its influences to the pirephery.

Cerebellum is involved not only in the coordination of reflex motor acts but also in those of vegetative functions.Cerebellectomy causes inhibition of the gastrointestinal tract functions. The basal ganglia (especially the corpus striatum) take part in complex unconditioned reflexes in which there are always vegetative components.

Thanks to the direct interconnections of the basal ganglia and their connections with the brain stem reticular formation and the hypothalamas,vegetative responces may be elicited by stimulation of the basal ganglia. Stimulation of the corpus striatum causes functional changes in many internal organs.

Stimulation of various areas of the cerebral cortex causes changes in many vegetative fuctions.The frontal lobe of the cerebral cortex plays a major role in the regulation of vegetative functions and is considered containing the highest centers of the vegetative nervous system. Its stimulation causes changes in the respiration,digestion, blood circulation, sexual activity.

The limbic system or visceral brain plays an important role in the regulation of the visceral activity. Destruction of the amygdala causes increased appetite and leads to obesity due to overeating. Destruction and stimulation of the hippocampus influence salivation, swallowing.

Afferent signals from the visceral receptors first arrive the somatic sensory zones of cerebral cortex.The cortical neurons involved in the regulation of the visceral functions are considered as the cortical represetation of the interoceptive analyser.

The role of the cerebral cortex in control of vegetative functions is demonstrated by experiments with development of conditioned reflexes to changes in the visceral activity and with hypnotic suggestion in man. Acceleration or diminution of heart rate, constriction of dilatetion of vessels,enhanced secretion of urine and sweat, changes in the metabolic rate may be caused by suggestion. In some persons influence of the cerebral cortex is so strong that they can voluntarily accelerate their heart rate, produce raising of hairs and goose flesh (usually observed in chilling),variations in the pupillary diameter (dependent on the smooth-muscle tone of the iris).

# LECTURE 6

# BLOOD SYSTEM PHYSIOLOGY

**Functions, Physical and Chemical Properties of Blood. Blood Plasma Composition. Physiological Solutions**

The blood together with the lymph and tissue fluid forms the internal environment of organism and speaking of homeostasis we mean mainly the stability of blood composition as the principal part of the internal environment.

The blood system consists of the following parts: 1) the peripheral blood circulating in blood vessels, 2) the hemopoietic organs (the red bone marrow, the lymph nodes, the spleen), 3) the organs of blood destruction, 4) the regulating neurohumoral apparatus.

The blood system realizes many vital functions. Circulating in blood vessels the blood carries out the transport function which determines some other functions. The respiratory function consists of binding and transport of oxygen and carbon dioxide. Providing all the cells of organism with nutritive (glucose, amino acids, fats, vitamins, mineral substances, water) the blood fulfills the nutritious (trophic) function. The blood takes away from the tissues the final products of metabolism (urea, uric acid), i. e. fulfills the excretory function. The thermoregulatory function consists of cooling of power-consuming organs and warming of organs which lose the warmth. The blood maintains the stability of biological constants of organism (pH, osmotic pressure, isoionia). The blood fulfills the protective function (immunity, phagocytosis).

One of the significant functions of blood is its participation in the humoral regulation of organism’s functions. The blood transfers the hormones and other physiologically active substances from cells where they are formed to other cells of organism. The blood realizes also creatory connections that is, the macromolecules which are carried by blood plasma and blood cells realize intercellular transmission of information. This provides regulation of the intracellular processes of protein synthesis, preservation of the cell differentiation degree, restoration and maintenance of the structure of tissues.

The chemical and morphological composition of blood to a considerable extent reflects the processes proceeding in organs and tissues and therefore it is very important to study it in details. In the healthy adult organism there is 4.5 - 6 litres of blood and this makes at an average 68% or 1/13 of body mass.

Volume of circulating blood is relatively constant, thanks to the strict balance between the entrance of water into organism and its excretion from the organism. Loss of 1/3 - 1/2 of blood mass results in death.

Blood consists of liquid part-plasma and blood cells (erythrocytes, leukocytes and trombocytes) which are suspended in plasma.

Per cent of cells in blood is called hematocrit. The hematocrit of normal men averages

about 42, whereas that of normal women - 38. This means that in men 42 per cent of the blood volume is cells, and the remainder (58 per cent) is plasma; in women 38 per cent - cells and 62 per cent - plasma.

Everyone knows that the blood is red.

But there is a slight difference between arterial and venous blood. The arterial blood contains 20% of oxygen and its colour is scarlet, but the venous blood is dark-red, because it contains only 12% of oxygen. Blood’s colour may be of practical significance. For instance, if in the course of operation the surgeon observes that the blood grows darker, he must stop the operation and do everything possible to prevent the hypoxemia (oxygen deficiency).

The blood is of salty taste due to the existence of salts, especially the sodium chloride.

Specific gravity of blood is 1.050 - 1.060, of blood cells - 1.090, of plasma - 1.025 - 1.034. Blood’s specific gravity is measured by areometer and may be of diagnostic significance, informing about the functional state of excretory system and some other organs.

Viscosity of blood is 5 in comparison with the viscosity of water which is conditionally taken as 1. Viscosity of the blood plasma is 1.7-2.2. The viscosity of blood is created by blood cells and partly by plasma proteins. It is measured by viscosimeter. The blood viscosity is increased when the blood is thickened (loss of water by organism) or the number of blood cells in peripheral blood is augmented. That is, the greater the hematocrit - the more friction there is between successive layers of blood, and this friction determines the viscosity. Therefore, the viscosity of blood increases drastically as the hematocrit increases.

The greater the viscosity, the less the flow in a vessel if all other factors are constant. If we consider the viscosity of whole blood at normal hematocrit to be about 5, this means that five times as much pressure is required to force whole blood as to force water through the same tube. When the hematocrit rises to 60 or 70 (in polycythemia), the blood viscosity can become as great as 10 times that of water, and blood flow through vessels is greatly retarded.

Osmotic pressure of blood is equal to 7.6 - 8.1 atm. It is created by mineral substances of plasma. Speaking of osmotic pressure we mean the pressure which forces the water to pass through the semipermeable membrane to the concentrated solution. It is measured by the osmometer. The osmotic pressure determines the water exchange between blood and tissues, takes part in the processes connected with the filtration. According to the osmotic pressure 3 kinds of salt solutions are distinguished: 1) isotonic solutions with the osmotic pressure equal to that of blood, 2) hypertonic solutions the osmotic pressure of which is higher than that of blood, 3) hypotonic solutions with the osmotic pressure lower than that of blood.

The osmotic pressure created by proteins is called the oncotic pressure. The oncotic pressure is equal to 0.03-0.04 atm or 25-30 mm Hg. It is 200 times less than the osmotic pressure though the amount of proteins in blood plasma is approximately 10 times more than that of mineral substances. This is connected with the fact that the osmotic pressure exerted by particles (molecules or ions) in a solution is determined by the number of particles per unit volume of fluid, but not by the mass of particles. And the protein molecules, being much larger than that of mineral substances, their number is very small.

The oncotic pressure exercises an influence on the processes of formation of tissue fluid, lymph, urine, absorption of water in intestine. The oncotic pressure plays an important part in the regulation of the water balance of organism.

The active reaction of blood is weak alkaline. The normal pH of arterial blood is 7.4 while the pH of venous blood and of interstitial fluids is about 7.35 because of extra quantities of carbon dioxide that form carbonic acid in these fluids.

A person is considered to have acidosis whenever the pH is below 7.4 and to have alkalosis when it rises above 7.4.

Regulation of hydrogen ion concentration is one of the most important aspects of homeostasis. Even the slight changes in pH can cause marked alteration in the rates of chemical reactions in the cells, some being depressed and others accelerated. Because the ferment systems of organism can function normally only when pH is normal. In general, when people become acidotic, they are likely to die in coma, when they become alkalotic, they may die of tetany or convulsions.

The lower limit at which a person can live more than a few hours is about 6.8, and the upper limit - 7.8.

The intracellular pH ranges between 6 and 7.4, averaging about 7. Rapid rate of metabolism in cells increases rate of acid formation and consequently decreases pH. Poor blood flow causes acid accumulation and also a decrease in pH.

In organism several special control, systems prevent acidosis or alkalosis:

1. All the body fluids are supplied with acid-base buffer systems which immediately combine with any acid or base and thereby prevent excessive changes in hydrogen ion concentration.
2. If the hydrogen ion concentration changes measurably, the respiratory center is stimulated, breathing rate alters. The rate of carbon dioxide removal from the body fluids automatically changes and this causes the hydrogen ion concentration to return toward normal.
3. When the hydrogen ion concentration changes, kidneys excrete either an acid or alkaline urine, helping to readjust the hydrogen ion concentration back to normal.

The buffer systems can act within a fraction of a second to prevent excessive changes in hydrogen ion concentration. It takes 1-12 minutes for the respiratory system to make acute adjustments. The kidneys require many hours to several days to readjust the hydrogen ion concentration.

An acid - base buffer is a solution containing a weak acid and its salt which is formed by a strong base. This chemical compounds prevent marked changes in pH when added to the solution. For instance, if only a few drops of concentrated hydrochloric acid are added to a beaker of pure water its pH immediately falls from a neutral 7 to as low as 1. However, if satisfactory buffer system is present, the hydrochloric acid combines instantaneously with the buffer and the pH falls only slightly.

Blood contains the following **buffer systems**: 1) the bicarbonate buffer system, 2) the phosphate buffer system, 3) the protein buffer system, 4) the hemoglobin buffer system.

The **bicarbonate buffer** system consists of a mixture of carbonic acid (H2CO3) and sodium bicarbonate (NaHCO3) in the same solution. Carbonic acid is a very weak acid for its degree of dissociation into hydrogen ions and bicarbonate ions is poor in comparison with that of many other acids. When a strong acid, such as hydrochloric acid is added it is converted into the very weak carbonic acid and pH of the solution is lowered only slightly:

HCl + NaHCO3 = H2CO3 + NaCl.

When a strong base, such as sodium hydroxide, is added, the hydroxyl ion of the sodium hydroxide combines with a hydrogen ion from the carbonic acid and forms water. The other product formed is sodium bicarbonate. The result is exchange of the strong base NaOH for the weak base NaHCO3:

NaOH + H2CO3 — NaHCO3 + H2O

The bicarbonate buffer system is not especially powerful, but it is more important than all the others, because the concentration of each of the two elements of this system can be regulated - carbon dioxide by the respiratory system and the bicarbonate ion by the kidneys. As a result the pH of the blood can be shifted up or down by the respiratory and renal regulatory systems.

The **phosphate buffer system** is composed of H2PO4- and HPO4--. It acts in identical manner:

HCl + Na2HPO4 = NaH2PO4 + NaCl

NaOH +NaH2PO4 = Na2HPO4 + H2O

The **protein buffer system** operates the same way as the bicarbonate buffer system thanks to the amphoteric nature of proteins.

The **hemoglobin buffer system** is the stronger. It forms 75% of blood buffer capacity.

The blood buffer capacity is measured by the amount of acid or base which is necessary to change the pH of 10 ml blood on one unit in corresponding direction (Van Slyke).

In the process of metabolism more acid products, than alkaline ones are formed. Therefore buffer systems provide greater stability to the action of acids, than alkali. For instance to change the blood plasma reaction in the direction of alkalosis it is enough to add 40-70 times more NaOH than to pure water. But to cause acidosis it is required 300- 400 times more HCl in comparison with the pure water.

The alkaline salts of weak acids containing in blood form the blood alkali reserve. Alkali reserve of blood is determined by the amount of carbon dioxide which can be bound by 100 ml of blood at the carbon dioxide pressure equal to 40mm Hg.

In spite of the activity of buffer systems, in some physiological and many pathological conditions acidosis or alkalosis occur. Any factor that decreases pulmonary ventilation rate, increases the concentration of dissolved carbon dioxide in the extracellular fluid which leads to increased carbon acid and hydrogen ions, resulting in acidosis. This is called respiratory or gaseous acidosis. Excessive pulmonary ventilation decreases the hydrogen ion concentration, resulting in respiratory alkalosis. All other abnormalities of acid - base balance are called nongaseous (including metabolic) acidosis or alkalosis. Every type of acidosis or alkalosis can be compensated or non-compensated.

The blood plasma consists of 90 - 92% water and 8 - 10% the dry residue. The dry residue contains organic and inorganic substances.

The organic substances of plasma consist of proteins (7-8%), non-protein substances containing nitrogen and organic substances without nitrogen.

The blood plasma proteins are: albumins (4.5%), globulins (2-3.5%) and fibrinogen (0.4%). The significance of plasma proteins is very varied. They create the oncotic pressure, support the blood pH, provide the blood viscosity, prevent the erythrocyte sedimentation, take part in blood coagulation (fibrinogen), are the necessary factors of immunity, carriers of some hormones, mineral substances, lipids, cholesterol. The plasma proteins serve as a reserve for the construction of tissue proteins and realize the creatory connections.

Nitrogen containing non-protein substances of plasma consist of proteolysis products (amino acids, polypeptides) which are used in organism for protein synthesis and the protein disintegration products (urea, uric acid, creatine, creatinine, ammonia) which must be excreted from organism. Organic substances of plasma containing no nitrogen are glucose, the neutral fats, lipids. The blood glucose level (80-120 mg%) is of vital significance.

The inorganic substances of plasma (0.9%) consist of different cations (Na+, K+, Ca2+, Mg2+) and anions (Cl-, HPO42-, HCO3-) fulfilling in organism varied important functions.

**The blood plasma composition**

|  |  |  |  |
| --- | --- | --- | --- |
| Organic substances  | Percent  |  | Inorganic substances  |
|   |   | 91.  | Water  |
| Proteins  | 7  | 0.3  | Sodium  |
| Lipids  | 0.3  | 0.02  | Potassium  |
| Neutral fats  | 0.2  | 0.012  | Calcium  |
| Glucose  | 0.12  | 0.002  | Magnesium  |
| Urea  | 0.03  | 0.35  | Chlorides  |
| Uric acid  | 0.004  | 0.16  | Bicarbonates  |
| Creatine  | 0.006  | 0.03  | Phosphates  |
| Amino acids  | 0.008  | 0.02  | Sulfates  |

The mineral substances existing in blood in amounts less than 0.001% are called microelements or trace elements. In spite of their small quantity the trace elements, such as manganese, zinc, copper, molybdenum, cobalt perform vital functions in organism. Their connection with ferments, hormones, vitamins is very significant.

Taking into consideration the composition and compounds of blood plasma, different isotonic and physiological solutions are prepared. The simplest of all is the 0.85 (0.9) % solution of NaCl for the man and warm-blooded animals and 0.65 (0.6)% NaCl for cold-blooded animals. Different physiological solutions were offered by Ringer, Locke, Tyrode and others.

**The composition of physiological solutions (the amount of substances in per cent)**

|  |  |  |  |
| --- | --- | --- | --- |
| Compounds | Ringer solution | Ringer- Locke solution | Tyrode solution |
| for man and warm-blooded animals | for cold blooded animals |
| NaCl  | 0.8  | 0.6  | 0.9  | 0.8  |
| KCl  | 0.042  | 0.01  | 0.042  | 0.02  |
| CaCl2  | 0.024  | 0.01  | 0.024  | 0.02  |
| NaHCO3  | 0.01  | 0.01  | 0.02  | 0.01  |
| MgCl2  | -  | -  | -  | 0.01  |
| NaH2PO4  | -  | -  | -  | 0.005  |
| Glucose  | -  | -  | 0.1  | 0.1  |

The Ringer-Locke and Tyrode solutions are for man and warm-blooded animals. Before using they must be saturated by oxygen and warmed to body temperature.

**Erythrocytes. Hemoglobin**

The erythrocytes or red blood cells are the most abundant of all the cells of the body. Their major function is to transport hemoglobin, which in turn, carries oxygen from lungs to tissues and carbon dioxide - in the opposite direction.

Besides simply transport of hemoglobin erythrocytes have other functions. They contain a large amount of carbonic anhydrase, which catalyzes the reaction between carbon dioxide and water, increasing its rate many thousandfold. Rapidity of this reaction makes it possible to transport large quantities of carbon dioxide from tissues to lungs in the form of the bicarbonate ion (HCO3-). Also, as the hemoglobin is an excellent acid-base buffer, erythrocytes are responsible for most of the buffering power of whole blood.

Erythrocytes are also carriers of the substances, realizing creatory connections, which provide conservation of the structure of organs and tissues. For example, when a rat’s liver is injured, erythrocytes begin to transport from bone marrow to the liver substances recovering the structure (nucleotides, peptides, amino acids).

Shape and structure of erythrocytes promote fulfilment of their functions optimally.

Human erythrocytes and those of mammals transport in themselves the hemoglobin, but they have no nucleus. Therefore, they spend infinitesimal part of the oxygen which they transport (about 200 times less than erythroblasts and normoblasts which have a nucleus).

Erythrocytes are biconcave discs having a mean diameter of about 7.5 micrometer and a thickness of about 7.5 micrometer or less. Their average volume is 83 cubic micrometers. Such a shape increases the general surface of erythrocytes which is 1500 times more than that of human body. The shape of erythrocytes can change as they pass through capillaries. Actually the erythrocyte is a “bag” that can be deformed into almost any shape.

Unlike that of all other cells of organism, the erythrocyte membrane’s permeability is low for Na+ and K+ cations and high for HCO3- and Cl- anions, O2, Co2, H+, OH-. In human erythrocytes there are more K than Na ions. In plasma there is an opposite ratio of these ions. About 90 per cent of dry substance of erythrocytes is hemoglobin, the rest - other proteins, lipides, glucose, mineral salts.

In normal blood of men the average number of erythrocytes per cubic millimeter (1 microlitre-mcl) is 4.5-5 millions (4.5-5 x 1012/litre) and in normal blood of women – 4-4.5 millions in 1 mcl (4-4.5 x 1012/litre). Increase of this number is called polycythemia (erythrocytosis) or erythremia and decrease - anemia. These changes may be of relative or absolute character.

The relative erythrocytosis means increase of erythrocytes in the volume unit of blood without increase of their total number in organism. It occurs when the blood is thickened or erythrocytes are thrown from depot into the peripheral blood.

The absolute erythrocytosis or polycythemia means increase of erythrocytes number in organism.

Whenever the tissues become hypoxic because of too little oxygen in atmosphere (at high altitudes) or because of failure at delivery of oxygen to tissues (in cardiac failure), the blood forming organs automatically produce large quantities of erythrocytes (red cell count arises to 68 million/mm3). This condition is called secondary polycythemia. Common type of the secondary polycythemia in natives who live at high altitudes is called physiological polycythemia.

Polycythemia vera or erythremia is a tumorous condition of the organs that produce blood cells. In the polycythemia vera the red blood cell count may be as high as 7-8 millions and the hematocrit - 60-70 per cent. It usually causes also excess of production of white blood cells and platelets. The total blood volume also increases, rarely to almost twice normal.The blood viscosity increases sometimes from the normal 5 to 10. As a result, the entire vascular system becomes intensely engorged and many of the capillaries 0become plugged by the viscous blood. The flow of blood through the vessels is often very sluggish. A person with polycythemia vera ordinarily has a ruddy complexion but often with a bluish (cyanotic) tint to the skin. In the secondary polycythemia cyanosis is also almost always evident.

The relative erythropenia occurs when blood is diluted in result of the rapid increase of fluid in blood flow.

The absolute erythropenia develops in result of low formation or rapid destruction of erythrocytes or after loss of blood.

As the blood viscosity depends mainly on the concentration of erythrocytes, in severe anemia it may fall to as low as 1.5. This decreases resistance to blood flow in the peripheral vessels so that far greater than normal quantities of blood return to the heart. One of the major effects of anemia is greatly increased work load on the heart.

The increased cardiac output in anemia partly offsets many of its effects. But when the anemic person begins to exercise, acute cardiac failure often ensues.

Blood of healthy men contains 13-16 gm/dl (130-160 gm/l) of hemoglobin, that of women -12-14 gm/dl (120-140 gm/l). This is called an absolute content of hemoglobin. The absolute content of hemoglobin means its amount in grammes in 1 dl (100 ml) of blood. Its average level for men is 14.5 gm/dl (145 gm/l), for women 13 gm/dl (130 gm/l). The ideal content of hemoglobin is 16.67 gm/dl. This amount is conditionally accepted as 100 per cent. And this is called the relative content of hemoglobin.To convert the absolute content of hemoglobin into relative content one must multiply it by 6 (100: 16.67 = 6) and vice versa.

In organism there is approximately 700 gramme of hemoglobin. In some lower animals hemoglobin circulates as free protein in plasma. The fact that human hemoglobin is in the erythrocytes and not in blood plasma is very important. Dissolving of this amount of hemoglobin in plasma would: 1) increase the blood viscosity and make difficult the heart activity and blood flow; 2) increase the oncotic pressure of blood and cause the dehydration of tissues; 3) result in the filtration of hemoglobin in renal glomerulus, secretion with urine and loss of hemoglobin by organism.

Hemoglobin is the respiratory pigment. According to its chemical structure hemoglobin is the chromoprotein. It consists of 1 molecule of globin (protein) and 4 molecules of heme. In the heme there is an iron atom, which can join and give back O2 molecule. Hemoglobin is synthesized by erythroblasts and normoblasts of bone marrow. When the erythrocytes are destroyed, after the splitting off the heme the hemoglobin is converted into biliary pigment bilirubin.

The human hemoglobin has some varieties. In first 7-12 weeks of intrauterine development of embryo its red blood cells contain the HbP (primitive); on the 9 week- HbF (fetal) and before the birth-HbA (adult) appear.

Hemoglobin has 3 **physiological combinations** in which the valency of iron does not change and it remains as divalent.

In pulmonary capillaries hemoglobin is combined with oxygen and forms oxyhemoglobin (HbO2). 1 gramme of hemoglobin combines with 1.34 ml of oxygen. In peripheral capillaries the oxyhemoglobin is decomposed, gives up the oxygen to cells and is converted into reduced hemoglobin (HHb) or desoxyhemoglobin. Then hemoglobin combines with the carbon dioxide of tissues and forms the carbohemoglobin (HbCO2). The carbohemoglobin is decomposed in pulmonary capillaries, the carbon dioxide is given off the organism and hemoglobin once. again is combined with oxygen.

Besides these unstable combinations there are two stable combinations of hemoglobin where the valency of iron changes and it becomes trivalent.

Hemoglobin combines with carbon monoxide 150 times easier than with oxygen and forms the carboxyhemoglobin (HbCO) of dark red colour. When the amount of carbon monoxide in inspired air gets as far as 0.1 per cent, the 80 per cent of hemoglobin forms the stable combination (carboxyhemoglobin) and cannot fulfil its function. Inhalation of pure oxygen increases the disintegration rate of carboxyhemoglobin 20 times.

Methemoglobin (MetHb) is also a pathological combination. It is formed when hemoglobin combines with atomic oxygen or OH- group under the influence of strong oxidizers. In skeletal muscles and myocardium there is myoglobin, i. e. the muscle hemoglobin.

Different combinations of hemoglobin absorb the light waves differently and this forms the basis of oxyhemometry - the method of valuation of blood saturation with oxygen. It is possible to distingiush the combinations of hemoglobin by the method of spectral analysis.

**Colour Index. Hemolysis. Erythrocyte Sedimentation Rate (ESR)**

The number of erythrocytes and content of hemoglobin separately do not give full information about the saturation degree of erythrocytes by hemoglobin. Because alterations of these two indices are not always parallel.

Therefore, after count of erythrocytes and determination of hemoglobin content in the blood colour index is calculated. The colour index contains an information about the extent of saturation of erythrocytes by hemoglobin and their colouring into red. The normal colour index is 0.8-1. This state is called normochromasia and the erythrocytes with normal colour index are called normochromic erythrocytes. Accordingly hyperchromasia (hyperchromic erythrocytes) take place when the colour index is more than 1 and hypochromasia (hyperchromic erythrocytes) - when it is less than 0.8.

In isotonic solutions, as well as in blood, between the quantity of water, entering the erythrocytes and that of leaving them the dynamic equilibrium is established and therefore, volume and shape of erythrocytes do not change. In hypertonic solutions less water enters and more-leaves the erythrocytes and their volume is decreased. This is called plasmolysis. In hypotonic solutions, on the contrary, the erythrocytes receive a large quantity of water and give back less. Their volume increases and they swell. This is called turgor.

In more hypotonic solutions the erythrocytes membrane cannot stand such degree of turgor and burst. This is called osmotic hemolysis. The remains of erythrocytes form the “erythrocyte shadows”. The hemoglobin becomes free and colours the solutions red. The hemolytic blood is called also the “laky blood”. It is shining and transparent.

Thanks to erythrocytes membrane elasticity they can exert resistance to hypotonic solutions and endure the certain degree of hypotonicity and the hemolysis doesn’t occur. This is called the osmotic resistance of erythrocytes. The resistance of membrane of all erythrocytes is not equal. Therefore, the maximal and minimal limits of resistance are distinguished. They are determined by the concentration degree of hypotonic solution. The concentration of the solution where the erythrocytes with the least resistance are hemolyzed, corresponds to the minimal resistance. The maximal resistance is determined by the concentration of the solution where the most resistant erythrocytes are not hemolyzed.

The minimal resistance of normal erythrocytes of peripheral human blood corresponds to the 0.40% NaCl solution and the maximal resistance - to 0.34% NaCl. Such inversion of maximal and minimal figures is connected with the fact that the osmotic resistance is parallel to the hypotonicity degree of the solution and the more hypotonicity - the less concentration.

Besides the osmotic hemolysis there are other forms of hemolysis. The mechanical hemolysis, for instance, can be observed when a bottle or ampoule with blood is powerfully shaken. When the blood is freezed and defreezed the thermal hemolysis occurs. The substances, destroying the erythrocyte membrane (alcohol, ether, chloroform, benzene) cause the chemical hemolysis. The biological hemolysis is caused by the incompatible blood transfusion, snake-bite or immune hemolysins.

If blood is poured into a test-tube and anticoagulants are added, gradually the blood cells will be settled (because of their higher specific gravity in comparison with blood plasma). The main part of sediment consists of erythrocytes, on them the thin white layer of leukocytes is hardly noticeable, but the thrombocytes practically are not visible. Therefore, speaking of the sedimentation of blood cells we use the term “erythrocyte sedimentation rate” (ESR). The ESR of normal blood of men is 1-10 mm/hour, that of women- 2-15 mm/hour. As a physiological state the ESR increases in pregnancy. But otherwise the increase of ESR is the proof of existence of inflammatory process in organism (rheumatism, angina, appendicitis, tuberculosis), when the ESR can rise to 45-60 mm/hour.

The reason of erythrocyte sedimentation is their sticking together when they form “monetary columns”. For instance, when the ESR is 75 mm/hour, every such column consists of 60000 erythrocytes. If the erythrocytes would settle singly their sedimentation rate wouldn’t be more than 0.2 mm/hour.

The ESR depends on the properties of blood plasma, and in the first place, on the content of high-molecular proteins (globulins and especially fibrinogen).

These proteins decrease the electric charge and promote formation of longer monetary columns. To observe the significance of plasma properties to the ESR the man erythrocytes were placed into the pregnant woman plasma and in this condition their sedimentation rate rised to 50 mm/hour.

The ESR is determined by Panchenkov’s apparatus.

**Blood Groups**

For a long time transfusion of blood from donor (the person whose blood is transfused) to recipient (the person to whom the blood is transfused) was practised. But quite often such attempts led to heavy consequences and even resulted in death of recipient. Subsequent inverstigations showed that in human blood cells, especially on the surface of the cells membranes, there are at least 30 commonly occuring antigens and hundreds of other rare antigens, each of which can at times cause antigen-antibody reactions. Bloods of different persons usually have different antigenic and immune properties, so that antibodies in the plasma of one blood react with antigens on the surface of the erythrocytes of another. It is easy for blood from a donor to be mismatched with that of recipient. And this is the reason why in many instances of blood transfusion immediate or delayed agglutination and hemolysis of the erythrocytes occur, resulting in typical transfusion reactions that occasionally lead to death.

Most of the mentioned antigens are weak and can be important for studying the inheritance of genes, to establish parentage and so forth. But two particular groups of antigens more than all others cause blood transfusion reactions: O-A-B system of antigens and Rh system.

The O-A-B system was discovered in the beginning of our century by Landsteiner and Jansky.

Two realated antigens - type A and type B occur on the surfaces of erythrocytes. Some people have one of them on their cells, others-both simultaneously and some people have neither (it depends on the way these antigens are inherited).

Strong antibodies (αandβ) that react specifically with either the type A or type B antigen occur in the plasmas of persons who don’t have corresponding antigens. If after blood transfusion these antibodies meet the proper antigens (A and α, B and β), they bind with them and cause agglutination of the erythrocytes. Therefore, these antigens (A and B) are called agglutinogens and the plasma antibodies (α and β) are called agglutinins. On the basis of the presence or absence of the A and B agglutinogens in erythrocytes the blood is grouped (or “typed”) for the purpose of transfusion. The bloods of donors and recipients are classified into four major groups.

|  |  |  |  |
| --- | --- | --- | --- |
| Blood groups  | Agglutinogens (in rythrocytes)  | Agglutinins (in plasma)  | Blood groups occurrence frequency among the people of different countries (in per cent) |
| accroding to Jansky’s classification  | according to international classification  |
| I  | 0  | 0  | αβ  | 40 - 50  |
| II  | A  | A  | β  | 30 - 40  |
| III  | B  | B  | α  | 10 - 20  |
| IV  | AB  | AB  | 0  | 3 - 5  |

If blood of one type is transfused to a recipient of another blood type a transfusion reaction occurs in which donor’s erythrocytes are agglutinated. Because donor’s blood plasma immediately becomes diluted by all the plasma or recipient and the titer of the infused agglutinins decreases to a level too low to cause agglutination. But the infused blood doesn’t dilute the agglutinins in the recipient’s plasma to a major extent and they can still agglutinate the donor’s eryhtrocytes.

Thus, the necessary condition for agglutination to occur, is the meeting of donor’s agglutinogens with recipient’s agglutinins. Therefore, to prevent the agglutination, before the blood is transfused from one person to another, properties of donor’s and recipient’s blood must be studied so that the bloods will be appropriately matched.

|  |  |
| --- | --- |
| The blood group and agglutinogens of donor  | The blood group and agglutinins of recipient |
| I | II | III | IV |
| α β | β | α | 0 |
| I | 0 | - | - | - | - |
| II | A | + | - | + | - |
| III | B | + | + | - | - |
| IV | AB | + | + | + | - |

As it is evident from the table, only the I group blood can be transfused to the recipients of any group and only to the IV group recipient the bloods of any group can be transfused. Therefore, the persons, whose blood belongs to the I group, are called the universal donors and the persons who have the IV group blood are called the universal recipients. The blood of every group can be transfused to the recipient having the blood of the same group.

II

II

I

I

IV

IV

III

III

To transfuse precisely the same group is preferable. Because, firstly, when the large quantity of the universal donor’s (I group) blood is transfused, for instance, to the recipient of IV group, the donor’s agglutinins are not diluted sufficiently and they cause agglutination of recipient’s erythrocytes. Secondly, in the blood of the 10-20% persons having I group the immune agglutinins anti A and anti B were found. These persons are called “the dangerous universal donors”.

Transfusion of incompatible blood can cause the posttransfusion shock which quite often leads to the death. One of the mechanisms of such a fatal outcome is releasing of coagulation factors when the agglutination occurs and the blood cells are destroyed. These factors cause intravascular blood coagulation and block of microcirculatory vessels of all organs and tissues by thrombus.

Although the method of blood typing is very simple, but in 7 - 10% of cases the blood group is wrongly determined and incompatible blood is transfused. To avoid such complication, the biological test on compatibility is used. At first only 10-15 ml of blood is infused, and if there are no undesirable symptoms, the whole blood is transfused 3 - 5 minutes later.

In 1930 K. Landsteiner was awarded the Nobel Prize for the discovery of blood groups. In his speech he presumed that in future the new agglutinogens will be discovered and the number of blood groups will increase until it reaches the number of people living in the world. And his supposition proved to be true. Many variants of every agglutinogen were found. For instance, agglutinogen A exists in more than 10 variants. A1 is the strongest, but the aggluatination properties of all other variants are weaker. The blood of such persons by mistake can be taken for the I group and when tranfused to the I and III group recipients cause posttransfusion shock.

In 1940 K. Landsteiner and I. Viner discovered Rhesus factor or Rh-Hr agglutinogen. Its name is due to the fact that this factor was first found in the blood of the Macaque Rhesus monkeys. Along with the O-A-B system, Rh system is the most important when the blood is transfused. Blood of the 85% people consists this factor, i. e. their blood is Rh - positive, and in the blood of the rest 15% people this factor is absent, i.e. their blood is rh-negative.

Rhesus system has 6 types of Rh antigens: C, D, E, c, d, e. Between the O-A-B system and the Rh system there is one major difference. In the o-A-b system the agglutinins responsible for causing transfusion reactions develop spontaneously. However, speaking of Rh system, the person first must be massively exposed to an Rh antigen (by transfusion of blood or by having a baby with the antigen) before enough agglutinins to cause a significant transfusion reaction will develop.

If the Rh-positive blood is transfused to the rh-negative person, in his blood the immune anti-Rh antibodies develop. The second transfusion of Rh-positive blood can cause the posttransfusion complications.

In most instances of erythroblastosis fetalis the mother is rh-negative and the father is Rhpositive. The baby inherits the Rh-antigen from the father. The mother develops anti-Rh agglutinin that diffuses through the placenta into the fetus and causes the agglutination of erythrocytes. Rh-conflict occurs only when the anti Rh-agglutinin concentration is high enough. An rh-negative mother having her first Rh-positive child usually doesn’t develop sufficient anti Rh agglutinins to cause any harm. But about 3% of second Rh-positive babies exhibit signs of erytroblastosis fetalis, and about 10% of the third babies exhibit the disease. The incidence rises progressively with subsequent pregnancies.

To this day in human erythrocytes more than 200 different agglutinogens are found. 140 of them are united in 20 systems and the rest are general or individual ones. This determines antigen uniqueness of the blood, and in this sense we can say that every man has his own blood type. These systems of agglutinogens differ from O-A-B system: they don’t contain natural agglutinins in plasma (as α-and β-agglutinins), but in certain conditions against them the immune antibodies-agglutinins can be developed.

Among the systems of agglutinogens, existing besides O-A-B system and Rh system, the most important ones are M, N, S, P and many others.

100% of people has Kell-Chellano system. It consists of two agglutinogens (K and k), which form 3 blood groups (KK, kk,Kk). Kidd’s system consists of Jka and Jkb agglutinogens, forming 3 blood groups. Luteran’s system also consists of 2 agglutinogens (Lu a and Lu b) forming 3 groups. Duffy’s system consists of Fy a and Fy b agglutinogens which form 3 groups. Diego’s system consists of one agglutinogen (Di) and 2 blood groups.

All of these systems of agglutinogens are of significance only when the blood is frequently transfused or during the pregnancy, incompatible by any of these agglutinogens. Therefore, it is not recommended to transfuse to the patient the blood of the same donor repeatedly.

Many of the different antigens of erythrocytes that cause transfusion reactions and still many more are present in other cells of the body as well. Consequently, any foreign cells transplanted into a recipient can cause immune responses and immune reactions.

Determination of AB0 blood Group using monoclonal antibodies anti-A and anti-B:



**Leukocytes. Differential Blood Count**

White blood cells or leukocytes play an important role in protective and recovery processes of organism. The leukocytes are the mobile units of the body’s protective system. They protect organism against microbes, viruses, pathogenic protozoa, any heterologous agents. Blood leukocytes and tissue cells originally derived from the leukocytes all work together in two different ways to prevent disease: 1) actually destroying invading agenst by the process of phagocytosis; 2) by forming antibodies and sensitized lymphocytes which may destroy the invader.

Most of the leukocytes are transported to areas of serious inflammation, thereby providing a rapid and potent defence against any infectious agent that might by present. When a tissue becomes inflamed, at least a dozen different products (bacterial toxins, degenerative products of the inflamed tissues, reaction products of the “complement complex” and those caused by plasma clotting in the inflamed area) are formed that can cause chemotaxis toward the inflamed area.The leukocytes move through the tissues by ameboid motion. They squeeze through the pores of the blood vessels by the process of diapedesis (emigration).

Granulocytes and monocytes have special capability to “seek out and destroy” any foreign invader. Every type of leukocytes consists certain ferment including protease, peptidase, diastase, lipase, deoxyribonuclease.

Adult people have 4000 - 9000 leukocytes per microliter (in 1 mm3) of blood (4-9 x 109/litre). That is, the normal number of white blood cells is 500 - 1000 times less than that of red blood cells. The increase of the number of leukocytes is called leukocytosis, the decrease - leukopenia. These are the symptoms of different diseases, whereas the excessive increase (to more than 15 - 20 x 10 9/litre) of leukocytes number is an independent disease called leukosis or leukemia (white blood disease).

Leukocytes are divided into 2 large groups: 1) granulocytes, 2) agranulocytes.

Granulocytes or polymorphonuclear leukocytes have a granular appearance. In clinical terminology they are called simply “polys”.

These are basophils, eosinophils and neutrophils. They are dyed accrodingly by basic (basophils), sour (eosinophils) and neutral (neutrophils) paints. Depending on the form of nucleus 3 types of neutrophils (corresponding to their development stage) are distinguished: juvenile neutrophils (metamyelocytes), stab (band, immature) neutrophils and segmented (mature) neutrophils. The agranulocytes are: monocytes and lymphocytes.

Granulocytes and monocytes protect organism against invading agents by ingesting them - that is, by process of phagocytosis. Lymphocytes (as well as occasional plasma cells) function mainly in connection with the immune system. But a function of certain lymphocytes is to attach themselves to specific invading organism and destroy them. This action is similar to those of the granulocytes and monocytes.

When evaluating changes of the leukocytes number in clinic the greater signifycance is attached to the changes of interrelations among different types of leukocytes. Percentage of different types of leukocytes is called the differential blood count or leukogram. The normal leukogram is approximately as presented at the table.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Granulocytes (70%)  |  | Agranulocytes (30%)  |
| basophils  | eosinophils  | neutrophils  |  | monocytes  | lymphocytes  |
| juvenile  | stab  | segmented  |
| 0 - 1  | 1 - 5  | 0 - 1  | 1 – 5  | 45 - 65  | 2 - 10  | 20 - 30  |

The basophils, as well as mast cells located immediately outside many of the capillaries, produce histamine, heparin and smaller quantities of bradykinin and serotonin. Basophilia is observed during regenerative (final) phase of acute inflammation and in lesser degree - in chronic inflammation. Heparin prevents the blood coagulation, histamine dilates the capillaries and these changes promote resorption and healing.

The basophils and mast cells play an important role in some types of allergic reactions because the type of antybody that causes allergic reactions (IgE) has a special propensity to become attached to these cells.

Eosinophils have the phagocytic ability, but because of their small number their role in this process is not great. The main function of eosinophils is to decontaminate (render harmless) and destroy the toxins of albuminous origin, heterologous proteins, the antigen-antibody complexes.

The eosinophils produce histaminasa. When eosinophils phagocytize the granules of basophils and mast cells, this ferment destroys the histamine which they contain.

Allergic states, helminthic invasion, antibacterial therapy lead to eosinophilia because they cause degranulation of large numbers of basophils and mast cells. Assimilation and neutralization of histamine decrease the changes in the focus of inflammation.

The eosinophils attach themselves to the parasites and release substances that kill many of them. The eosinphils produce also plasminogen and therefore, take part in the fibrinolysis.

Neutrophils form a largest group of leukocytes. It is mainly neutrophils and monocytes that attack and destroy invading bacteria, viruses and other injurious agents. But unlike the monocytes, the neutrophils are mature cells, that can attack and destroy bacteria and viruses even in the circulating blood. Their main function is to protect organism from invading microbes and their toxins.

The neutrophils are the vanguard of leukocytes. By the help of pseudopodia they pass through the capillary wall and come first to the place where the tissues are damaged. Their migration rate reaches 40 mcm/minute. Thanks to their own ferments and bactericidal substances, the neutrophils phagocytize, digest and annihilate the living or dead microbes, destroyed cells of own organism, heterologous particles. One neutrophil is able to phagocytose 20-30 microbes, but it can also be killed, when the bacteria continue to multiply.

The neutrophils realize also other antimicrobic effects, for instance, secreting lysosomic cation proteins and histones. They produce interferon which has an antiviral effect. Some physiologically active substances (adrenaline, acetylcholine, hormones, complement’s components) exercise a positive or negative influence on the function of neutronphils. Their activity depends also on the products of vital functions, toxins of microbes.

In the forms of leukogram the types of neutrophils are usually arranged from left to right in the following order: juvenile neutrophils, stab neutrophils and segmented neuthrophils. Therefore, increase of the juvenile and stab neutrophils number is called the shift (deviation) to the left and that of segmented neutrophils-shift to the right.

To judge more exactly about these nuclear shifts the nuclear shift index is calculated: the number of myelocytes, juvenile and stab neutrophils is divided to the number of segmented neutrophils. The normal nuclear shift index is 0.05-0.1. The shift to the left causes increase of this index, whereas its decrease is connected with the shift to the right.

The shift to the left may be of regenerative and hyperregenerative character. The regenerative shift to the left indicates the rejuvenation of neuthrophil cells: the number of the juvenile and stab neutrophils in the peripheral blood is increased, the nuclear shift index is risen to 0.25-0.45 and usually the neutrophil leukocytosis is observed. This proves that the granulopoiesis is activated.

The hyperregenerative shift to the left is characterized by not only the increase of juvenile and stab neutrophils number, but also less mature cells-myelocytes are revealed in the blood. The total number of leukocytes may be increased, but soon the excessive activation of granulopoiesis leads to the exhaustion of the myeloid tissue and tendency to the lowering of the leukocytes number is observed. The hyperregenerative shift to the left occurs under the serious infectious and pyo-septic processes.

The nucleaer shift to the right is characterized by decrease of juvenile and stab neutrophils, increase of juvenile and stab neutrophils, increase of segmented neutrophils and appearance of hypersegmented neutrophils. This is connected with weakening of granulopoiesis.

When the acid reaction is developed in the focus of inflammation, the neutrophils lose their activity and they are replaced by monocytes whose maximal activity is exhibited just in the acid medium.

The monocytes as well as neutrophils move through tissues by ameboid motion, display marked phagocytic and bactericidal activity. As phagocytes they are more stronger than neutrophils and can phagocytize 100 microbes.

In the inflammatory focus the monocytes phagocytize the microbes as well as killed leukocytes, the damaged cells of inflamed tissues, and thus, clean the focus and prepare it to the regeneration. Therefore, the monocytes are called “the yard-keepers of organism”.

The monocytes are the central link of the mononuclear phagocytic system. The distinctive features of the elements of this system are the ability of phagocytosis and pinocytosis, the existence of receptors for antibodies and complement, the community of origin and morphology.

The blood monocytes are immature cells that have very little ability to fight infectious agents. But when they enter the tissues, they begin to swell (sometimes increasing their diameters as much as fivefold to as great as 80 micrometers) and a large numbers of lysosomes develop in the cytoplasm, giving the cytoplasm the appearance of a bag filled with granules. These cells are called macrophages (macrophagocytes). They are extremely capable of combating disease producing agents.

Macrophages also take part in the development of immunity, in the inflammatory and regenerative processes, in the lipide and iron metabolism. They secrete lysozyme, complement, interferon, elastase, collagenase, plasminogen’s activator and fibrogen factor which strengthens the synthesis of collagen and accelerates the formation of fibrous tissue. The antitumoral and antiviral effects of macrophages are connected with these substances.

The most important function of the neutrophils and macrophages is phagocytosis. Phagocytes must be selective of the material that is phagocytized, otherwise some of the normal cells will be ingested. Whether or not phagocytosis will occur depends especially upon three selective procedures: 1) if the surface of a particle is rough, the probability of phagocytosis is increased; 2) most natural substances of the body have protective protein coats that repel the phagocytosis, while dead tissues and foreign particles frequently haven’t such coats; 3) the body has a specific means (immune system) that recognize certain foreign materials.

In addition to digestion of ingested bacteria, neutrophils and macrophages contain also bactericidal agents that kill most bacteria even when the lysosomal enzymes fail to digest them. Much of the killing effect results from several powerful oxidizing agents formed by enzymes in the membrane of the phagosome or by the special organelle called the peroxisome.

A large portion of monocytes, on entering the tissues and after transforming into macrophages, become attached for months or years unless they are called upon to perform specific protective functions. They have the same capabilities as the mobile macrophages to phagocytize large quantities of bacteria, viruses, necrotic tissue or other foreign particles in the tissue. When appropriately stimulated, they can once again become mobile macrophages.

The combination of monocytes, mobile macrophages, fixed tissue macrophages and a few specialized endothelial cells in the bone marrow, spleen and lymph nodes is called the reticuloendothelial system. They all exhibit similar phagocytic properties and almost all of these cells originate from monocytic stem cells. Now the reticuloendothelial system is called the mononuclear phagocytic system. This system includes the histiocytes in the skin and subcutaneous tissues, macrophages of the lymph nodes, alveolar macrophages, the Kupffer cells in the liver sinuses, macrophages of the spleen and bone marrow.

The adult persons have 1012lymphocytes. Unlike all other leukocytes, the lymphocytes are able not only to penetrate into the tissues, but they can also come back into the blood. And they live not some days as other leukocytes, but 20 years or more (some of them live even the whole lifelong of the people).

The lymphocytes represent the central link of immune system of organism. Immunity is the ability of the human body to resist almost all types of organisms or toxins that tend to damage the tissues and organs. Much of immunity is caused by a special immune system that forms antibodies and activated lymphocytes that attack and destroy the specific organisms or toxins.

There are two basic, but closely allied, types of immunity: 1) cell-mediated immunity - is achieved through the formation of large numbers of activated lymphocytes that are specifically designed to destroy the foreign agent; 2)humoral immunity - the body develops circulating antibodies, which are globulin molecules that are capable of attacking the invading agent.

Both the antibodies and the activated lymphocytes are formed in the lymphoid tissue of the body.

Thus, the lymphocytes answer for the formation of the immunity and realize the immune control (“censorship”) in organism. So, lymphocytes provide the protection of the organism against the heterologous substances and maintain the constancy of internal genetic environment. Thanks to the existence of receptors in the membrane of lymphocytes they are able to distinguish the own cells of organism from the foreign particles. The lymphocytes realize synthesis of protective antibodies and lysis of heterologous cells. They provide the reaction of transplant rejection, the immun memory, the destruction of own mutant cells of organism and so forth.

All the lymphocytes are divided into 3 groups: T lymphocytes, B lymphocytes and O lymphocytes.

Both T (thymus dependent) and B (bursa dependent) lymphocytes are derived originally in the embryo from pluripotent hemopoietic stem cells and the lymphocytes that are formed end up in the lymphoid tissue but before doing so they are further differentiated or “preprocessed” different ways.

Those lymphocytes that are eventually destined to form activated lymphocytes first migrate to thymus gland and are preprocessed there. These are T lymphocytes. They are responsible for cell-mediated immunity.

The other group of lymphocytes that are destined to form antibodies are preprocessed in the liver during midfetal life and in the bone marrow in late fetal life and after birth. This population of cells was first discovered in birds in which the preprocessing occurs in the bursa of Fabricius, a structure not found in mammals. Therefore, they are called B lymphocytes. B lymphocytes are responsible for humoral immunity.

The 0 (zero) lymphocytes aren’t preprocessed in the organs of the immune system, but when necessary, they can change into T or B lymphocytes.

The 40-70 % of all lymphocytes in the blood are T lymphocytes, the 20-30%- B lymphocytes and 10-20% - O lymphocytes.

There are many different types of T lymphocytes. They are classified into 3 major groups: 1) helper T cells; 2) suppressor T cells; 3) cytotoxic T cells or killer cells.

The helper T cells help in the functions of the immune system in different ways. They do this by forming lymphokins, that act on other cells of the immune system as well as on bone marrow cells. In the absence of the lymphokines from the helper T cells, the remainder of the immune system is almost paralysed. It is the helper T cells that are inactivated or destroyed by acquired immunodeficiency syndrome (AIDS) virus, which leaves the body almost totally unprotected against infectious disease and leads to the rapid lethal effects of AIDS.

Some of the specific regulatory functions are the following: 1) stimulation of growh and proliferation of cytotoxic T cells and supressor T cells, 2) stimulation of B cell growth and differentiation to form plasma cells and antibodies, 3) activation of the macrophage system, 4) feedback stimulatory effect on he helper cells themselves.

The suppressor T cells are capable of suppressing the functions of both cytotoxic and helper T cells as well as that of B lymphocytes. These suppressor functions serve the purpose of regulating the activities of the other cells, keeping them from causing excessive immune reactions that might be severely damaging the body. Therefore, the suppressor T cells, along with the helper T cells, are classified as regulatory T cells. The suppressor T cells play an important role in limiting the ability of the immune system to attack own tissues of the organism.

The cytotoxic T cells are direct attack cells capable of killing microorganisms and at times even some of the body’s own cells. Therefore, they are called killer cells. Thus, the killer cells directly realize the cell mediated immunity reactions. The killer cells also play an important role in destroying cancer cells, heterologous transplant cells, mutant cells or other types of cells that are “foreign” to the person’s own body. This way they maintain genetic homeostasis.

T lymphocytes play a leading role in immune control. When their function is weakened, the danger of the development of tumors and autoimmune diseases (when the own tissues of organism are perceived as foreign particles) and the tendency to the different infections is increased.

Under the influence of heterologous agent lymphocytes can be transformed into nondifferentiated young cells (blasts) which then are converted into mature cells (plasma cells and immune lymphocytes).

The lymphocytes provide the integrity of organism not only by protecting it against the heterologous agents. They carry macromolecules with information which is necessary for the controlling of the genetic apparatus of other cells of body, that is, the leukocytes take part in realizing of creatory connections.

The leukocytes are one of the most responsive cell systems of organism. Therefore, under different influences their number and quality are changed. The leukocytosis is more frequently observed. The physiological leukocytosis and the reactive leukocytosis are distinguished.

The physiological leukocytosis is connected with the redistribution of the leukocytes among the blood vessels of different organs and tissues. More often it is conditioned by transition of leukocytes from depot (spleen, bone marrow, lungs) into the peripheral blood vessels. There are some types of physiological leukocytosis. The hard physical work causes the myogenic leukocytosis. The digestive leukocytosis occurs after the meal. The pain and emotions also cause the leukocytosis. The physiological leukocytosis is of short duration, the number of leukocytes is increased slightly, the leukogram is not changed.

The reactive or true leukocytosis is connected with the strengthening of leukocytes production by the hemopoietec organs. In the reactive leukocytosis the leukocytes number is increased to a greater degree than in the physiological type. But the principal difference between them is that during the reactive leukocytosis the leukogram is changed: the number of young forms of neutrophils (myelocytes, juvenile and stab neutrophils) in the blood is increased. This proves the activation of granulocytopoiesis. According to the nuclear shift to the left the seriousness of the disease and the resistibility of the organism is evaluated.

The reactive leukocytosis is developed as the reaction of the organism to the pathogenic influences (in the inflammatory processes, infectious diseases and so on).

Lately the leukopenia occurs more frequently than earlier. It is due to the urbanization, the rise of the radiation background, the wide use of different drugs and so forth. Irradiation of the body by gamma rays caused by a nuclear explosion, or exposure to drugs and chemicals containing benzene or anthracene nuclei is quite likely to cause aplasia of the bone marrow. Specially serious leukopenia is observed in radiation sickness. The fall of lukocytes number as lower as 0.5 x 10 9/litre (500 in 1 mcl) causes the death.

**Thrombocytes. Blood Coagulation. Hemopoiesis and its Regulation**

Thrombocytes or platelets take part in blood coagulation. They are fragments of giant cells of the red bone marrow-megakaryocytes. The human thrombocytes and that of mammals don’t have nuclei. They are colourless convexo-convex formations. The diameter of thrombocytes is 0.5-4 mcm, that is, they are 2-8 times smaller than erythrocytes.

The number of thrombocytes in each microliter of blood is normally 200000-400000 (200400 x 10 9/litre). Their number may change significantly. For example, after the hard physical work the number of thrombocytes is increased 3-5 times. It is increased also after the meal or under the influence of emotions. The thrombocytes number is more in the day-time than at night. This changes may be connected with the rhythm of work and rest.

The thrombocytes are the smallest and the tenderest of all blood cells and therefore, when the blood vessel is damaged and the wound is bleeding, they are broken up the first. Then the factors are released which take place in blood coagulation. Besides the thrombocytic factors of blood coagulation the platelets contain the set of ferments, adrenaline, norepinephrine, lysozyme, adenosine triphosphate, adenosine triphosphatase and so forth. They prevent the bleeding not only by promoting the blood coagulation. They also release serotonin which constricts the vessels and by this way decreases loss of blood. So, the platelets take part in both mechanisms of hemostasis that are described below.

When the thrombocytes adhere to the vascular wall they form 10-12 processes which provide the attachment.

The thrombocytes also transport the substances realizing the creatory connections. When the endothelium of blood vessels doesn’t interact with the thrombocytes it is subjected to dystrophy and begins to let through the erythrocytes.

When a vessel is severed or ruptured, the bleeding occurs and leads to blood loss. Prevention of blood loss,i.e. the arrest of bleeding is called hemostasis. The blood coagulation is the transition of blood from liquid state to the jelly-like clot. The blood removed from a person begins to coagulate after 3-4 minutes and after 5-6 minutes it is completely changed into jellylike clot. There are two main mechanisms by which the hemostasis is achieved: 1) vascularthrombocytic hemostasis, 2) coagulative hemostasis.

The vascular-thrombocytic mechanism is able to arrest independently the bleeding from the microcirculatory vessels where the arterial pressure is low and which are more frequently traumatized (abrasion, cut of skin). It is called also microcirculatory hemostasis.

If the rent in a vessel is small, the thrombocyte plug by itself can stop blood loss completely, but if there is a large hole, a blood clot in addition to the platelet plug is required to stop the bleeding, that is, the coagulative hemostasis mechanism becomes necessary.

The hemocoagulation system includes the blood, the tissues which produce, use and excrete from the organism the necessary substances for this process and neurohumoral regulatory apparatus.

The **plasma factors** of blood coagulation are numbered by Roman numerals in chronological order of their discovery:

**Factor I** - fibrinogen - is the most high-molecular protein of plasma. When blood is coagulated fibrinogen is converted into fibrin which forms the basis of blood clot. Besides the blood coagulation, fibrin, as a structural material, takes part in the healing of wounds. The fibrinogen content sharply increases in pregnancy, in postoperative period, in all inflammatory processes and infectious diseases. It is decreased during menstruation and in liver diseases.

**Factor II** - prothrombin.

**Factor III** - tissue thromboplastin - it is present in the membranes of all cells of organism including the vascular endothelium. It is necessary for the formation of tissue prothrombinase.

**Factor IV** - calcium - only its ions take part in blood coagulation and they are necessary for all phases of this process.

**Factors V** and **VI** - proaccelerin and accelerin - they are inactive and active phases of the same factor and together are called accelerator-globulin (Ac-G). This factor takes part in the I and II phases of hemocoagulation.

**Factor VII** - proconvertin or stable factor or serum prothrombin conversion accelerator (SPCA) - it is required for tissue prothrombinase formation.

**Factor VIII** - antihemophilic globulin (AHG) or antihemophilic factor A - is necessary for the blood prothrombinase formation. Its genetic deficit is the cause of hemophilia A.

**Factor IX** - Christmas factor or antihemophilic factor B or plasma thromboplastin component (PTC). In its genetic deficit hemophilia B is observed. It takes part in the I phase of blood coagulation.

**Factor X** - Stuart-Prower factor-takes part in the formation of tissue and blood prothrombinase and forms the part of them.

**Factor XI** -plasma thromboplastin antecedent (PTA) or antihemophilic factor C - is required for blood prothrombinase formation and activates the factor IX. The factor XI deficit is the cause of hemophilia C.

**Factor XII** - Hageman factor - is activated in the time of contact with a heterologous surface (for instance, the place, where the vessel is injured) and therefore, is called also the contact factor. It initiates the blood prothrombinase formation and all the hemo-coagulation process. After the activation it remains on the surface of the injured vessel and prevents the generalization of blood coagulation. Hageman factor has an effect on factor XI and forms a complex with it. Hageman factor also activates the kallikrein-kinin system, the complement system and fibrinolysis. The genetic deficit of this factor is the cause of Hageman disease.

**Factor XIII** - fibrin - stabilizing factor (fibrinase, fibrinoligase, transglutaminase) - blood cells and the tissues also contain this factor. It is necessary for formation of the final or insoluble fibrin “I”. Factor XIII is activated by thrombin and calcium ions. It is necessary also for regeneration: in congenital deficit of this factor the healing of wounds is worse.

Besides these factors plasma contains also prekallikrein or Fletcher factor, high molecular weight kininogen (HMWK) or Fitzgerald factor.

Thrombocytic (platelet) factors of blood coagulation are numbered by Arabic numerals. The most important of platelet factors are the following:

**Factor 3** - thromboplastic factor or platelet thromboplastin - is used in the I phase of blood coagulation.

**Factor 4** - antiheparin factor - binds the heparin and thus accelerates the hemocoagulation.

**Factor 5** - coagulating factor or fibrinogen-determines the adhesion and aggregation of thrombocytes.

**Factor 6** - thrombosthenin - provides the consolidation and contraction of clot of blood. It consists of A and M subunits which are similar to actin and myozin.

**Factor 10** - vasoconstrictive factor or serotonin. It is adsorbed by thrombocytes from the blood.

**Factor 11** - aggregation factor - for its chemical nature it is adenosine diphosphate. The strongest stimulator of aggregation is thromboxane. In the endothelium of blood vessels there is prostacycline - the strongest inhibitor of aggregation. The balance between these substances determines the aggreagation of thrombocytes.

Erythrocytes also take part in hemostasis. Their shape is convenient for the adhesion of fibrin threads and their porous surface catalyses the hemocoagulation process. Except the thrombosthenin, almost all the thrombocytic factors of blood coagulation were found also in erythrocytes.

As the number of leukocytes is not so large as that of erythrocytes, their role in hemostasis of healthy persons is not significant. The leukocytes contain thromboplastic and antiheparin factors, natural anticoagulants (the heparin of basophils), activators of fibrinolysis.

Around all the blood cells there is “plasmatic atmosphere” consisting of adsorbed coagulation factors, and this promotes the hemocoagulation process.

The role of tissues (especially that of the vascular wall) in hemostasis is significant. All tissues contain the compounds similar to V, VII, X, XIII plasma factors, active thromboplastin, antiheparin factor, natural anticoagulants, the substances causing the adhesion and aggregation of thrombocytes, the activators and inhibitors of fibrinolysis.

Thus, over 50 substances that affect blood coagulation have been found in blood and tissues, some promoting coagulation (procoagulants) and others inhibiting it (anticoagulants). Whether or not the bloood will coagulate depends on the degree of balance between these two groups of substances. Normally the anticoagulants predominate and the blood doesn’t coagulate. When a vessel is ruptured, procoagulants in the area of damage become activated and overpower the anticoagulants. Then the coagulation occurs, that is, the clot develops, and closing the wound, arrest the bleeding. So, the blood coagulation is the defence reaction purposeful to prevent the loss of blood.

The modern ferment theory of blood coagulation was propounded by A. A. Schmidt (1872) and verified by P. Moravitz (1905). But then was thoroughly supplemented and improved.

The blood coagulation is very complicated process. It is described schematically consisting of prophase, 3 main phases and metaphase. In the prophase the vascular-thrombocytic hemostasis is realized. In the I phase - prothrombinase (prothrombin activator complex) in the II phasethrobin and in the III phase-fibrin is formed. The metaphase consists of two simultaneously proceeding processes- the retraction (contraction, consolidation) and fibrinolysis (dissolution) of blood clot.

The **vascular-thrombocytic hemostasis** consists of following successive processes:

1. The reflex spasm of injured blood vessels under the influence of the vasoconstrictive substances (serotonin, adrenalin, norepinephrine) which are released from the destroyed thrombocytes. The spasm may arrest the bleeding or decrease it only temporarily.
2. The adhesion (sticking) of thrombocytes to the place of injury, where negative electric chrge of vessel is changed to the positive (the charge of thrombocytes is negative).
3. The reversible aggregation (congestion) of thrombocytes. It begins almost simultaneously with the adhesion under the influence of “external” adenosine diphosphate which is released from the injured blood vessel and “internal” adenosine diphosphate which is released from thrombocytes and erythrocytes. The crumbly platelet plug is formed which lets through itself blood plasma.
4. The irreversible aggregation of thrombocytes (when the platelet plug becomes impenetrable for the blood) - occurs under the influence of thrombin. The thrombocytes loose their structure and form a homogeneous mass. The thrombin destroys the thrombocytes membrane and their contents pass into the blood. Releasing of factor 3 includes the coagulative hemostasis mechanism. On the thrombocyte aggregates a small quantity of fibrin threads is formed and in their network the erythrocytes and leukocytes are kept.
5. The retraction of thrombocytic thrombus (platelet plug) - its consolidation and attaching in the injured vessels as a result of thrombosthenin contraction. The platelet plug is a loose plug, but it is usually successful in blocking the blood loss if the vascular opening is small. Then, during the subsequent process of blood coagulation, fibrin threads are formed that attach to the platelets, thus forming a tight and unyielding plug.

The I phase of blood coagulation is the most complicated and the longest of all phases. In this phase a complex of substances called prothrombin activator (prothombinase) is formed in two basic ways which interact constantly with each other: 1) the extrinsic pathway that begins with trauma to the vascular wall and surrounding tissues, 2) the intrinsic pathway that begins in the blood itself.

In both the extrinsic and intrinsic pathways a series of blood clotting factors play major roles. For the most they are inactive forms of proteolytic enzymes. When converted to the active forms, their enzymatic actions cause the successive chain reactions of the clotting process.

The extrinsic mechanism of prothrombin activator (tissue prothrombinase) formation begins with a traumatized vascular wall or extravascular tissue and occurs according to the following basic steps: 1) Traumatized tissue releases a complex of several factors called tissue thromboplastin, including phospholipids and lipoprotein complex containing glycoprotein that functions as a proteolytic enzyme. 2) The lipoprotein complex of tissue thromboplastin further complexes with the blood coagulation factor VII and in the presence of tissue phospholipids and calcium ions acts on the factor X to form the activated factor X. 3) The activated factor X complexes with the tissue phospholipids released as part of the tissue thromboplastin or released from thrombocytes and also with the factor V to form the complex called prothrombin activator (tissue prothrombinase).

The intrinsic mechanism of prothrombin activator (blood prothrombinase) formation begins with trauma to the blood itself or exposure of the blood to collagen in a traumatized vascular wall and then continues through the following series of cascading reactions: 1)Trauma to the blood or exposure of the blood to vascular wall collagen alters the factor XII and the trombocytes. The factor XII is converted into “activated factor XII” and from damaged thrombocytes factor 3 is released. 2) The activated factors XII acts on the factor XI to activate it. This reaction also requires HMW kininogen and it is accelerated by prekallikrein. 3) The activated factor XI acts on the factor IX to activate it. 4) The activated factor IX acting in concert with the factor VIII and with the thrombocyte phospholipids and factor 3, activates the factor X. 5) This step in the intrinsic pathway is the same as the last step in the extrinsic pathway: the activated factor X combines with the factorV and thrombocyte or tissue phospholipids to form the prothrombin activator complex (blood prothrombinase).

Formation of tissue prothrombinase lasts 5-10 seconds, but that of blood prothrombinase - 5-10 minutes.

In the II phase of blood coagulation the prothrombin activator (prothrombinase) causes convertion of prothrombin to thrombin. This is done instantly - during 2-5 seconds. In the presence of the factors V, X and calcium ions prothrombinase adsorbs the prothrombin and converts it into thrombin.

The III phase of blood coagulation proceeds in 3 stages: 1) Thrombin acts on fibrinogen forming fibrin monomer. 2) Under the influence of calcium ions fibrin monomer molecules polymerize within seconds into long fibrin threads that form the reticulum of the clot. The resultant clot is weak and can be broken apart with ease. This is soluble fibrin S. 3) In the presence of the factor XIII (fibrin- stabilizing factor) and fibrinase of tissues, thrombocytes and erythrocytes the final or insoluble fibrin I is formed.

The blood clot is composed of meshwork of fibrin threads running in all directions and entrapping blood cells, platelets and plasma. The fibrin threads adhere to damaged surfaces of blood vessels. Therefore, the blood clot becomes adherent to any vascular opening and prevents the blood loss.

So, blood coagulation is the chain fermentative process. In its course the coagulation factors are activated successively on the phospholipid matrix and their complexes are formed. Acting as the catalysts of the interaction and activation of coagulation factors, the cell membrane phospholipids accelerate the course of hemocoagulation process.

In the metaphase simultaneously the retraction and fibrinolysis of blood clot go on.

Within a few minutes after a clot is formed, it begins to contract and expresses most of the fluid from the clot within 20-60 minutes. As distinct from blood plasma, the expressed fluid is called serum, since all its fibrinogen and most other clotting factors have been removed. Because of lack of these factors serum cannot clot.

Retraction provides the consolidation and attaching of thrombus in the damaged blood vessel. The retraction is realized only when the number of thrombocytes is sufficient. It occurs under the influence of thrombosthenin of platelets. When contracted, thrombosthenin compresses the initial volume of the clot twice or thrice and it is attached in the vessel more firmly. Retraction comes to an end during 2-3 hours after the clot is formed.

**Fibrinolysis**, that is, disintegration of fibrin which makes the base of thrombus, begins simultaneously with the retraction, but its rate is less. Fibrin is decomposed down under the influence of proteolytic ferment plasmin (fibrinolysin) which is in the blood in inactive form of plasminogen (profibrinolysin). The plasminogen is converted into plasmin under the influence of activators which are in blood (intrinsic mechanism) and tissues (extrinsic mechanism). Plasmin is a proteolytic enzyme. It digests the fibrin threads and other substances in surrounding blood (fibrinogen, factorV, factor VIII, prothrombin, factor XII). When a clot is formed, a large amount of plasminogen is trapped in it. After being activated the plasmin causes the lysis of the clot.

The lysis of blood clots provides slow clearing of extraneous clotted blood in the tissues and allows reopening of clotted vessels. Plasmin system removes very minute clots from numerous tiny peripheral vessels which otherwise would all become occluded.

Small amounts of plasmin are formed in the blood all the time, which could seriously impede the activation of the clotting system. But the blood also contains alpha 2-antiplasmin that binds with plasmin and inhibits it. Therefore the rate of plasmin formation must rise above a certain critical level before it becomes effective.

The natural stimulator of fibrinolysis is intravascular coagulation of blood or its acceleration. At healthy persons fibrinolysis activation occurs in answer to the strengthening of hemocoagulation.

Together with the coagulative system blood contains also anticoagulative system. The balance between them provides the liquid state of blood. Existence of the physiological anticoagulant system was proved in the following experiment. If the sufficient amount of thrombin is injected into the vein of animal rapidly, the animal perishes as a result of intravascular blood coagulation. But when the same dose is injected slowly, the animal does not perish, because the anticoagulant system has sufficient time to be activated and prevents the coagulation.

The antociagulants, existing in organism are divided in 2 groups: 1) primary anticoagulants, 2) secondary anticoagulants - these are formed in the process of blood coagulation and fibrinolysis.

The first group includes some antithromboplastins, which inhibit the formation and action of prothrombinase, antithrombin III, antithrombin IV, heparin. As a very active anticoagulant heparin is widely used in clinical practice. Heparin inhibits all the phases of hemocoagulation, supresses the activity of many plasma factors, in small doses it stimulates fibrinolysis. It also decreases vascular wall permeability, inhibits antigen-antibody reaction, has analgetic and antiinflammatory effects.

The secondary anticoagulants are “waste” factors of coagulation. The formed fibrin adsorbs and neutralizes up to 90 per cent of thrombin and therefore, fibrin is called antithrombin I.

So, in all phases of hemocoagulation the strengths of self-restraint of process are acting. The content of anticoagulants sharply increases in answer to the acceleration of blood coagulation.

For promotion of almost all the blood coagulation reactions calcium ions are required and therefore, in the absence of these ions blood clotting does not occur. So, when blood is removed from a person, it can be prevented from clotting by reducing the calcium ion concentration below the threshold level for clotting, either by deionizing the calcium by reacting it with substances such as citrate ion, or precipitating the calcium with substances such as oxalate ion. Such blood is called the decalcified blood. Naturally, the defibrinated blood also does not coagulate.

Numerous factors influence on blood coagulation. Acceleration of blood coagulation is called hypercoagulability, its deceleration is called hypocoagulability.

As long ago as in the beginning of our century W. Cannon noted that the sensation of pain, the emotions or fear and anger, that is, the states of organism causing excitation of sympathetic part of vegetative nervous system and hyperadrenalemia, result in acceleration of blood coagulation.

Role of the nervous system in coagulation processes was proved in the following experiment. A rat’s paw was denervated and into the vein the thrombin was injected slowly. The blood was coagulated only in the denervated paw. Because the rise of thrombin’s level in the circulating blood by the reflex way leads to the secretion in the vascular wall of substances preventing coagulation. The denervation as well as narcosis suppresses this reflex.

Irritation of vagus nerve (or injection of acetylcholine) as well as adrenalin injection, that is, stimulation of both parts of the vegetative nervous system (sympathetic and parasympathetic) lead to the same result-hypercoagulability. So, the primary hypocoagulability does not exist and it is always secondary - after the primary hypercoagulability - as the result of the waste of the part of blood coagulation factors.

Acceleration of hemocoagulation in healthy persons causes the secondary stimulation of fibrinolysis and this provides disintegration of fibrin’s surplus. The physical work, emotions, pain also activate the fibrinolysis.

The brain cortex realizes its influence on the blood circulation through vegetative nervous system and some endocrine glands.

The blood coagulation system is included into the more vast system - the system of regulation of aggregate state of blood and colloids.

Hemopoiesis is the process of formation and development of blood cells. Erythropoiesis (erythrocytopoiesis), leukopoiesis and thrombopoiesis (thrombocytopoiesis) are distinguished.

The erythrocytes, granulocytes, monocytes and thrombocytes are produced by the red bone marrow which is in the flat bones and metaphysis of tubular bones. Its mass is 1.5-2 kg. In the bone marrow there are cells called pluripotential hemopoietic stem cells from which all the cells in the circulating blood are derived.

Lymphocytes are produced mainly in the various lymphogenous organs (lymph glands, the spleen, the thymus, the tonsils and various lymphoid rests in the bone marrow, gut and elsewhere). In a day approximately 200-250 milliard (billion) erythrocytes are produced and destroyed. When the erythrocytes are delivered from the bone marrow, into the circulatory system, they normally circulate an average 120 days.

The first cell that can be identified as belonging to erythrocyte series is the proerythroblast. It divides several more times, forming mature erythrocyte-normocyte. The first-generation cells are called basophil erythroblasts. In the succeeding generation (polychromatophil erythroblast, orthochromatic erythroblast) the cells become filled with hemoglobin, the nucleus condenses to a small size and its final remnant is extruded from the cell, the endoplasmic reticulum is reabsorbed. The cell at this stage is called a reticulocyte. The remaining basophilic material in the reticulocyte disappears within 1-2 days, and the cell is then mature erythrocyte. The reticulocytes are larger than erythrocytes-normocytes. Their concentration among all the red cells of the blood is normally no more than 1%. The reticulocytosis is the proof of activation of hemopoiesis.

For the erythropoiesis the building materials and the stimulators of the process are required. For the synthesis of heme 20-25 mg iron in a day is needed. 95% of this quantity is provided by the hemoglobin of the destroyed erythrocytes and 5% (1mg) is received by the food.

For the formation of erythrocytes vitamin B12is the extrinsic factor of hemopoiesis. The parietal cells of gastric glands secrete a glycoprotein called intrinsic factor, which combines with vitamin B12of the food and makes the B12available for absorption by the gut. In pernicious anemia the basic abnormality is an atrophic gastric mucosa that fails to produce normal gastric secretions.

As a result of early differentation of the pluripotential hemopoietic stem cell aside from the cells commited to formation of erythrocytes, two major lineages of leukocytes are also formed - the myelocytic and the lymphocytic lineages beginning accordingly with myeloblast and lymphoblast. Megakaryocytes are also formed in the bone marrow. They fragment in the bone marrow and the small fragments known as thrombocytes (platelets) pass into the blood.

The main reason that white blood cells are present in the blood is simply to be transported from the bone marrow or lymphoid tissue to the areas of the body where they are needed. Life of granulocytes is normally 4-8 hours circulating in the blood and another 4-5 days in the tissues.

The monocytes also have a short transit time (10-20 hours) in the blood before wandering through the capillary membranes into tissues. But in the tissues they swell to much larger sizes to become tissue marcophages and in this form can live for months or even years unless destroyed by performing phagocytic function.

Lymphocytes enter the circulatory system continually along with the drainage of lymph from the lymph nodes. After few hours they pass back into the tissues by diapedesis, then reenter the lymph and return to the blood again and again. They have life spans of months or years, but this depends on the body’s need for these cells. Part of lymphocytes live through all the man’s life.

The thrombocytes in the blood are totally replaced approximately once every 10 days, that is, about 30000 thrombocytes are produced each day for each microliter of blood.

The balance between the produced and destroyed blood cells is regulated by nervous and humoral mechanisms.

Stimulation of bone marrow nerves in experiment causes erythrocytosis. The sympatethic nerves stimulation increases neutrophils number in the blood. Stimulation of vagus nerve leads to redistribution of blood leukocytes in one direction, the stimulation of sympathetic nerves - in opposite direction. The sympathetic innervation stimulates hemopoiesis whereas the parasympathetic innervation inhibits it.

Organs of hemopoiesis have numerous receptors and a rich efferent innervation. So, they have two-way connections with the central nervous system. The hypothalamus exercises especially marked influence on the hemopoiesis which is realized through pituitary body and vegetative centers.

Somatotropic hormone, adrenocorticotropic hormone, hormones of adrenal glands, thyroid hormones as well as male hormones, stimulate the erythropoiesis. But female hormones inhibit it. To some extent this fact explains the different number if erythrocytes in men and women.

The nervous and endocrine factors exercise their influence upon hemopoiesis through hemopoietins (erythropoietins, leukopoietins and thrombopoietins), which are known as “hormones of hemopoiesis”.

The amount of erythropoietins is increased in the hypoxia (loss of blood, being at very high altitudes).

Among the leukopoietins there are neutropoietins, basophilopoietins, eosinopoietins, monocytopoietins and lymphocytopoietins. Production of leukopoietins is stimulated by the products of decomposition of leukocytes and tissues, nucleic acid, some hormones, microbes and so on.

Thanks to existence of thrombocytopoietins the exact balance between the produced and destroyed thrombocytes becomes established.

# LECTURE 7

# BLOOD CIRCULATION

**The Specialized Excitatory and Conductive System of the Heart. Heart Automatism. Physiological Properties of Heart Muscle**

To fulfill its functions, so important for the organism, the blood must move in vessels continuosly and this is realized owing to the rhytmical activity of heart, and partly, to the elasticity of blood vessels.

Heart is the central organ of blood circulation system. The heart consists of actually two separate pumps: a left heart that pumps the blood through greater (systemic or peripheral) circulation and a right heart that pumps the blood through lesser (or pulmonary) circulation. Each of these two separate hearts is a two chamber pump composed of an atrium and ventricle.

The greater circulation begins from the left ventricle which pumps the arterial blood into aorta. The blood flows through arteries, arterioles, capillaries and veins of all the body. The venous blood by the vena cava superior and vena cava inferior flows into the right atrium where the greater circulation ends. So, the greater circulation provides all the body with arterial blood.

The venous blood flowing off the tissues enters the right atrium and then – the right ventricle. Here begins the lesser circulation. The right ventricle pumps the venous blood into pulmonary trunk. When flowing through the lungs, the blood gives up the carbon dioxide and is saturated with oxygen. Then the arterial blood flows into left atrium via the pulmonary veins where the lesser circulation ends.

The heart activity includes the rhythmical contractions (systole) and relaxations (diastole) of the heart muscle. The atria contract also simultaneously (0.3 second). After that the pause (0.4 second) follows, i.e. all four chambers of the heart relax at the same time. But these four chambers of the heart never contract at the same time.

The period from the beginning of one heart beat to the beginning of the next one is called the cardiac cycle (0.8 second).The successive contractions of atria and ventricles create the pressure difference which causes the flow of the blood in vessels only in one direction.

Atria function mainly as a blood reservoirs and as an entryways to ventricles, but they also pump meanly to help move the blood into the ventricles. Ventricles supply the main force that propels the blood through either the greater or the lesser circulation.

The heart is composed of three major types of cardiac muscle: atrial muscle, ventricular muscle and specialized excitatory and conductive muscle fibers. The atrial and ventricular types of muscle belong to the special type of striated muscle. Specialized excitatory and conductive muscle fibers contract only feebly because they exhibit rhythmically and varying rates of conduction. They form the specialized excitatory and conductive system of the heart. This system controls cardiac contractions, and heart automatism also is due to this system.

In the heart excitation occurs periodically under the influence of the processes going on in the heart itself. This is called heart automatism.

The specialized excitatory and conductive system of the heart includes:

1. the sinus (sinoatrial) node (S – A node), or Keith – Flack node (in frog – Remak node), in which the normal rhythmic impulses are generated ;
2. the internodal pathways that conduct impulses from the sinus node to the

atrioventricular node;

1. the atrioventricular node (A – V node) or Aschoff – Tawara node (in frog – Bidder node), in which the impulses from the atria are delayed before passing into the ventricles;
2. the atrioventricular bundle (A- V bundle) or bundle of His, which conducts impulses from the atria into the ventricles;
3. the left and right bundles of Purkinje fibers, which conduct cardiac impulses to all parts of the ventricles.

The fibers of the heart’s specialized conducting system have capability of self – excitation. The excitation primarily occurs in the sinus node. It is located in the superior lateral wall of the right atrium in the region of the openings of the superior vena cava and the inferior vena cava.

The sinus node is the normal pacemaker of the heart. It controls the beat of the heart, because its rate of rhythmic discharge is greater than that of any other part of the heart.

The sinus node have the greatest capability of automatism. Farther from the venous end of the heart to the arterial end – less the automatism. This is called the diminishing gradient of automatism (Gaskell). So, the sinus node is the first degree centre of automatism and the atrioventricular node is the second degree centre. Usually the automatism of all lower located parts of the heart’s specialized conducting system is suppressed by more frequent impulses from the sinus node. The sinus rhythm of the heart is 70- 75 in 1 minute.

If the sinus node is damaged the atrioventricular node may become the pacemaker. The atrioventricular rhythm is 40 –50 in 1 minute. When this node also has been damaged and the atrioventricular bundle has become the pacemaker the rate of the heart’s beat is about 30- 40 in 1 minute. When even this bundle does not function and excitation is spontaneously occuring in the Purkinje fibers, then the heart rate will be no more than 20 in 1 minute.

Occasionally some other part of the heart develops a rhythmic discharge rate that is more rapid than that of the sinus node.

In this case the pacemaker of the heart shifts from the sinus node to that part of the heart. A pacemaker elsewhere than the sinus node is called an ectopic pacemaker. It causes an abnormal sequence of contraction of the different parts of the heart.

Another cause of shift of the pacemaker is blockade of transmission of the impulses from the sinus node to other parts of the heart.

The simple way to observe the heart automatism is to cut the frog’s heart out of the organism and perfuse it by the Ringer solution. Such isolated heart contracts during many hours and even days.

The automatism of warm – blooded heart can be demonstrated by Langendorff’s method. Cannula is put into the aorta of the isolated heart and by the rubber tube it is connected with the glass vessel situated much higher than the heart. The vessel is filled with Ringer – Locke or Tyrode solution saturated with oxygen and warmed up to 37- 38o. Under the pressure of the fluid flowing into the aorta the aortic valve (semilunar valve) closes and the solution flows into the coronary arteries which provide the blood supply of the heart. Under such conditions the heart can contract rhythmically for hours.

With the aid of the coronary arteries perfusion method it is possible to restore the contractions of the human or animal heart several hours after the death.

To explain the nature of heart automatism myogenic and neurogenic theories exist. In favour of the myogenic theory is the fact that separate cells of myocardium cultivated out of the organism contract spontaneously without any stimulation.

The neurogenic theory connects the cause of heart automatism with the specialized excitatory and conductive system of the heart. Using different methods it was proved that the excitation in the heart primarily occurs in the sinus node. When thin electrodes are applied to different parts of the heart, the electrical changes (as the characteristic manifestation of excitation) are recorded first exactly in the region of sinus node and then they are spread to other parts of atria and to the ventricles.

Local warming of the sinus node causes acceleration of heart activity, whereas its cooling has an opposite effect – sharp deceleration or even temporary stopping of systoles. The same result is observed when the sinus node is damaged or poisoned by some specific substances.

The ligatures of Stannius in most convincing way demonstrate the role of the specialized excitatory and conductive system in heart automatism and the degree of automatism ability of each part of this system. Electrophysiological investigations revealed that in automatically excitable cells of heart pacemaker between two systoles (in diastole) the membrane potential is decreased and this was called the slow diastolic depolarization. When the depolarization reaches the critical level, an excitation occurs and it is spread to other cells. Probably, the automatism is connected with the peculiarities of metabolism in the pacemaker’s cells. For instance, in the cells of sinus node and atrioventricular node content of sodium is higher than in the contractile myocardium.

The cardiac muscle, though striated, but differs from skeletal muscle by its morphological and functional peculiarities. Unlike the skeletal muscle, the cardiac muscle fibers are made up of many individual cells connected in series with each other. Thanks to close contacts of these cells (nexus) ions move with ease along the axis of the cardiac muscle fibers, so that action potentials travel from one cardiac muscle to another. Thus, cardiac muscle is a syncytium of many heart muscle cells, in which the cardiac cells are so interconnected that when one of these cells becomes excited, the excitation spreads to all of them. Normally, action potentials can be conducted from the atrial syncytium into the ventricular syncytium only by way of the specialized conductive system-atrioventricular bundle. This division of the muscle mass of the heart into two separate functional syncytiums allows the atria contract a short time ahead of ventricles and provides that in normal heart the atria and ventricles never contract simultaneously.These two points are very important for the effectiveness of heart pumping.

The principal physiological properties of heart muscle (myocardium) are: excitability, conduction, contractibility, refractory period. All these properties are characteristic also for the skeletal muscles. But in comparison with that of skeletal muscles, the heart muscle excitability and conduction are lower, the refractory period is longer.

Since the cardiac muscle forms a syncytium and any excitation spreads to all of the heart muscle cells, the weak stimulation do not cause contraction of myocardium. But if the stimulation is strong enough and reaches the threshold level, the heart muscle responds with all its strength and the further strengthening of the stimulation do not influence on the heart contractions. This is called the law “All or nothing”. The law “ All or nothing” is not of absolute character: temperature, muscle, strain, fatigue, feeding solution and so on can change such respond of the heart muscle. For instance, stimulating the isolated heart muscle, one can observe the “staircase phenomenon” that is, more stimulations – stronger the contractions. The basis of “staircase phenomenon ” is the potentiation of heart muscle contractions when the excitation frequency is changed, but the length of the heart muscle fibers do not change.Therefore, this is attributed to the homoiometric self – regulation.

Using the cardiopulmonary preparation which makes it possible to regulate the blood flow to the heart, the Frank – Starling law of the heart was established. According to this law, more the blood flow to the heart, i.e. more strained the heart muscle fibers are in diastole – the stronger their contractions in systole. Since the length of the heart muscle fibers change, this is attributed to the heterometric self – regulation.

Cardiac muscle, like all excitable tissues, is refractory to re- stimulation during the action potential, that is, for the time being excited the heart muscle do not respond to any other stimulation. The normal (when the heart rate is 70 – 75 beats per minute) refractory period of the ventricle is 0. 25 – 0.3 second which is approximately the duration of the action potential. This is called the absolute refractory period.

The systole of ventricles lasts about 0.3 second and it coincides with the absolute refractory period. So, during systole the myocardium has 0 excitability and do not respond to any (even very strong) stimulation. This is very important property of cardiac muscle - it makes impossible the tetanic contractions of heart (which would be equivalent to the cardiac arrest).

There is also the relative refractory period of about 0.5 second during which the muscle is more difficult than normal to excite but it can be excited if very strong stimulation is applied. The relative refractory period coincides with the diastole of ventricles. After that there is a very short period of exaltation or the period of supernormal excitability when the cardiac muscle responds even to the subliminal stimulations. Then the heart muscle excitability becomes normal.

The refractory period of atrial muscle is shorter than that for the ventricles (absolute refractory period about 0.5 second). Therefore, the rhythmical rate of contraction of the atria can be much faster than that of the ventricles.

So, when the heart is stimulated in systole, the cardiac muscle do not respond. But when in diastole the strong stimulation is applied, the extrasystole is observed. Nearer the stimulation to the end of the diastole, higher the amplitude of extrasystole, because to the end of the diastole heart muscle excitability becomes higher.

After the extrasystole the compensatory pause follows. It is longer than usual ones. Because the next impulse from sinoatrial node, which must evoke the heart muscle contraction, comes to the heart when the cardiac muscle is in the absolute refractory period (caused by extrasystole) and does not answer to that impulse. But during the long compensatory pause the cardiac muscle rests longer, the ventricles accept more blood and the heart muscle fibers are more strained. Therefore, according to “ the law of the heart” (Starling) the next contraction of the heart is stronger, that is, its amplitude is higher – it is called the compensatory systole.

The compensatory systole maintains the work of the heart, whereas the compensatory pause maintains its rhythm.

As a rule, each wave of excitation in heart muscle fibers is followed by contraction. But the excitation is the function of cell membrane and the contraction – that of myofibrils. The connection between them is reached by the help of sarcoplasmic reticulum which provides the calcium ions. These ions are necessary for the process of contraction and for the conjugation of excitation with contraction, but they are not necessary for the excitation of the muscle. Therefore, in some cases, there is a gap between the excitation and contraction. For instance, in the dying heart the electrical phenomena are yet registered when the heart contractions have already stopped.

The velocity of conduction of the action potential in both atrial and ventricular muscle fibers is about 0.3 to 0.5 meter per second. This makes about 1/ 250 the velocity in very large nerve fibers and about 1/10 the velocity in skeletal muscle fibers. The velocity of conduction in the specialized conductive system varies from 0.02 to 4 meters per second in different parts of the system. The conductive system is organized so that the cardiac impulse will not travel from the atria into the ventricles too rapidly. This allows time for the atria to empty their contents into the ventricles before the ventricles begin to contract. In the internodal pathways and atrioventricular node the velocity of conduction is quite low –0.02-0.05 m/sec (about 1/12 that in normal cardiac muscle). Thus, the atrioventricular node and its associated conductive fibers delay the transmission of the cardiac impulse from the atria into the ventricles.

**Electrocardiography**

The surface of myocardium in resting state as well as that of any other muscle, is positively charged (polarization). When excited, it acquires the negative charge (depolarization). For example, during the systole of atria their surface is charged negatively, whereas the ventricles carry the positive charge. So, the electrical current appears. In the systole of ventricles they acquire the negative charge whereas the atria are positively charged. The electrical current of opposite direction appears. During the pause the atria as well as ventricles are resting and since all the surface of the heart is positively charged there is no potential difference and electrical current does not appear.

As the cardiac impulse passes through the heart and the potential difference between excited and non-excited parts of the heart appears, electrical currents spread into the tissues surrounding the heart, and a small proportion of these spreads all the way to the surface of the body. If electrodes are placed on the skin on opposite sides of the heart, electrical potentials generated by these currents can be recorded; the recording is known as an electrocardiogram. The method of electrocardiography (ECG) is widely used in medicine as a method of diagnosis allowing to establish pecularities of heart activity disturbance.

Now the devices has been elaborated which allow to record the electrocardiogram at a great distance or to pass by the phone the potential difference occuring during heart activity. The teleelctrocardiographs permit to record the ectrocardiogram of the sportsmen during the competitions and of cosmonauts in the space flights.

To record the electrocardiogram from the body surface 3 standard bipolar limb leads (I, II, III) and 6 chest leads or precordial leads (V1 - V6) are applied.

The term “bipolar” means that the electrocardiogram is recorded from two specific electrodes on the body, in this case, on the limbs. So, a “lead” is a combination of two wires and their electrodes to make a complete circuit with the electrocardiograph. The standard leads are the following:

1. the negative terminal of the electrocardiograph is connected to the right arm and the positive terminal to the left arm;
2. the negative termianl of the electrocardiograph is connected to the right arm and the positive terminal to the left leg;
3. the negative terminal of the electrocardiograph is connected to the left arm and the positive terminal to the left leg.

A triangle, called Einthoven’s triangle, is drawn around the area of the heart. This is a diagrammatic means of illustrating that the two arms and the left leg form apices of a triangle surrounding the heart. Einthoven’s law states that if the electrical potentials of any two of the three bipolar limb electrocardiographic leads are known at any given instant, the third one can be determined mathematically by simply summing the first two (when making this summation the positive and negative signs of the different leads must be observed).

From Einthoven’s triangle it is also evident that the largest waves are recorded in the II lead, because its direction is parallel to the axis of the heart. Otherwise the electrocardiograms in these three leads are very similar to each other and it does not matter greatly which lead is recorded when one wishes to diagnose the different cardiac arrhythmias, for their diagnosis depends mainly on the time relationships between the different waves of the cardiac cycle. But when it is necessary to diagnose damage in the ventricular or atrial muscle or in the conducting system, it does matter greatly which leads are recorded, for abnormalities of the cardiac muscle change the patterns of the electrocardiagrams markedly in some leads and yet may not affect other ones.

When using the chest leads an electrode is placed on the anterior surface of the chest over the heart at one of the 6 separate points. This electrode is connected to the positive terminal of the electrocardiograph, while the negative electrode (the indifferent electrode) is connected through electrical resistances to the right arm, left arm and left leg all at the same time. The chest leads are unipolar leads. Each of them records mainly the electrical potential of the cardiac musculature immediately beneath the electrode. Therefore, relatively minute abnormalities in the ventricles, particularly in the anterior ventricular wall, frequently cause marked changes in the electrocardiograms recorded from chest leads.

In “augmented unipolar limb lead” two of the limbs are connected through electrical resistances to the negative terminal of the electrocardiograph, while the third limb is connected to the positive terminal. When the terminal is on the right arm, the lead is known as the a VR lead; when on the left arm - the aVL lead and when on the left leg- the a VF lead. These are all similar to the standard limb lead recording except that the recording from a VR lead is inverted.

The normal electrocardiogram is composed of a P wave, a QRS complex and a T wave. Both the P wave and the components of the QRS complex (the Q wave, the R wave and the S wave) are depolarization waves.

The **P wave** is caused by electrical potentials generated when the atria depolarize before the contraction. The QRS complex is caused by potentials generated when the ventricles depolarize before the contraction, that is, when the depolarization wave spreads through the ventricles. The Q wave is connected with the excitation of the internal surface of ventricles, right papillary muscle, apex cordis; the R wave - with the excitation of surface and base of both ventricles. To the end of the S wave the excitation spreads completely all over both ventricles and there is no potential difference among different areas of the ventricles.

The **T wave** is a repolarization wave. It reflects the recovery of normal membrane potential of myocardium cells.

Rarely in the electrocardiogram a U wave of unknown origin is recorded.

During the process of depolarization (when the excitation occurs) the normal negative potential inside the fiber is lost and the membrane potential actually reverses; that is, it becomes slightly positive inside and negative outside.

The monophasic action potential of ventricular muscle normally lasts 0.25-0.35 second. The upsweep of this action potential is caused by depolarization and the return of the potential to the base-line is caused by repolarization. Simultaneous recording of the electrocardiogram from the same ventricle shows that the QRS complex appears at the beginning of the monophasic action potential and the T wave appears at the end. No potential at all is recorded in the electrocardiogram when the ventricular muscle is either completely polarized or completely depolarized.

The total duration of ventricles’ electrical systole, i.e. the Q-T interval almost coincides with the mechanical systole, though the latter begins slightly later. To express the dependence of electrical systole (S) on heart rate, i.e. on duration of cardiac cycle (C) the following formulas has been offered:

Fridericia’s formula:

S= 8.22 C (C -in 0.01 second). Bazett’s formula:

3

 S= 0.37 C (C - in seconds).

The normal properties of electrocardiogram (the direction, duration, amplitude of waves, the intervals between them and so on) and their typical changes in different heart diseases are well studied. In the electrocardiogram of healthy man the P wave, the R wave and the T wave are directed up, the Q wave and the S wave are directed down.

The amplitude and duration of waves, complexes and intervals of electrocardiogram of healthy man are presented in the table.

|  |  |  |
| --- | --- | --- |
| Wave  | Amplitude (mV)  | Duration (sec.)  |
| P Q R S T  | 0.05-0.30 0 - 0.20 0.60-1.60 0-0.03 0.25-0.50  | 0.08-0.10 max. 0.03 max. 0.03 max. 0.03 max. 0.25  12-0.20 0.06-0.10 0.30-0.46 0.10-0.35 0.70-0.80  |
| Intervals and complexes  |
| P-Q QRS QRST S-T R-R  |

The size of potential difference between different areas of myocardium is changed during cardiac cycle. The conventional line connecting two points with the greatest potential difference at a given instant in the cardiac cycle is called the electrical axis of the heart. It has the vectorial features. A vector is an arrow that points in the direction of the electrical potential generated by the current flow with the arrowhead in the positive direction. The lenght of the arrow is drawn proportional to the voltage of the potential.

The simultaneous recording of the potential difference and vector’s direction changes is called vectorelectrocardiography (VECG).

Any change in the impulse transmission through the heart can cause its abnormal electrical potentials and alter electrocardiogram wave’s shape. Therefore, almost all serious abnormalities of the heart muscle can be detected by profoundly analyzing the contours of the different waves in the different electrocardiographic leads.

Some of the most distressing types of heart malfunction are resulted not by abnormal heart muscle but by abnormal rhythm of the heart: the heart rate is too fast or too slow to pump proper amounts of blood; the interval between heartbeats is too short for the ventricles to fill; the beat of the atria is totally uncoordinated with the beat of the ventricles, so that the atria no longer function as primers for the ventricles and so forth.

The causes of the cardiac arrhythmias are usually one or combination of the following abnormalities in the rhythmicity - conduction system of the heart: 1) abnormal rhythmicity of the pacemaker; 2) shift of the pacemaker from the sinus node to other parts of the heart; 3) blocks at different points in the transmission of the impulse through the heart; 4) abnormal pathways of impulse transmission through the heart; 5) spontaneous generation of abnormal impulses in almost any part of the heart.

The electrocardiography allows to analyse the rhythm of the heart in detail. The normal heart rate is 60-80 beats per minute. The heart rate faster than 90-100 beats per minute is called tachycardia; slow heart rate, less than 60 beats per minute (40-50), is called bradycardia. Physiologically the tachycardia is recorded during intensive muscular work, emotional excitation; the bradycardia - in athletes during the rest.

The three general causes of tachycardia are: increased body temperature, stimulation of the heart by sympathetic nerves and toxic conditions of the heart. Any vagal stimulation is a cause of bradycardia because of the inhibitory effect that parasympathetic nervous signals have on heart function.

Any one of many circulatory reflexes or other nervous effects that alter the strength of the sympathetic and parasympathetic nerve signals to the sinus node can result in the sinus arrhythmia. In young people the regular change of heart activity rhythm connected with the breathing (the respiratory arrhythmia) is recorded.

In rare instances the impulse from the sinus node is blocked before it enters the atrial muscle. Such sinoatrial block causes the sudden cessation of P waves with resultant standstill of the atria.

Different conditions can cause the atrioventicular block by decreasing the rate of conduction of the impulse through atrioventicular bundle or totally blocking the impulse.

The normal lapse of time between the beginning of the P wave and the beginning of the QRS complex, i.e. the P-Q interval is approximately 0.16 second. The prolonged P-Q interval withnesses the aggravation of atrioventricular conduction. When the P-Q interval increases above a value of 0.20 second in a heart beating at a normal rate, the patient is said to have first degree incomplete heart block.

When the atrioventricular conduction is slowed until the P-Q interval is 0.25-0.45 second, the impulse passes into the ventricles following one atrial contraction and fails to pass following the next one or two. The atria beat at a considerably faster rate than the vantricles, and it is said that there are “dropped beats” of the ventricles. This condition is called second degree incomplete heart block. At times every other beat of ventricles is dropped, so that a “2:1 rhythm” develops in the heart (atria beating twice for every single beat of the ventricles). Other rhythms (3:2 or 3:1) also can develop.

When the condition causing poor conduction in the atrioventricular node or bundle becomes extremely severe, complete block of the impulse from the atria into the ventricles occurs and the P waves become completely dissociated from the QRS-T complexes. Furthermore, there is no relationship whatsoever between the rhythm of the atria and that of ventricles, for the ventricles have “escaped” from control by the atria, and they are breathing at their own natural rate.

A contraction of the heart before the time that normal contraction would have been expected is called a premature contraction (premature beat, ectopic beat) or extrasystole.

If out of turn excitation occurs in sinoatrial node when the refractory period is ended, but the next automatic impulse has not yet appeared, sinus extrasystole is observed. The pause after such extrasystole is of normal duration.

Out of turn excitation in ventricles do not influence on the sinus node automatism and the next impulse from this node reaches the ventricles when they are in the refractory period caused by extrasystole. Therefore, the myocardium of ventricles do not respond to this impulse and the ventricle extrasystole is followed by compensatory pause.

Abnormalities in any part of the heart can cause rapid rhythmic discharge of impulse that spread in all directions throughout the heart. Owing to the rapid rhythm in the irritable focus it becomes the pacemaker of the heart. The heart rate becomes very rapid in paroxysms. This state is called paroxysmal tachycardia. The paroxysms begin suddenly, last from few seconds to few hours (sometimes much longer) and end as suddenly as they had begun, the pacemaker of the heart shifting back to the sinus node.

Extremely rapid and asynchronous contractions of muscle fibers of atria and ventricles are called atrial flutter (when the rate of contractions is 240-360 beats per minute) or atrial fibrillation (360-600 beats per minute) and ventricle flutter or fibrillation (150-300 beats per minute in both cases, but in flutter contractions are relatively rhythmical and in fibrillation - with different intervals).

The most serious of all cardiac arrhythmias is ventricular fibrillation. It results from cardiac impulses that have gone berserk within the ventricular muscle mass, stimulating first one portion of the venticular muscle, then another, eventually feeding back to re- excite the same ventricular muscle over and over again-never stopping. Therefore, many small portions of the ventricular muscle contract at the same time, while equally as many other portions relax. There is not a necessary coordinate contraction of all of the heart muscle at once for a pumping cycle of the heart and the ventricular chamber pumps either no blood at all or negligible amounts.

A final serious abnormality of the cardiac rhythmicity-conduction system is cardiac arrest. This results from cessation of all rhythmic impulses of the heart. That is, no spontaneous rhythm at all remains.

**Cardiac Cycle. Heart Sounds and other External Manifestations of Heart Activity. Stroke Volume of the Heart and Cardiac Output**

Each cardiac cycle that is initiated by the impulse from sinus node, consists of the systole of atria, the systole of ventricles and pause. The ventricles are in the state of diastole during the pause and the systole of atria.

When the systole of atria begins, the openings of the vena cava superior and vena cava inferior are compressed and therefore, the blood can flow only through the atrioventicular valves (bicuspid or mitral valve and tricuspid valve) into proper ventricle. But these valves do not let the blood flow in the opposite direction during the systole of ventricles. Because the borders of their cusps are fastened to the papillary muscles via the chordae tendineae. Therefore, during the systole of ventricles the blood flows only forward - into aorta and pulmonary trunk. Here also the semilunar valves do not let the blood backward - into the ventricles.

So, in whole cardiovascular system the blood flows only forward.

During the diastole of atria and ventricles the pressure in the chambers of heart falls to zero and the blood flows from the veins into atria and then - into ventricles. The following factors promote filling of the heart by blood:

1.Remainder of the motive power created by the precedeng systole of ventricles.

2. The chest is the hermetically closed cavity in which, thanks to the elastic draught of lungs, there is the negative pressure. During the inspiration this cavity is extended, the pressure in atria becomes negative. This creates the sucking power and the blood flow into the atria becomes stronger.

3.During the systole of ventricles the atrioventricular septum is dragged down and this creates the additional sucking force.

4.Veins have valves letting the blood only to the heart. Therefore, when the skeletal muscles contract, they compress the veins and promote the blood flow to the atria. This is called the **venous pump.**

So, blood continually flows from the great veins into the atria. About 75% of blood flows directly through the atria into the ventricles even before the atria contract. Atrial contraction causes an additional 25%. The heart can continue to operate satisfactorily under normal resting conditions even without this extra 25% effectiveness because it normally has the capability of pumping 300-400% more blood than is required by the body. Therefore, the fail of atrial function is noticed only when a person exercises.

Normally, during atrial contraction the right atrial pressure rises 4 to 6 mm Hg and the left atrial pressure rises about 7 to 8 mm Hg.

As it is evident from the table, the systole of ventricles (0.33 second) is divided into two periods - the period of tension and the period of ejection.

|  |  |  |  |
| --- | --- | --- | --- |
| Systole of ventricles (0.33 second)  |  | Diastole of ventricles (0.47 second)  |  |
| period of tension (0.08 second)  | period of ejection  (0.25 second)  | proto-diastolic period  | period of isometric relaxation  | period of filling of the ventricles (0.25second)  | presystolic period  |
| asynchronous contraction  | isometric contraction  | rapid  | slow  |   |   | rapid  | slow  |   |
| 0.05  | 0.03  | 0.12  | 0.13  | 0.04  | 0.08  | 0.08  | 0.17  | 0.10  |

The **period of tension** consists of two phases: asynchronous contraction and isometric contraction. During the phase of asynchronous contraction the wave of excitation and contraction gradually spreads in the myocardium. The part of muscle fibers contract, but another fibers, which are not yet excited, are strained. Therefore, the shape of ventricles is changed, but hte pressure in them is near zero. To the end of this phase the pressure begins to increase rapidly. At the beginning of the next phase of the period of tension the atrioventricular valves slap and the first (systolic) heart sound occurs. The semilunar valves are also closed. Therefore, during a short time the muscles of ventricles contract, their tension is increased, but the muscle fibers do not shorten and the volume of ventricles do not change. Because the blood, as well as any other fluid, is not compressible. The contractions of ventricle muscles when all the valves are closed, is called the phase of isometric (isovolumic) contraction. During this phase the pressure in the ventricles rapidly increases. The left ventricle’s shape becomes round and it hits on the inner surface of the chest. This is the cause of the cardiac/apex beat which is felt in the V intercostal region, 1 centimetre to the right from the left medioclavicular line.

When the left and right ventricular pressure rise above the pressures in the aorta (80 mm Hg) and pulmonary trunk (8 mm Hg) ventricular pressure push the semilunar valves open and the period of ejection begins, that is, the blood begins to pour out of the ventricles. About 70% of the emptying occurs during the first third of the period of ejection and the remaining 30% during the next two thirds. Accordingly the two phases of this period are distinguished: the phase of rapid ejection and the phase of slow ejection.

In the **period of ejection** the left ventricular pressure rises up to 120-130 mm Hg and the right ventricular pressure rises up to 25 mm Hg. But the end of the phase of slow ejection the myocardium of ventricles begins to relax and the intraventricular pressures fall. The diastole of ventricles begins (0.47 second).

In the beginning of the diastole the blood from the aorta and pulmonary trunk rushes back to the ventricles, semilunar valves slap and the second (diastolic) heart sound occurs.

The time from the beginning of the relaxation of the ventricles to the slapping of the semilunar valves is called the **protodiastolic period**.

After the slapping of the semilunar valves the ventricular pressure falls to zero. The left and right atrioventricular valves are closed yet. The volume of the blood in the ventricles and the length of the fibers of the myocardium do not change. Therefore, this period is called the period of isometric (isovolumic) relaxation.

As soon as the ventricular pressures fall lower than that in the atria, the high pressures in the atria push the atrioventricular valves open and the period of filling of the ventricles begins. This period is divided into two phases: rapid filling and slow filling of the ventricles. At the beginning of the middle third of diastole the third heart sound occurs. It results from the vibrations of the ventricles’ walls in the phase of their rapid filling as well as the ossillation of blood back and forth between the walls of the ventricles initiated by inrushing blood from the atria.

The last period of the diastole of ventricles corresponds to the systole of atria which pump into the ventricles the additional amount of the blood. Since after this period the new cycle of the ventricles’ activity (the next systole) begins, it is called the presystolic period. In this period inrush of blood into the ventricles, which initiates vibrations similar to those of the third heart sound, cause the forth (atrial) heart sound.

Since the heart sounds and cardiac beat make it possible to have an information about the functional state of the heart in living organism, they are attributed to the external manifestations of heart activity, that is, the mechanical, electrical, sound phenomena accompanying the heart activity. On those external manifestations are based some methods of investigation of heart activity, such as cardiography, esophagocardiography, phonocardiography, electrokymography, ballistocardiography, dynamocardiography and others. The arterial pulse also may be refered to the external manifestations of the heart activity because its character reflects the heart activity as well as the functional state of arterial system.

The method of ausculation by the stethoscope or phonendoscope allows to hear the first and second heart sounds.

The first (systolic) heart sound is the result of the simultaneous slapping of the leaflets of the mitral and tricuspid valves as well as the vibration of the taut valves immediately after closure along with vibration of the adjacent blood, walls of the heart. Since in the origin of the first heart sound contractions of the strong ventricular muscles take part, it is called also the muscular sound.

The second (diastolic) heart sound results from simultaneous sudden closure of the aortic and pulmonary valves. When the semilunar valves close, they bulge backward toward the ventricles, and their elastic stretch recoils the blood back into the arteries, which causes a short period of reverberation of blood back and forth between the valves and the ventricular walls. The vibrations set up in the arterial walls are then transmitted along the arteries. The second heart sound is called also the valve sound.

When the vibrations of the vessels or ventricles come into contact with a “sounding board”, such as the chest wall, they create sound that can be heard.

The areas for listening to the heart sounds are not directly over the valves, but on the points where the sounds are well transmitted and better heard. The first heart sound is auscultated in mitral and tricuspid areas. The mitral area is over the apex of the heart, the tricuspid area is on the xiphoid process of the brest bone.

The second heart sound is auscultated in aortic and pulmonic areas. Both areas are in the II intercostal region: the aortic area - at the right edge of the breast bone and the pulmonic area - at the left edge of the breast bone.

The first heart sound is dull, long and low; the second heart sound is ringing, short and high.

The method of recording of the heart sounds is called phonocardiography. In the phonocardiogram besides the first and second heart sounds the third and fourth heart sounds are also recorded. The latter two heart sounds are not heard during the auscultation.

When there are abnormalities of the valves (valvular lesions, stenosis) many abnormal heart sounds, known as “heart murmurs”, occur.

A valve in which the leaflets adhere to each other so extensively that blood cannot flow through satisfactorily is said to be stenosed. If the valve edges are so destroyed by scar tissue that they cannot close completely regurgitation (backflow) of blood occurs when the valve should be closed.

For example, in aortic stenosis during systole the blood jets at tremendous velocity through the small opening of the valve. This causes severe turbulence of the blood in the root of the aorta, intence vibration of the aortic walls and a loud murmur occurs. But in aortic regurgitation during diastole blood flows from the aorta backward into the left ventricle, causing a murmur.

The method of recording of thoracic wall vibrations caused by cardiac beat is called cardiography. Esophagocardiography is applied by means of the bulb, introduced into esophagus. The esophagocardiogram reflects mainly the contractions of the left atrium.

Electrokymography is the method of electrical recording of the movements of cardiac

shade outline on the screen of the X-ray apparatus.

Ejection of the blood from the ventricles and its movement in large vessels cause vibrations of all the body resulted from the jet propulsion. The method of recording of these vibrations is called ballistocardiography.

Movements of the heart in the chest and the transference of the blood mass from the heart into the vessels is followed by displacement of the chest’s centre of gravity as regards the surface on which the person is lying. Dynamocardiography is the method of recording of these movements.

The main physiological function of heart is to pump the blood into the vascular system. The quantity of blood pumped into the aorta each minute by the heart is called the cardiac output. This is also the quantity of blood that flows through the circulation and is responsible for transporting substances to and from tissues.

The quantity of blood flowing from the veins into the right atrium each minute is called venous return. Obviously, the venous return and the cardiac output must be equal to each other except at a time when blood might be temporarily stored in or removed from the heart and lungs.

Each time ventricles contract, they push into aorta and pulmonary trunk 65-70 ml of blood. This is called the stroke volume of the heart. The normal heart rate is 70-75 beats per minute. This means that during 1 minute the ventricles push into the vascular system approximately 5 litres of blood. This is called cardiac output. For women this value is 10-20% less.

The cardiac output varies widely with the level of activity of the body. Such factors as the level of body metabolism, whether the person is exercising, age and size of the body as well as a number of other factors can influence the cardiac output. The cardiac output is regulated throughout life almost durectly in proportion to the overall bodily metabolic activity. Therefore, declining cardiac index is indicative of declining activity with age.

The cardiac output changes markedly with body size. It increases approximately in proportion to the surface area of the body. Therefore frequently the cardiac index is calculated. Cardiac index is the cardiac output per square meter of body surface area. The normal adult man weighing 70 kilograms has a body surface area of approximately 1.7 square meters, and the normal average cardiac index is about 3 litre/min per square meter of body surface area. Accordingly the stroke index is the stroke volume per square meter of body surface area. The normal value of stroke index is 45-55 ml/m2.

Several methods were offered to determine the cardiac output. The most precise is the method of Fick which requires to know: 1) the difference in the content of oxygen in arterial and venous blood; 2) the volume of the oxygen consumed by the person per minute.

Let us assume that 400 ml of oxygen enters in 1 minute through lungs into the blood and the oxygen content of the arterial blood is 8 volume% more than that of venous blood. This means that each 100 ml of blood in lungs absorbs 8 ml of oxygen. Consequently, to acquire all the oxygen which enters into the blood in lungs per minute (400 ml) the following amount of the blood must pass through the lungs:

 = 5000 ml. This is the cardiac output.

Influence of different conditions on the stroke volume can be investigated on the cardiopulmonary preparation. By the way of ligating the aorta, vena cava superior and vena cava inferior the greater circulation of the animal is cut off and replaced by the system of plastic tubes. The coronaty circulation and the lesser circulation are preserved.

Changing the resistance to the blood flow in the artifitial greater circulation, it is possible to increase or decrease flow of the blood to the right atrium. The experiments on the cardiopulmonary preparation allowed Starling to establish “the law of the heart”. This preparation permits also to study the cardiac output in different conditions.

During the muscular work the cardiac output increases up to 25-30 litres. This may be resulted from the rapid heart rate and increased stroke volume. In trained persons (sportsmen) the muscular work increases the cardiac output mainly by increasing the stroke volume. But in nontrained persons it is reached by the high heart rate. During intensive muscular effort the heart rate may be as high as 200 beats per minute and more.

|  |  |  |
| --- | --- | --- |
| The first heart sound  | Mitral valve  | Over the apex of the heart (in the V intercostal region, 1 centimetre to the right from the left medioclavicular line)  |
| Tricuspid valve  | On the xiphoid process of the breast bone  |
| The second heart sound  | Aortic valve  | In the II intercostal region, at the right edge of the breast bone  |
| Pulmonary valve  | In the II intercostal region, at the left edge of the breast bone  |

**Control of Heart Activity. Intracardiac Mechanisms of Regulation. Nervous**

**Regulation of Heart Activity**

Depending on the functional state of organism and environmental factors requirement of the organism in blood supply changes and the heart activity is always adapting itself to circumstances to statisfy the changing needs of organism. There are intracardiac and extracardiac mechanisms of regulation of heart activity. Intracardiac mechanisms include intracellular mechanism of regulation, regulation of the intercellular relations and intracardiac peripheral reflexes. Extracardiac mechanisms consist of the extracardiac nervous (including neuroreflex) and humoral mechanisms of heart activity control. All of these regulation mechanisms are under the cortical control.

Intracelullar mechanisms of regulation ensure intensification of the synthesis of contractile proteins of myocardium and the structures providing their activity when the heart is overloaded. This leads to the working hypertrophy of myocardium (for instance, in sportsmen). These mechanisms provide also the change of intensity of myocardium activity according to the quantity of blood flowing into the heart (the Frank Starling law of the heart).

In the regulation of the intercellular relations an important role belongs to intercalative discs which connect the cells of myocardium and have different structures. Some of them fulfil only mechanical function and just connect the myofibrils, the others provide the transport of necessary substances through membrane of myocyte, the third ones (the nexus or close contacts) conduct the excitation from one cell to other one, i.e. they unite the cells of myocardium in the functional syncytium. The disturbance of intercellular relations leads to the asynchronous excitation of the myocardium cells and cardiac arrhythmias.

The relations of myocytes and connective cells of myocardium, that is, the creatory connections are also attributed to the intercellular relations. The connective cells are not simply the mechanical supporting structures, but they supply the contractile cells of myocardium by the products which are necessary for the maintenance of their structure and functions.

The processes of intercellular relations in myocardium may be controlled by the nervous system.

Intracardiac peripheral reflexes, i.e. the intracardiac nervous mechanisms represent higher level of the intraorganic regulation of heart activity. These are the reflexes the arches of which close not in the central nervous system, but in the intracardiac ganglia. After heart transplantation, when all the extracardial nervous elements are degenerated, only intraorganic nervous system of the heart remains to function.

When the right atrium of the isolated heart is stretched, this causes strengthening of left ventricle myocardium’s contractions. This peripheral reflex promotes vacation of place for the flowing in blood by the way of throwing the blood into the arterial system.

The strength of ventricles myocardium contractions increases in proportion to the rise of resistanse (blood pressure) in the arterial system. This is called the effect of Anrep.

The intracardiac nervous system is the lowest link of the nervous mechanisms regulating heart activity. The higher link in this hierarchy is the extracardial regulation of heart activity which is realized by sympathetic and parasympathetic (vagus) nerves.

For the first time in 1845 Weber brothers discovered that stimulation of vagus nerves inhibits the heart activity and even can stop the heart in the diastole. The significance of this discovery is much more than simply the study of heart activity regulation. Because it was the first time that the inhibiting effect of nerves was detected. Up to that time it was considered that the nerve stimulation causes only excitation.

In 1867 Cyon brothers discovered increasing the frequency effect of sympathetic nerves. In 1887 I. P. Pavlov established that sympathetic nerve contains also the fibers which just strengthen the heart contractions not changing the heart rate. He considered that these are the trophic fibers, i.e. they influence the heart activity by the way of stimulation of the metabolism.

The sympathetic nerve fibers of heart begin in the lateral horns of five upper segments of thoracal section of spinal cord and the greater part of these fibers set off for the heart from the ganglion stellate. The parasympathetic nerve fibers begin in the reticular formation of the medulla oblongata and come up to the heart as a component of vagus nerve.

Both sympathetic and parasympathetic nerves of heart consist of the fibers influencing the cardiac rhythm (rhythmical fibers) and the fibers which influence the atrength of heart muscle contractions (dynamic or trophic fibers).

The following effects of the extracardial nerves on heart activity are distinguished:

1) effect on the rate of the heart beat - the chronotropic effect;

2) effect on the strength of heart muscle contractions - the inotropic effect;

3) effect on the excitability of myocardium - the bathmotropic effect;

4) effect on the conduction of myocardium - the dromotropic effect.

All of these effects of sympathetic nerves are positive and of parasympathetic (vagus) nerves - negative. That is, the sympathetic nerves increase the heart rate, strengthen the heart contractions, raise the excitability and conduction of myocardium. The vagus nerve, on the contrary, decreases the heart rate, weakens the heart contractions, reduces the excitability and conduction of myocardium.

The following mechanograms demonstrate the effect of stimulation of rhythmical and dynamic fibers of the sympathetic (n. S.) and vagus (n. V.) nerves on heart activity.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Normal heart  |   | The stimulation  | The stimulation  | The stimulation  |
| activity  |   | of the rhythmical  | of the dynamic  | of the whole nerve  |
|   |   |  fibers  |  fibers  |  |

 n. S. n. S.

 n. S.

 n. V. n. V. n. V.

The extracardial nerves exercise their influence on heart activity with the aid of chemical substances called the transmitters or mediators, which are secreted in nerve endings. The parasympathetic mediator is acetylcholine, the sympathetic mediators are adrenaline (epinephrine), noradrenaline (norepinephrine) and others.

Existence of mediators was proved in 1921 by Loewi in following experiment. He stimulated the vagus or sympathetic nerves of isolated frog heart and then carried the liquid from this heart to another isolated heart which was not stimulated. In the activity of the second heart the changes were observed identical to those in the first heart. This means that during the stimulation of the nerves of the first heart the proper mediators were secreted in the nerve endings and passed into the liquid washing the heart.

After exercising their influence, the mediators are destroyed by the ferments: adrenaline - by aminoxidase, acetylcholine - by cholinesterase. Acetylcholine is destroyed more rapidly and therefore, its effect is only local. Adrenaline’s effect is more prolonged.

Under the influence of the extracardial nerves stimulation on the heart activity the following periods are distinguished:

1. The latent (occult) period - from the moment of stimulation to the moment when the heart activity begins to change. The latent period of the sympathetic nerves is longer than that of vagus nerves.
2. The period of action - from the moment when the heart activity changes till the cessation of stimulation.
3. The period of after-action- from the moment of stopping of stimulation till the moment when the heart activity is completely normalized. This period is connected with the mediators which exercise their influence on the heart activity even after the cessation of stimulation till they are destroyed by the ferments. Since acetylcholine is destroyed more rapidly than adrenaline, the after-action period of sympathetic nerves is longer.

So, as a result of sympathetic nerves stimulation the heart rate increases, heart muscle contractions strengthen and, if the stimulation is continued for a long time, the heart is stopped in systole.

When the vagus nerves are stimulated, the heart rate decreases, heart muscle contractions weaken and a long stimulation causes stopping of the heart in diastole. Sometimes, when the prolonged vagus nerve stimulation causes stopping of the heart, after a short time the heart begins to contract again. This is called escaping of the heart from the influence of the vagus nerves.

The centers of extracardial nerves of heart are always in the state of tonus, that is, they are always semi-excited and send impulses to the heart.

The central tonus of vagus nerves is more marked. After cutting of both vagus nerves in experiment the heart is released from their inhibiting effect and the heart rate is significantly increased. In the human body vagus nerves can be temporarily excluded by injection of atropine and then the heart rate increases markedly.

The central tonus of vagus nerves is maintained by reflex influences, that is, by the impulses which reach the vagus center by centripetal nerves, especially from the receptors of aortic arch and sinus carotid. Therefore, after cutting of these nerves the heart rate is increased as if the vagus nerves themselves were cut.

The central tonus of vagus nerves is maintained also by humoral way. Some chemical substances in blood, for example adrenaline as the hormone of suprarenal gland substantia medullaris and calcium ions, increase this tonus.

The humoral influences on the central tonus can be demonstrated by the crossed blood circulation method of Heymans. In this method the blood vessels of two dogs are connected in such a way that the blood of dog A passes through the head of dog B. The head of the dog B is separated from the trunk, leaving safe only the vagus nerves. So, if the injection of some substances into the blood of the dog A changes the heart activity of the dog B, it is obvious that the substance acts only through the center of vagus nerve.

The tonus of the vagus nerves nuclei changes also depending on the phases of breathing. To the end of the expiration it increases and therefore, the heart rate is decreased. This results in the respiratory arrhythmia which disappears after cutting of vagus nerves or injection of atropine.

The stable rise of the vagus nerves central tonus causes bradycardia and its stable fall - tachycardia.

The central tonus of sympathetic nerves is not so marked as that of vagus nerves.

The next (third) degree in the hierarchy of nervous centers regulating the heart activity are the centers of the hypothalamic area. The electrical stimualtion of different zones of hypothalamus leads to marked changes in heart activity. Hypothalamus is the integrated center which can change any parameters of the activity of any part of the cardiovascular system to provide the organism’s requirements during its reactions in response to changing of the environmental conditions.

**Reflex, Humoral and Cortical Regulation of Heart Activity**

Irritation of some areas of the body results in change of heart activity by reflex way. These areas are called reflexogenic zones.

The change of heart activity was observed in experiments when different structures of the central nervous system such as centers of spinal cord, medulla oblongata, hypothalamus, cerebellum, cerebral cortex were stimulated. This proves that all the levels of the central nervous system take part in the reflex control of heart activity. Some of them inhibit (decelerate and weaken) and others excite (accelerate and strengthen) the heart contractions. In inhibiting reflex the efferent nerve is vagus nerve (vagal reflexes), in exciting reflexes – sympathetic nerve (sympathetic reflexes).

The reflex changes of heart activity occur when mechanoreceptors (pressoreceptors or baroreceptors) and chemoreceptors situated all over the body, especially in the vascular system (vascular reflexogenic zones), in the heart itself (in endocardium, myocardium, epicardium), in the blood vessels of many viscera, are stimulated. For instance, increase of pressure in pulmonary artery causes deceleration of heart contractions.

The reflexogenic zones belong to the self- regulation mechanisms of the cardiovascular system. The most significant reflexogenic zones are those in aortic arch and sinus carotid (where the common carotid artery is bifurcated).

The natural irritant of baroreceptors of these areas is increased blood pressure. Then afferent impulses from the excited baroreceptors reach the vagus nerve center (in medulla oblongata) and result in the reflex inhibition of heart activity as well as the vasodilation, and the blood pressure falls to the normal level.

More demonstrative vagal reflexes are Dagnini - Aschner reflex and Holtz reflex.

The **Dagnini – Aschner reflex** or oculocardiac reflex may be easily demonstrated on man. The pulse is counted, then the person slightly presses his eyeballs by fingers. The repeated pulse count detects the decrease of pulse rate 10- 20 beats per minute.

The **Holtz reflex** is demonstrated on frog and it is simply to analyse the reflex arch in this example. The light thrashing of the stomach or electrical stimulation of the guts of frog cause the cardiac arrest or the marked decrease of heart rate. The reflex arch in this case is the following:

1. receptors of the celiac plexus;
2. afferent fibers of the splanchnic nerve;
3. nuclei of vagus nerve in the medulla oblongata (the celiac plexus and spanchnic nerve belong to the sympathetic part of the vegetative nervous system, whereas in the central nervous system the impulse is passed to the parasympathetic nuclei); **4)** vagus nerve (as the efferent nerve); **5)** heart (as a working organ).

It is easy to make sure that really this is the arch of Holtz reflex. It is enough to cut vagus nerves or splanchnic nerves, or to destroy the spinal cord and then the thrashing of the stomach will not stop the heart contractions.

All above – mentioned reflexes promote decreasing of heart rate and the arterial blood pressure when they are increased. But when the pressure increases in the right atrium, vena cava superior and vena cava inferior, as a result of the venous congestion the stretch receptors of the atria are irritated and elicit Bainbridge reflex. Their afferent signals are transmitted through the vagus nerves to the medulla of the brain. Then efferent impulses are transmitted back through sympathetic nerves to increase the heart’s rate and strength of contractions. Thus, Bainbridge reflex helps to prevent damming of blood in the veins, the atria and the pulmonary circulation.

During the muscular work, painful irritations, emotional states (joy, anger, rage) also the reflex acceleration and strengthening of heart activity is observed. These changes are caused by the impulses transmitted to the heart through the sympathetic nerves. But in these cases the humoral factors have a great significance.

The humoral regulation of heart activity is realized by different biologically active substances (hormones, ions and so forth) circulating in the blood.

More significant and at the same time more complicated is the action of catecholamines (adrenaline, norepinephrine). As the hormones of the substantia medullaris of adrenal gland their content in the blood is increased in the physical overwork or emotional overstrain. They strengthen sharply the heart activity, that is, increase the heart rate and strengthen contractions of myocardium. Biologically this is very important and necessary in such states of organism.

But on the other hand, the catecholamines, effecting directly on the vagus nerve center, raise the tonus of the vagus nerves nuclei and cause the opposite changes. Thus, when the content of catecholamines in blood is exsessively raised, the heart rate is not too increased.

The parasympathetic mediator acetylcholine inhibits the heart activity.

Hormones of the adrenal cortex, angiotensin strengthen contractions of myocardium. Thyroxin increases the heart rate.

Hypoxemia, hypercapnia, acidosis suppress the contracting activity of myocardium. Role of the electrolytes in the normal heart activity is significant. Changes of the concentrations of the sodium and potassium salts in the blood influence markedly on the automatism, excitation and contraction of the heart.

Potassium ions in high concentrations in blood (hyperkalemia) suppress all parameters of heart contractions, decrease the heart rate, excitation and conduction of myocardium. The considerable surplus of potassium ions cause the stopping of the heart in diastole. The hypokalemia also results in sharp changes in heart activity.

Calcium ions exercise the opposite influence on heart activity. They strengthen the heart contractions, increase the heart rate, excitation and conduction of myocardium. The calcium ions surplus causes stopping of the heart in systole.

To study the effect of hormones and electrolytes on heart activity, the heart is isolated by Schtraub method.

The highest degree of heart activity control is realized by cerebral cortex, especially by the limbic system. The signals from these structures result in the integrate reorganization of cardiovascular system functions. The anatomical nearness of cortical centers responsible for the motor and cardiovascular reactions promotes the optimal vegetative ensuring of behavioural reactions of organism (for instance, increased heart rate during emotions).

The fact directly witnessing the participation of cerebral cortex in the heart activity control is changing of cardiovascular functions (heart rate, blood pressure and so forth) when certain cortical structures are stimulated. But there are also many other facts.

Different emotions (positive and negative) change the heart activity. Since formation of emotions in the function of cerebral cortex, this fact testifies that it takes part in heart activity control.

Even at the mere mention of the events, causing strong emotions in the person, his heart rate and strength of heart contractions change.

This is conditioned reflex which is also connected with the cerebral cortex. The changes of heart activity (tachycardia and so forth) in sportsmen before starting and in students before exams are also of conditioned reflex character.

It is possible to change the heart activity by the way of developing the conditioned reflex. For example, if any stimulant, for instance, light, is repeatedly combined with injection of adrenaline which increases the heart rate, then the light itself without the adrenaline injection will increase the heart rate.

By the conditioned reflex mechanism the cerebral cortex provides adaptation of organism to the future events and therefore, the conditioned reflex ensures also the proper reconstruction of heart functions in the degree, necessary to provide the future activity of organism. In extremely difficult situations, when the neurosis develops, together with the behavioural disorders the heart activity as well as the functions of all the cardiovascular system are disturbed. In some cases these disturbances are fixed as the pathological conditioned reflexes and then the heart activity disorders may be caused by the influence of only the conditioned signals.

It is possible to change the heart activity by the way of hypnotic suggestion. This fact once more confirms participation of cerebral cortex in the heart activity control, for it is known that the hypnosis and suggestion are connected with functions of the cerebral cortex.

At last, some persons, especially yogis, can change their heart rate or even temporarily stop their heart contractions at will. And it is known that voluntary acts are connected with cerebral cortex.

**Basic Principles of Hemodynamics. Blood Pressure. Arterial Pulse.**

**Blood Flow in Arteries, Capillaries, Veins**

Hemodynamics as a science studies the flow of blood in vessels. It is part of hydrodynamics - the section of physics studying the flow of fluids. To establish the laws of the blood flow in vessels hemodynamics uses the laws of hydrodynamics about the flow of fluids generally in tubes. But with that end in view it is necessary to take into consideration the special features of blood vessels, and in the first place - their elasticity.

The significance of vascular elasticity for the uninterrupted flow of the blood in vessels is well demonstrated in the simple experiment of Marey. By the help of the bulb the water from a cistern is pumped simultaneously into two tubes - the rubber tube and the glass tube. From the glass tube the water flows only when the bulb is pressed, but from the rubber tube – continuously. Because when the bulb is pressed, the rubber tube is filled with water and dilated. In the intervals between two pressings it is stricted owing to its elasticity and pushes the blood forward.

Identically in the cardiovascular system part of the kinetic energy which is developed by the heart during the systole, is expended on the strain of aorta and large arteries, that is, it is turned into the energy of elastic strain of arterial walls. During the diastole the strained arterial walls try to abate the tension and push the blood into capillaries. So, the blood flow is maintained during the diastole.

When Ohm’s law is applied, according to the laws of hydrodynamics the quantity of the fluid (Q) flowing through any tube is directly proportional to the pressure difference between two ends of the tube (P1-P2 = P) and inversely proportional to the resistance (R) against the flow of the fluid:

Q =∆P/ R

When this law is applied to the human vascular system it must be taken into consideartion that at the end of this system (where the venae cavae flow into the right atrium) the pressure is near zero. Therefore, the equation takes the following form, where the Q means quantity of the blood which is pumped by the heart per minute, i.e. volumetric velocity of blood flow or cardiac output, P - the mean pressure in aorta, R -the vascular resistance:

The pressure in aorta:

P = QR

This means that the pressure in aorta is directly proportional to the cardiac output and to the peripheral resistance.

Since it is possible to measure the pressure in aorta and cardiac output, it is easy to calculate such an important index of vascular system state as the **peripheral resistance**:

R=P/ Q

Dividing the volumetric velocity by the section area of the vessel one can calculate also the linear velocity of blood flow:

V= Q/πr2

According to the Poiseuille’s law:

Q=πR4/8η*l*

In this formula Q is the blood flow volumetric velocity, ∆P - pressure difference between the ends of the vessel, r - the radius of the vessel, *l* - the lenght of the vessel, η - the viscosity of the blood.

In this equation the blood flow velocity is directly proportional to the fourth power of the radius of the vessel. This fact illustrates once again that the diameter of a blood vessel plays the greatest role of all factors in determining the velocity of blood flow through the vessel.

Taking into consideration that P = QR:

R=8ηl/ πr 4

This means that the **vascular resistance** is derectly proportional to the lenght of the vessel and the viscosity of the blood, but it is inversely proportional to the radius of the vessel.

The vascular system consists of many separated tubes, connected in parallel or successively. When successively connected, the total resistance is equal to the sum of the resistances of each tube:

R = R1 + R2 + R3 +... Rn

When the tubes are connected in parallel, their total resistance is calculated by the following formula:

R=1/1 R1 +1 R2 +1 R3 +...+1 R n

Of course, the exact determination of the vascular resistance by these formulas is impossible. Because the diameter of vessels as well as the viscosity of blood are always changing.

The vascular wall’s properties are: elasticity, contractility, tonus and conductivity. In each vessel one or some of these properties are prevailing.

Therefore, the following 4 **types of blood vessels** are distinguished:

1) The compensative vessels - the aorta and the arteries of elastic type. Owing to their elasticity the blood pumped by the heart to the periphery is distributed evenly in the arteries.

2) The resistive vessels - arterioles and venules. The thickness of their walls is more than the size of the lumen and their smooth muscle fibers are always in state of tonus. Thanks to their function the total volume of the vascular lumen adapts itself to the volume of the circulating blood and the blood supply of the cells and tissues is provided according to their requirements.

3) The metabolic vessels - capillaries and venules. In these vessels the metabolism between the blood and the tissues is realized.

4) The volumetric vessels - the small veins. 75 - 80% of total amount of the blood in organism is accumulated in these vessels.

If all the vessels of greater circulation of each type were put side by side, their total cross - sectional areas would be as following: aorta - 2.5 cm2, small arteries - 20 cm2, arterioles - 40 cm2, capillaries - 2500 cm2, venules - 250 cm2, small veins - 80 cm2, venae cavae - 8 cm2.

The much (four times) larger cross-sectional areas of the veins than those of the arteries explain the very large storage of blood in the venous system.

Because the same volume of blood flows through each segment of the circulation each minute, the velocity of blood flow is inversely proportional to its cross-sectional area. Thus, under resting conditions, the velocity averages 33 cm/sec in the aorta but 1/1000 of this in the capillaries, or about 0.3 mm/sec. Since the capillaries have a length of only 0.3 - 1 mm, the blood remains in them for only 1-3 seconds and all diffusion that takes place through the capillary walls must occur in this exceedingly short time.

In the venous system the blood flow velocity increases again, but never reaching that of in aorta, because the cross - sectional area of venae cavae (8 cm2) is more than that of aorta (2.5 cm2).

Since the heart pumps blood continually into the aorta, the pressure in the aorta is high, averaging about 100 mm Hg. Because the pumping by heart is pulsatile, the arterial pressure fluctuates between a systolic level of 120 mm Hg and a diastolic level of 80 mm Hg.

The pressure in the capillaries of the greater circulation varies from 35 mm Hg near the arteriolar ends to 10 mm Hg near their venous ends. Their average “functional” pressure in most vascular beds is about 17 mm Hg.

The blood pressure falls progressively to approximately O mm Hg by the time it reaches the termination of the venae cavae in the right atrium.

With each beat of the heart a new surge of blood fills the arteries. But thanks to the combination of distensibility of the arteries and their resistance the pressure pulsation are reduced almost to zero by the time the blood reaches the capillaries and therefore, tissue blood flow is hardly affected by the pulsatile nature of heart pumping.

In the normal adult the pressure at the height of each pulse, the systolic pressure, is 110125 mm Hg and at its lowest point, the diastolic pressure, is 60-80 mm Hg. The difference between them, 35-40 mm Hg, is called the pulse pressure.

The systolic pressure is called also the maximal pressure and the diastolic pressure - the minimal pressure. The maximal pressure is created by the systole of ventricles, the minimal pressure is provided by the vascular tonus. Usually, they are indicated as a fraction, the numerator of which shows the maximal pressure and denominator - the minimal pressure. For example, 120/80 means that in this case the maximal pressure is 120 mm Hg and the minimal pressure - 80 mm Hg.

The high blood pressure is called hypertonia or hypertension and the low blood pressure - hypotony or hypotension.

The human blood pressure is measured by indirect means, most usually by the palpatory method of Riva-Rocci and the auscultatory method of Korotkov, usuing the sphygmomanometer (tonometer). In both cases a blood pressure cuff connected with the monometer is inflated around the upper arm. The cuff pressure is brought to the level when the pulse disappears.

In Riva-Rocci method further the cuff pressure is gradually diminished and simultaneously the pulse is palpated on the wrist. At the moment when the pulse appears, the manometer shows the maximal pressure. But it is hardly palpable thready pulse. The moment when the pulse becomes of normal size and fullness, the manometer shows the minimal pressure. But it is very difficult to determine this moment exactly. Therefore, the second method is used more frequently.

In auscultatory method when the cuff pressure is gradually diminished, simultaneously a phonendoscope (or stethoscope) is placed over the antecubital artery. The moment when the vascular sound is heard, corresponds to the maximal pressure. The sounds result from the whirlwind movement of the blood in the place where the vessel is restricted being pressed by the cuff. These sounds are called Korotkov sounds. When the artery’s diameter is recovered completely, the sounds disappear, and this moment corresponds to the minimal pressure.

Besides the systolic pressure the mean arterial pressure is also determined. This is the pressure between maximal and minimal pressures (not equal to the average of systolic and diastolic pressures, but nearer to the diastolic pressure, than to the systolic pressure) which could be able in the absence of the pulse fluctuations to provide the same hemodynamic effect that of natural fluctuating pressure. So, the mean pressure expresses the energy of the uninterrupted blood flow.

The mean pressure is measured by the method of Sechenov, applying the mercurial manometer with the tap between two elbows. The hole in the tap is narrow and this prevents the rapid fluctuations of the mercury during the systolic increase and diastolic decrease of the pressure. In this case the curve of the blood pressure is almost the straight line. The difference between mercury levels in two elbows of the tap corresponds to the mean pressure. The mean pressure in healthy adult persons is 90-95 mm Hg.

In experiment the blood pressure is recorded using the method of cannula insertion into an artery (usually into the common carotid artery). The cannula is connected with the mercurial manometer which helps to record the fluctuations of the pressure on the cylinder of kymograph.

In the **curve of blood pressure** 3 types of waves are distinguished.

The first degree waves or pulse waves are connected with the changes of pressure caused by heart contractions (systolic increase and diastolic decrease of the pressure), that is, they reflect the pulse pressure. The second degree waves are respiratory waves: inspiration is followed by the decrease of arterial pressure and expiration - by its increase. In some cases the third degree waves are observed. They are connected with periodical changes of vasomotor center’s tonus (Mayer waves or vasomotor waves). During the strong excitation of respiratory center the large respiratory waves (Traube - Hering waves) are recorded.

As it was already mentioned the arterial blood pressure depends on cardiac output and peripheral resistance (P = QR). Therefore, all the factors which increase the cardiac output lead to the rise of blood pressure, whereas the factors decreasing the cardiac output result in the fall of the pressure. For example, the volume of the circulating blood has a significant influence on the blood pressure. Its increase (the transfusion of a great amounts of blood) results in the rise of blood pressure and vice versa - when the volume of the circulating blood is diminished the blood pressure falls.

The peripheral resistance depends on the length and diameter of the vessels and blood viscosity

R = 8ηl/πr4

Although the diameter of the arterioles is lightly larger than that of capillaries, but they are longer and therefore, the maximal resistance against the blood flow is created by arterioles.

The dependence of blood presure on vascular diameter is demonstrated by the vagus narve stimulation which leads to vascular dilatation and the blood pressure falls.

More the blood viscosity - more the peripheral resistance and higher the blood pressure.

The rhythmical vibrations of arterial wall caused by increase of the pressure during systole are called the arterial pulse. The pulse may be observed on any superficial artery, especially on those located on the bony base.

The pulse wave appears in aorta during the ejection of blood from ventricle. The pulse wave spreading velocity does not depend on the blood flow velocity and even it is much more. The maximal linear velocity of blood flow is no more than 0.3-0.5 m/sec, whereas the pulse wave spreads with the velocity 5.5-9.5 msec.

The graphic recording of the arterial pulse wave is called **sphygmography**. In sphygmogram the ascending part - anacrotism and the descending part - catacrotism are distinguished. On the descending part the dicrotic rise or incisura is recorded.

The anacrotism is connected with dilation of the artery when it is filled with the blood during the systole. The catacrotism reflects recovery of the initial diameter of the artery during the diastole. The incisura reflects the opposite wave of the blood in aorta at the beginning of the diastole. This is the moment when the second heart sound occurs.

Studying the pulse one must pay attention to its rhythm, rate, velocity, fullness, tension and size or amplitude.

The pulse which reflects the normal heart activity is the rhythmic pulse. When the rhythm

is disturbed, the arrhythmia, i.e. the arrhythmic pulse is observed. The arrhythmia itself may be rhythmic or arrhythmic. In rhythmic arrhythmia one can reveal a certain regularity in the disturbance of the rhythm of the pulse.

The normal pulse rate corresponds to the heart rate: 60-80 beats per minute. In some cases this frequency may be increased (frequent pulse) or decreased (rare pulse).

Unlike the pulse rate which is the quantitative index, the pulse velocity characterises the ascent and descent of each pulse wave. The abrupt pulse and the slow pulse are distinguished.

The fullness of the pulse depends on the degree of filling of the arteries with the blood during systole. The full pulse and the deficient pulse are observed.

When palpating the pulse one feels the resistance of the artery to the fingers. This is called the tension of the pulse. The hard pulse and the soft pulse are distinguished.

The amplitude of pulse wave is very significant index. The large pulse, the small pulse and the thready pulse are observed.

The blood flow in different organs is not the same. For example, in thyroid gland it makes 560 ml per minute, in the brain - 65 ml per minute. The vessels of working organs dilate and the volumetric velocity of blood flow is increased.

Many methods were offered to determine the linear and volumetric velocity of blood in arteries. The more exact method is the ultrasonic method. On two points of the artery the piezoelectrical sensing elements are placed which convert the mechanical vibrations into the electrical ones and vice versa. Taking into consideration the difference in the speed of the ultrasound between these two elements in the direction of the blood flow and in the opposite direction, the linear velocity of the blood flow is calculated.

It is possible to determine the volumetric velocity of the blood flow by the method of occlusion plethysmography. The person puts his hand (or foot) into the plethysmograph. The pressure cuff is put on the hand and slightly inflated to let the arterial blood into the hand and not to let out the venous blood. The volume of the hand increases accordingly to the amount of the blood which flows into it. This amount is measured by the rise of the water’s level in plethysmograph and the volumetric velocity is calculated.

Although the capillaries are very small and short vessels (their diameter is 5-7 mcm, length 0.5-1.1mm), but they are innumerable and the total length of all the capillaries of human body is approximately 100 000km. Their total cross - sectional area is 1000 times more than that of aorta and therefore, the blood flow velocity decreases from the 33 cm/sec in the aorta to the 0.3mm/sec in capillaries. The total surface of capillaries is very large -1500 hectares. But in this surface there is only 250 ml of the blood.

All these circumstances promote the metabolism between the blood and intercellular fluid. More intensive the metabolism in tissue- more capillaries in1 mm of cross-sectional area. For instance, in the gray substance of brain there are considerably more capillaries than in the white substance.

In every organ the blood is flowing only in the capillaries which are “on duty”. During the intensive activity of the organ the number of functioning capillaries increases significantly.

In some areas of the body (skin, lungs, kidneys) there are arteriovenous shunts (anastomosis). When they are opened, part of the blood enters the veins passing by the capillaries.

The blood flow velocity in veins is more than in the capillaries and less than in aorta - 6-14 cm/ sec in veins of average calibre and 20 cm/sec in venae cavae.

In veins located near the thoracic cavity the pressure is close to zero. It changes depending on the phases of breathing and during the inspiration the pressure in these veins becomes negative, that is, lower than the atmospheric pressure. Therefore, the injury of these veins is very dangerous - the atmospheric air can enter the vein and cause an embolism which leads to the death.

The following factors promote the blood flow in veins:

1. pressure difference between the beginning and the end of the venous system;
2. existence of the valves;
3. contractions of skeletal muscles around the veins which, owing to existense of valves, promote the flow of the blood only in the direction to the heart;
4. pulsation of near - by artery, which also promotes the blood flow to the heart;
5. sucking effect of the atria caused by the negative pressure during the systole of ventricles when the atrioventricular septum is pulled down.

In the large veins near the heart (for example, in jugular veins) the venous pulse is recorded **(phlebogram)**. Its origin is absolutely different from the arterial pulse. In the phlebogram the a, c, v waves are distinguished.

The ***a*** wave is recorded during the contraction of atria when the openings of venae cavae are closed and the blood flow from them into the right atrium is stopped. Therefore, the venae cavae are dilated. The ***v*** wave is recorded during the contraction of ventricles when the blood cannot enter from atria into ventricles and from venae cavae - into atria. The ***c*** wave reflects the pulsation in the common carotid artery.

The time that blood needs to pass through the greater and lesser circulations is called the time of the complete circuit of the blood. When the heart rate is 70-80 beats per minute the time of complete circuit of the blood makes approximately 20-23 seconds This corresponds to 27 systoles of the heart. 4/5 of this time falls on the greater circulation and 1/5 - on the lesser circulation.

To determine the time of the complete circuit of the blood a substance is injected into the vein which has certain marked physiological effect, but does not exist in the blood, and the time is measured when it causes the characteristic effect.

For instance, into the ulnar vein the lobeline is injected which influences the respiratory center and the time is measured when it causes the cough (after accomplishing the complete circuit the lobeline effects the respiratory center).

Up-to-date method consists of sodium radioactive isotope injection into the cubital vein. Then by the help of the electronic counters the time is determined when the radioactive radiation appears in the area of heart and different vessels.

**Regulation of Blood Flow in Vessels. Regulation of Circulating Blood Volume.**

**Blood Circulation in Heart and Lungs. Flow of Lymph. Microcirculation**

The central and local mechanisms regulating circulation are distinguished. The central mechanisms determine the level of arterial pressure and the systemic circulation. The local mechanisms regulate the level of blood flow in separate organs and tissues.

This division is conventional, because the cantral mechanisms take part in realizetion of local regulation processes, and control of the systemic ciculation depends on activity of the local regulatory mechamisms.

Constancy of arterial blood pressure is maintained owing to exact correspondence between stroke volume and total peripheral resistance of vascular system which depends on the vascular tonus.

The vascular tonus is due to the follwoing factors:

 Owing to existence in some areas of vascular wall smooth muscles the automatism foci which generate the rhythmical impulses, these muscles are always partly contracted, that is, they are in the state of basal tonus.

 Vascular wall smooth muscles are under constant influence of the tonic impulses coming by the sympathetic nerves.

In 1871 Ovsyannikov established that the vasomotor center is located in medulla oblongata.

Localization of the vasomotor center was determined by the way of the brain stem section on different levels. When the section is made higher than lamina quadrigemina the arterial pressure does not change. But the section between the medulla oblongata and spinal cord causes fall of the pressure.

The **vasomotor center** is located in the medulllla oblongata at the bottom of the fourth ventricle of the brain. It consists of the following areas all of which are located bilaterally:

 Vasoconstrictor area (pressor center)-in the anterolateral portions of the upper medula oblongata. The neurons of this area secrete norepinephrine and their fibers are distributed throughout the spinal cord, where they excite vasoconstrictor neurons of the sympathetic nervous system.

 Vasodilator area (depressor center) - in the anterolateral portions of the lower half of the medulla oblongata. The fibers from these neurons project upward to the vasoconstrictor area and inhibit vasoconstrictor activity of that area, thus causing vasodilation.

 Sensory area - in the tractus solitarius in the posterolateral portions of the medulla oblongata and lower pons. The neurons of this area receive sensory nerve impulses mainly from the vagus and glossopharyngeal nerves and the impulses from this area help to control activity of both the vasoconstrictor and vasodilator areas. Thus, reflex control of many circulatory functions is provided.

Stimulation of the pressor center causes constriction of the arteries and increase of the pressure, but when the depressor center is stimulated the arteries are dilated and the pressure falls.

**The vasoconstrictive center** of the medulla oblongata influences on the nervous centers of the sympathetic part of the vegetative nervous system which are located in the side horns of the throracal segments of the spinal cord. Here are the vasoconstrictive centers regulating the tonus of vessels in different parts of the body. After cessation of medulla oblongata vasoconstrictive center’s activity the spinal cord centers are capable to maintain the pressure in a certain degree.

**The vasodilative center** of the medulla oblongata realizes its influence through parasympathetic part of the vegetative nervous system.

Activity of vasomotor center is under the control of the higher nervous centers. Stimulation of many areas of the reticular substance of the pons, mesencephalon and diencephalon either excites or inhibits the vasomotor center. The hypothalamus plays a special role in the control of the vasoconstrictor system. The posteriolateral portions of the hypothalamus cause mainly excitation, whereas the anterior part can cause mild excitation or inhibition, depending on the precise part of the hypothalamus stimulated.

Different parts of the cerebral cortex, when stimulated, excite or inhibit the vasomotor center (motor cortex, anterior temporal lobe, the orbital areas of the frontal cortex, the anterior part of the cingulate gyrus, the amygdala, the septum, the hippocampus).

The vasoconstrictive effect of the sympathetic nerves was first revealed by Walter in 1842. He cut the sciatic nerve of frog on one side and then both hind limbs were cut on the same level. The denervated limb was bleeding more strongly. This means that its vessels, being released from the constrictive effect of the sciatic nerve’s sympathetic fibers, were dilated. When the severed nerve’s peripheral end is stimulated, the bleeding diminishes because of vasoconstriction.

In 1852 Claude Bernard cut the sympathetic nerve on one side of rabbit’s neck. The rabbit’s ear on that side was growing red and warmer, its volume slightly increased. This is a result of the vasodilation after the denervation when more blood is flowing into the ear. Indeed, the electrical stimulation of peripheral end of severed nerve has an opposite effect caused by vasoconstriction: the ear becomes pale, its temperature and volume are diminished.

Vasodilation was first revealed when some nerve branches belonging to the parasympathetic part of the vegetative nervous system were stimulated. For example stimulation of chorda tympani causes vasodilation in submaxillary gland and tongue.

On the whole, the vasoconstriction is realized by the sympathetic nerves which constrict all the vessels of the body with the exception of the coronary arteries of the heart, brain arteries and the arteries of the working muscles (which are dilated under the stimulation of sympathetic nerves). For instance, the main vasoconstrictive nerves of the abdominal cavity organs are sympathetic fibers which pass in the n. splanchnicus.

The vasodilation is realized by the parasympathetic nerves (mainly by the vagus nerves) which dilate all the vessels of the body with above - mentioned exception.

In the nerve endings of sympathetic vasoconstrictors adrenaline and norepinephrine are secreted, that is, they are adrenergic fibers. But the vasodilators (parasympathetic fibers as well as sympathetic ones) are of cholinergic nature, that is, in the nerve endings of these fibers acetylcholine is secreted. The histaminergic vasodilators also were revealed.

The arteries and arterioles are always in the state of tonus, that is, they are constantly constricted in a certain degree. This arterial tonus is due to the tonus of the vasomotor center in medulla oblongata which constantly sends impulses to the arteries and arterioles by the sympathetic nerves. Vasomotor center’s tonus is maintained by the impulses from the mechanoreceptors (pressoreceptors, baroreceptors) located all over the body and by the humoral (chemical) stimulants which influence directly the vasomotor center. Thus, the vasomotor center’s tonus is of reflex as well as humoral origin.

**The pressor or hypertensive reflexes** (constricting the arteries and arterioles and increasing the blood pressure) and depressor or hypotensive reflexes (dilating the arteries and arterioles and decreasing the blood pressure) are distinguished.

All the vascular reflexes are divided into two groups:

1. The proper reflexes - they are caused by the impulses from the receptors of the blood vessels themselves.
2. The conjugated reflexes - they are caused by the impulses from other systems and organs (for instance, irritation of the skin). These reflexes lead mainly to increase of the blood pressure.

The most important vascular **reflexogen zones** are aortic arch and carotid sinus. When the arterial pressure rises, pressoreceptors (baroreceptors) of these areas are irritated and the impulses set off to the central nervous system - from the carotid sinus by Hering’s nerve (sinocarotid nerve) and from the aortic arch by the depressor nerve of Cyon and Ludwig. Tonus of vasoconstrictor center is decreased, tonus of vagus nerves, on the contrary, increases and this results in fall of blood pressure.

Some experiments demonstrate significance of above - mentioned reflexogen zones in the normalization of blood pressure. Injection of blood through the cannula into the isolated carotid sinus under pressure causes fall of arterial pressure in the body. If sinocarotid or depressor nerves are cut in both sides, the stable hypertension occurs (200-250 mm Hg in place of normal 100-120 mm Hg in the carotid artery of dog).

Fall of arterial pressure decreases intensity of irritation of the aortic arch and carotid sinus receptors, influence of depressor and sinocarotid nerves on the vagus center weakens, arteries are constricted and blood pressure is normalized. This is regulation by the principle of negative feedback.

Increase of the pressure in the arteries of lungs, intestine, spleen also cause the reflex changes of the blood pressure in other areas of the body.

In the aortic and carotid bodies besides the pressoreceptors there are also chemoreceptors which are sensitive to the carbon dioxide and the deficiency of oxygen in the blood. They are irritated also by carbon monoxide, nicotine, cyanides. The impulses from chemoreceptors are conducted to the vasomotor center and cause the reflex vasoconstriction and increase of pressure. The chemoreceptors are revealed also in the vessels of the spleen, kidneys, bone marrow, adrenal glands. They are sensitive to different chemical combinations circulating in the blood (adrenaline, acetylcholine and so on).

So, irritation of the mechanoreceptors of the aortic arc and carotid sinus causes depressor reflexes, whereas irritation of the chemoreceptors of the same areas results in pressor reflexes. The humoral regulation of vascular tonus is realized by many substances circulating in the blood which are capable to change tonus of blood vessels (hormones, mediators, electrolytes and so forth).

The vasoconstrictive substances are: norepinephrine and epinephrine (adrenaline), vasopressin, angiotensin, serotonin.

Epinephrine and norepinephrine are hormones of adrenal medulla, they are also the sympathetic mediators. Epinephrine and norepinephrine constrict arteries and arterioles of skin, abdominal cavity organs, lungs.

Norepinephrine is an especially powerful vasoconstrictor hormone; epinephrine is less powerful and in some instances even causes mild vasodilation (in heart to dilate the coronary arteries during increased heart activity).

Angiotensin is one of the most powerful vasoconstrictor substances. As little as one millionth of a gram can increase the arterial pressure of human as much as 50 or more mm Hg.

When the arterial pressure falls too low, a small protein enzyme called renin is released by the kidneys. It acts on another plasma protein - angiotensinogen to release angiotensin I. Angiotensin I has mild vasoconstrictor properties but not enough to cause significant functional changes in circulatory function. Within a few seconds after formation of the angiotensin I it is converted into angiotensin II in the small vessels of lungs. Andiotensin II is an extremely powerful vasoconstrictor and has other effects as well that affect the circulation. But it persists in the blood only for a minute or two because it is rapidly inactivated by multiple blood and tissue enzymes collectively called angiotensinase.

Angiotensin II has two principal effects that can elevate arterial pressure:

1. Vasoconstriction - occurs very rapidly-very intensely in the arterioles and to considerably less extent in the veins.
2. The effect on the kidneys to decrease excretion of both salt and water. This increases the extracellular fluid volume, which then increases the arterial pressure slowly over a period of hours and days.

Vasopressin (antidiuretic hormone) is the hormone of the posterior pituitary gland (but it is formed in the hypothalamus). It constricts mainly the arterioles and capillaries. Vasopressin is the body’s most potent constrictor substance. It is even more powerful than angiotensin.

Serotonin is present in large concentrations in the chromaffin tissue of the intestine and other abdominal structures, in the platelets, brain and so forth. Serotonin can have either a vasodilator or a vasoconstrictor effect, depending on the condition or the area of the circulation.

The **vasodilative** substances are: acetylcholine, medullin, prostaglandins, bradykinin, histamin.

Acetylcholine is secreted as mediator in the endings of parasympathetic nerves and sympathetic vasodilators. But it is rapidly destroyed in the blood and therefore, it has only local effect on the blood vessels.

Medullin is produced in the medulla of kidney.

Several chemically related substances called prostaglandins are present almost in every tissue of the body to moderate amounts. Some of them are released into the local tissue fluids and into the circulating blood under both physiological and pathological conditions. Although some of the prostaglandins cause vasoconstriction, most of the more important ones seem to be mainly vasodilator agents.

Bradykinin is one of the kinins that are frequently formed in the blood and tissue fluids (submaxillary gland, pancreas, lungs and so on) where is also an enzyme kallikrein. Kallikrein promotes releasing of a kinin kallidin which is converted by tissue enzymes into bradykinin. Bradykinin causes very powerful arteriolar dilatation and increases capillary permeability. Even small amounts of bradykinin injected locally into tissues can cause marked edema bacause of the increase in capillary pore size.

Histamine is released in every tissue when it becomes damaged, inflamed or is the subject of an allergic reaction. Most of the histamine is derived from mast cells in the damaged tissue and from basophils in the blood. It has a powerful vasodilator effect on the arterioles and also considerably increases capillary porosity, allowing leakage of fluid and plasma protein into the tissues. This induces edema in many pathological conditions.

The reddening of the skin under the influence of different irritants (rubbing of the skin, the thermal influence,ultraviolet irradiation) is also explained by the effect of histamine which is intensively produced.

Injection of histamine in large doses causes sharp decrease of arterial pressure, disorders in the cerebral circulation and disturbance of central nervous system activity, i.e. the histamine shock is developed.

 Many different ions and other chemical factors can either dilate or constrict local blood vessels. An increase in calcium ion concentration causes vasoconstriction as the result of the calcium’s general effect to stimulate smooth muscle contraction. An increase in potassium ion concentration, as well as that of magnesium and sodium, causes vasodilation.

Both acetate and citrate as only anions to have significant effect on blood vessels, cause mild degree of vasodilation.

An increase of carbon dioxide concentration causes moderate vasodilation in most tissues and marked vasodilation in the brain. But acting on the vasomotor center, it has an extremely powerful indirect vasoconstrictive effect.

When the function of any organ is strengthened the metabolism processes become more intensive, concentration of metabolism products (carbon dioxide and carbonic acid, adenosine diphosphate, adenosine monophosphate, phosphoric acid, lactic acid and so on) in blood is increased and this results in dilation of vessels in working organ. So, these substances take part in the local mechanisms of regulation of circulation.

But many of these substances, reaching the vasomotor centers and increasing their tonus,exercise the opposite influence on the vessels. Such generalised increase of vascular tonus leads to rise of systemic blood pressure when the blood flow through working organs is significantly increased. For instances, in skeletal muscles in resting state there are 30 open (functioning) capillaries per sq millimetres of cross-sectional area, whereas during maximal muscular work this number is increased 100 times.

During intensive physical work the cardiac output can increase no more than 5-6 times. Therefore, the hundredfold increase of blood supply of working muscles is possible only by the way of redistribution of blood. The intesive muscular work causes reflex vasoconstriction in the organs of digestion and more blood is flowing into the muscles. Vasodilatation in the working muscles is reached not only by the local effect of metabolic products, but also by the reflex way. For example when one hand is working the vasodilatation is observed not only in this hand, but also in the other hand and even in legs.

T he muscle contraction itself as a mechanical factor promotes increase of local circulation. Humoral factors are also significant. For instanse, adrenaline considerably increases the systemic arterial pressure. But the vessels of working muscles and brain do not constrict under the influence of adrenaline and their blood circulation is improved.

Identically, when the brain activity is increased, more blood is flowing into the brain. This can be easily demonstrated in the following way. The person is balanced on the scales of Mosso and he is offered to solve a difficult problem. When he is intensively thinking over the problem his head becomes heavier and the balance is disturbed.

After the meal more blood flows into the digestive organs and the blood supply of the brain is aggravated. That’s why after the meal one is sleepy.

Redistribution of the blood occurs also when one changes his position from the horizontal to the vertical. Because the outflow of the venous blood from the legs becomes difficult and blood flow into the heart diminishes considerably.

For the normal blood supply of organs and tissues and the maintenance of the constant blood pressure certain ratio between the volume of the circulating blood and total capacity of all vascular system is necessary. This is reached by the number of nervous and humoral mechanisms of regulation.

In resting state of organism not more than 50-55% of all the volume of the blood is circulating, because the remaining 45-50% is accumulated in blood depots, i.e. in the spleen, liver, subcutaneous vascular plexus and lungs.

The reservoir function of spleen is realized owing to existence of the venous sinuses in it which have sphincters and can hold a large amounts of blood. In the vessels of the spleen the blood is thickened and it can hold 1/5 of all the erythrocytes of the organism. Therefore, the spleen is the main depot of erythrocytes. But the spleen is also the cemetery of the obsolete erythrocytes which are destroyed by the lymphoreticulohistiocytic system cells. These cells also absorb and render harmless the heterologous particles, bacteria, viruses, toxins.

In the spleen antibodies are produced, lymphocytes and monocytes are formed. So, the spleen is the important organ of immunity and fulfils also the hemopoietic function. But the hemopoietic function is completely realized in the fetus.

The large branches of the hepatic vein also have sphincters. But the blood in the liver is not excluded from circulation, only its flow is slowed down. The liver’s function as blood depot is regulated by reflex way.

All the venous system and especially the veins of skin also fulfil the role of blood depot. In

such states of organism as muscular work, loss of blood, hypoxia, carboxyhemoglobinemia, chloroform or ether anesthesia the blood leaves depots and the circulating blood volume increases.

When the circulating blood volume is decreased, for example, as a result of loss of blood, flow of the blood into the heart diminishes and the blood pressure falls. As a response to these changes other reactions of the organism also occur directed to normalization of blood pressure. First of all, by the reflex way the arteries are constricted and secretion of vasoconstrictive hormones (adrenaline, vasopressin) is intensified. Kidneys secrete more renin and this results in formation of large amounts of angiotensin II. Angiotensin maintains the arterial pressure not only by constricting arterioles, but also stimulates secretion of aldosterone by adrenal cortex. Aldosterone increases reabsorption of both sodium and water in tubules of kidneys and this way promotes recovery of the circulating blood volume. The heart rate is increased and the heart muscle contractions are strengthened by reflex way.

Thanks to these neurohumoral changes during the rapid loss of the 20-25% of the blood for a short time the sufficient level of blood pressure can be maintained.

The precise regulation of the vascular tonus and adaptation of the vascular system to different complicated situations are reached by the cortical control.

All above - mentioned facts about the cortical control of heart activity equally concern the cortical control of the vascular tonus and blood pressure.

Influence of the cerebral cortex on the blood vessels was first proved by the way of stimulation of certain areas of the brain.

The cortical vascular reactions in man were studied by the conditioned reflex method using the plethysmograph which permits to judge about changes of the vascular tonus: when arteries are constricted volume of the organ is decreased and vice versa.

The blood pressure is increased in sportsmen before competitions and in students before exams.

The negative as well as the positive emotions cause increase of the blood pressure.

The blood circulation of each organ and tissue is distinguished by its individual physiological peculiarities.

The blood supply of the heart is realized by coronary arteries. Unlike all other organs and tissues which receive the blood during systole of the heart, the heart itself receives the blood by coronary arteries mainly during the diastole. Because during the systole the contracted myocardium presses the vessels located in it and the coronary circulation weakens considerably.

Through the coronary arteries 200-250 ml of blood flows per minute and this makes approximately 4-6 % of cardiac output. During the physical work the coronary blood flow can increase up to 3-4 litres per minute. The heart extracts more oxygen from the blood than other organs. Myocardium is very sensitive to the oxygen deficiency which causes heart pain and disorder in heart activity.

At present it is supposed that sympathoadrenal effects on coronary arteries may be double (constriction or dilatation) depending on the concentration of catecholamines in the coronary blood and the character of receptors (α - or β-adrenoreceptors). Under the parasympathetic influences the heart activity is suppressed and the coronary blood flow is diminished.

Lungs receive the blood by both greater and lesser circulations. The lesser circulation through the pulmonary trunk delivers the venous blood into the capillaries of pulmonary alveoli for the respiratory gaseous exchange. The greater circulation through the bronchial arteries supplies the arterial blood for the tissues of lungs themselves. The blood passing through the bronchial arteries is much lesser than that of passing through the pulmonary arteries and it is no more than 1-2% of cardiac output.

Diameter of the pulmonary arterioles is 80 mcm, that of in the greater circulation - no more than 12 mcm. Therefore, resistance to blood flow in the arterioles of lesser circulation is tenfold lesser than that of in greater circulation and the right ventricle develops much lower pressure than the left ventricle. The maximal blood pressure in the pulmonary trunk is 25-30 mm Hg, the minimal pressure - 5-10 mm Hg, the pulse pressure - 15-20 mm Hg and the mean pressure - 5-6 times lesser than that of in aorta.

The total surface of the pulmonary capillaries is large (140 m2), the blood flow in them is much slower that that in the greater circulation and this promotes the gaseous exchange. Erythrocytes pass through the pulmonary capillaries during 0.7 sec.

There are the mechanisms regulating correlation between the ventilation and blood circulation of the lungs. Cutting of the alveoli from the ventilation causes spasm of their arteries. Therefore, the blood flows only through the ventilated alveoli and the blood flowing off the lungs is always maximally (94-96%) saturated with the oxygen.

The most purposeful function of the circulation-transport of nutrients to the tissues and removal of cellular excreta - occurs in the microcirculation. The microcirculation is directed flow of different fluids of the organism (blood, lymph, tissue and cerebrospinal fluids and so on) in the microscopic (blood and lymphatic) vessels, intercellular space and around the tissue microsystems. The microcirculatory system consists of the following parts:

**1)** arterioles, venules, precapillaries, true capillaries, arteriovenous shunts (anastomosis); **2)** interstitial pathways of transport of the substances; **3)** lymphatic pathways.

The average capillary pressure at the arterial ends of the capillaries is 15-20 mm Hg greater than that of at the venous ends. Because of this difference, fluid “filters” out of the capillaries at their arterial ends and then is reabsorbed into the capillaries at their venous ends. Thus, a small amount of fluid actually “flows” through the tissues from the arterial ends of the capillaries to the venous ends.

Almost a century ago Starling pointed out that under normal conditions amount of the fluid filtering outward from some capillaries equals almost (but not quite) exactly the quantity of fluid that is returned to the circulation by absorption through other capillaries. The very slight disequilibrium that does occur accounts for the small amount of fluid that is eventually returned by the way of the lymphatics.

The lymphatic system represents an accessory route by which fluids can flow from the interstitial spaces into the blood. The lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillary. This removal of proteins from the interstitial spaces is an absolutely essential function, without which we would die within about 24 hours.

Almost all tissues of the body have lymphatic channels that drain excess fluid directly from the interstitial spaces. All the lymph from the lower part of the body (most of that from the legs) as well as from the left side of the head, the left arm and the parts of the chest region enters the thoracic duct. Lymph from the right side of the neck and head, from the right arm and from parts of the thorax enters the right lymph duct. Both thoracic and right lymphatic ducts then empty into the venous system.

Unlike the blood, the lymph flows only in one direction (from the tissues to the heart) and passes through the lymph nodes where the heterologous particles (for instance, bacteria) are removed and destroyed.

The lymph is colourless and almost pellucid fluid. 6-8 hours after the fatty meal it becomes opaque and of milky colour. The pH of lymph is alkaline. Containing the fibrinogen, the lymph is able to coagulate. Since the lymph contains 3-4 times lesser proteins, its viscosity is also lesser than blood viscosity. The lymph does not contain erythrocytes, there are few granulocytes and in the lymph of thoracic duct-many lymphocytes which are formed in lymph nodes.

Lymph as it first flows from each tissue has almost the same composition as the interstitial fluid. The protein concentration of lymph flowing from most tissues is near 2 gm/dl. Lymph formed in the liver has a protein concentration as high as 6 gm/dl, and lymph formed in the intestines - 3-4 gm/dl. Because about two thirds of all lymph is derived from the liver and intestines, the thoracic lymph, which is mixture of lymph from all areas of the body, usually has a protein concentration of 3-5 gm/dl.

The lymphatic system is one of the major routes for absorption of nutrients from the gastrointestinal tract, being responsible principally for the absorption of fats. After a fatty meal thoracic duct lymph sometimes contains as much as 1-2% fat.

Formation of lymph is connected with passing of the water and some substances dissolved in the blood plasma from blood capillaries into tissues and from the tissues into the lymphatic capillaries.

In the fiftieth of last century Ludwig first explained the mechanism of lymph formation. He considered that this process is connected with the filtration of the fluid through the capillary wall and the motive power of the filtration is the hydrostatic pressure difference. Starling developed the filtration theory and pointed the significance of the osmotic pressure difference.

According to the ideas of today the wall of blood capillaries is semi-permeable membrane and through its ultramicroscopic pores the filtration occurs. For instance, the permeability of liver capillaries’ wall is higher and therefore, more than half of the thoracic duct lymph is formed in the liver. Permeability of blood capillaries may be changed under the influence of lymphogen substances (the extracts of crayfishes leeches, peptones, histamine and so on) which increase the lymph formation.

In normal conditions there is a balance between the velocity of lymph formation and the velocity of lymph outflow are almost the same that of venous blood flow: negative pressure in the thoracic cavity, the existence of valves, the contractions of the surrounding muscles and so forth. Besides, some lymph vessels’ walls contract rhythmically 8-22 times per minute.

The lymph flow velocity is very low. In the cervical lymphatic vessel of the horse this velocity is equal to 240-300 mm per minute, whereas in the veins the blood passes this distance during 1-2 sec.

The sympathetic fibers constrict the lymph vessels. The lymph flow is changed also by reflex way (painful irritations, increase of pressure in carotid sinus).

In a day 1000-3000 ml of lymph returns into the blood through the thoracic duct.

Microcirculation includes movement of blood and lymph, cellular fluids (transcapillary metabolism) cerebrospinal and interpleural fluids, juices of the glandular tissues, different substances dissolved in the tissue fluids. Such processes as exudation, resorption of the products that are formed in the necrotic areas, are also connected with microcirculation.

Functional units of microcirculation are tissue microsystems (the functional elements of organs), that is, cells, nerve endings, connective tissue fibers which are connected with each other and are situated around the microscopic vessels, and the intertitial substances that isolates them from other cells.

The main part of the tissue microcirculation is microhemocirculation, the anatomic basis of which is formed by arterioles, precapillaries, capillaries, postcapillaries, venules and arteriovenous anastomoses. When capillaries change from functioning state into resting state, before their lumen is completely closed, they turn into the plasmatic capillaries, that is, in them only plasma is moving, and they do not contain blood cells.

According to Starling’s theory there is dynamic equilibrium between the volumes volumes of fluid which passes from the arterial part of the capillaries into intercellular space by the way of filtration and that of reabsorbed in the venous part of the capillaries. Disturbance of this equilibrium leads to rapid transference of the intravascular and intervascular fluids which causes disorders in the activity of the cardiovascular system.

The hydrostatic pressure in capillaries (Phc) and oncotic pressure of the intercellular (tissue) fluid (Pot) promote the filtration (Phc + Pot), whereas hydrostatic pressure of the intercellular fluid (Pht) and oncotic pressure of the plasma in capillaries (Poc) prevent it (Pht + Poc), that is, these promote the reabsorption. Volume of the fluid which is filtrated or reabsorbed during 1 minute may be determined by the following formula:

V = K[(Phc + Pot) - (Pht + Poc)] (+V) shows filtration and (-V) - reabsorption.

The average values of above - mentioned pressures are given in the following table.

|  |  |  |
| --- | --- | --- |
| Capillaries  | Pressures (mm Hg)  |  |
| hydrostatic  | onc | otic  |
| in capillaries  | in tissues  | in capillaries  | in tissues  |
| Phc  | Pht  | Pot  | Poc  |
| Arterial part  | 32.5 17.5  | 3  | 25  | 4.5  |
| Venous part  |

Not taking into account the coefficient K, we can use the formula for orientation in the direction of processes going on in the arterial and venous parts of the capillaries. In the arterial part of the capillaries: V = (32.5 + 4.5) - (3 + 25) = 9 (Filtration pressure = 9 mm Hg).

In the venous part of the capillaries: V = (17.5 + 4.5) - (3 + 25) = -6. (Reabsorption pressure = 6 mm Hg).

Since the reabsorption pressure is somewhat lower than the filtration pressure, only 90% of the filtrated fluid is reabsorbed, and the rest 10% passes into lymphatic vessels.

From all the capillaries of the organism altogether 14 ml of fluid is filtrated per minute and 20 l daily, whereas volume of the reabsorption is 12.5 ml per minute and 18 l daily. So, 2 litres of the filtrated fluid is transported in the lymphatic vessels daily.

Decrease of the oncotic pressure of plasma (in hypoproteinemia) accelerates filtration, whereas its increase (in hyperproteinemia) results in acceleration of reabsorption. The factors which increase capillary permeability (kinins, histamine, histamine-like agents etc.) accelerate passage of fluid from the vessels into intercellular space.