KHAZAR UNIVERSITY

Nizhad Jabrayil oglu Mikayilzade

HUMAN PHYSIOLOGY
Lectures

To my beloved granddaughter Aydan

PREFACE

These are the complete texts of the 48 lectures delivered by the author in Khazar University. They embrace the course of human (normal) physiology program in medical universities and medical faculties of universities.

Before publishing these lectures the author had to decide the question: is there any necessity to publish them, whereas there are many physiology textbooks, including those in English? The answer was positive, and here are the arguments for it.

To begin with, we have the foreign editions in limited quantities, insufficient to provide each student. Thanks to Khazar University, I had an opportunity to use the well-known over the world "Textbook of Medical Physiology" by A. C. Guyton. This book was repeatedly republished and has been translated into many languages. Formerly, all our Khazar University students – foreigners that read it, insisted on publishing my lectures. Because as fine and detailed a textbook as Guyton's is, but they could not find in this book some problems of the physiology such as chronaxy, polar rule of excitation and dominant, the rules of transmission of excitation, etc. Instead, the book is overload by the problems of anatomy, histology, pathophysiology.

The chapter "higher nervous activity" is completely absent. Evidently, it was considered as a part of psychology. But the higher nervous activity was first studied profoundly on the scientific basis just by physiologists and its principal problems, such as conditioned reflexes, temporary connections, internal inhibition, purposeful activity, signaling systems, etc. are purely physiological problems. They must be explained just in physiology textbooks.

Taking into consideration that there is not a special textbook of physiological laboratory studies in English, description of experiments is given immediately after the text of corresponding lectures.

The book is supplied with English-Azerbaijani-Russian dictionary of physiological terms compiled by the author.

I am grateful to the founder and chancellor of Khazar University prof. Hamlet Isaxanli for the opportunity to deliver lectures in this university and publish the texts of my lectures.

I express my thanks to the dean Nigar Bagirova and Adelya Tumanova for their support and help in publishing my lectures.

I thank beforehand all the readers that will send me their critical remarks and wishes in connection with this book.

Nizhad Mikayilzade,
associate professor

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INTRODUCTION

Lecture 1

The Subject of Physiology and its Relation to other Disciplines.
The Methods of Physiology. Evolution 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 functio ns, 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 human 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.

Since in every life process such physical and chemical processes as conversions of substances and energy take place, it is natural that the physiology is closely connected with physics and chemistry. In result of physical and chemical directions in research of life processes

two independent disciplines - the biophysics and the biochemistry were formed.

To study the functions or organs one must first know their morphological peculiarrities. 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.

The relation of physiology and engineering was useful for both of them. On the one hand, the physiology applies the technical methods in its experiments. On the other hand, the employment of the principles and methods acting in organism is very perspective for technical progress. In this way, the new science, i. e. the bionics was born.

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.

Development of modern engineering and technology has good prospects for physiology to improve, vary and diversify its methods.

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 physiology has passed a long way of evolution. It is known that in ancient times there were not so many sciences as today and the great scientists of ancient East and West had encyclopaedic knowledge in all sciences. These scientists expressed their opinions in the field of philosophy and literature, as well as mathematics and medicine. It is true, that many of their ideas were erroneous, even fantastic, but to-day every specialist can find among them some rational and sane ideas concerning his own branch of science. Though the physiology as a science was shaped on the XVII century, some ideas of great eastern and western scientists of ancient times can be attributed to physiology. As far back as in the VI-V centuries BC Alkmeon carried out anatomical and physiological investigations. He the first gave the natural philosophy conception of human body as a microcosm and the balanced system of opposites.

Empedocle (490-430 BC) affirmed that man has passed a long way of evolutionary development.

Hippocrates (460-377 BC) distinguished four types of human body constitution. He classified the environmental factors from the view of their influence on human organism. Hippocrates considered that the physician must not treat the disease, but he must take into account the environment, individual peculiarities of organism and treat the concrete patient. It is a pity that this principle, which was shared also by Ibn Sina, now is forgotten and is ascribed to Russian therapeutist Mudrov who lived in the XVIII-XIX centuries.

Aristotle's (384-322 BC) service to biology and physiology is the doctrine of the biological expediency.

Galenus (130-201 AD) is the initiator of experimental medicine.

Al-Farabi (870-950) stated that the outward signs of things are perceived by senses, but their essence can be known only owing to the intellect.

Al-Biruni (Aliborono -973-1048) shared the views affirming that it is possible to cognize the nature by the help of organs of sense.

Ibn-Sina (Avicenna -980-1037) attached great importance to the influence of the external factors on organism. He made suppositions about the invisible agents of diseases. He knew the pulse perfectly.

Ibn an Nafis (1210-1288) formed the first real opinion about the lesser circulation. He the first dared to state that blood passes from right ventricle of the heart to the left one not through interventricular septum as Galenus tried to prove, but through lungs.

We can find some valuable ideas also in the works of great Azerbaijan poets-philosophers Nizami Ganjevi (1141-1209), Mahmud Shabustari (1287-1320), Mohammed Fizuli (1494-1556) and others.

These separate ideas, though very valuable, do not make the science. 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).

Formation of physiology just in this period was not by chance. Because in these centuries in Europe the trade relations between countries widened, the new markets were mastered, navigation and communication were developing. The feudalism was replaced by capitalism. A blow to the prestige of church favoured the flourishing of sciences.

On the other hand, the journeys and migration of population at a great distance, rise of big towns caused the epidemics of acute infectious diseases, the new diseases appeared. All this set the medicine urgent tasks. Till that time thanks to self-sacrificing work and achievements of Servetus (1511-1553), Vesalius (1514-1564), Colombo (1516-1559), Fallopius (1523-1562) the anatomy was developed significantly, the structure of organs was well studied. This prepared the ground for the development of physiology.

At that period in physiology, as well as generally in medicine such trends as iatrophysics and iatrochemisrty, mechanism, vitalism and metaphysics dominated.

They delayed the development of science, but all the same in the XVII-XVIII centuries some discoveries were made in physiology. The greatest discoveries in physiology of that period were made by R. Descartes (1596-1650) and L. Galvani (1737-1798). Descartes discovered the reflex and formulated the principle of reflex activity of nervous system. Galvani discovered "animal electricity", that is, bioelectric phenomena.

But iatrophysicists and iatrochemists also achieved some results by the way of employment of methods of physics and chemistry with the purpose of studying the life processes.

Borelli studied the mechanism of respiratory movements and significance of diaphragm for breathing. He applied the laws of hydraulics to study the movement of blood in vessels. Hales determined the role of retina in the origin of visual sensation. Reamur and Spallanzani investigated the chemism of digestion. Lavoisier and Laplace measured the power outlay of organism. Haller for the first time investigated in detail the excitability and sensitivity.

In the XIX century some discoveries and achievements in natural sciences accelerated development of the physiology: proof of the law of conservation and conversion of energy (Mayer, Joule, Helmholtz), synthesis of the first organic combination (urea) out of organism (Wohler), discovery of the cell (Schleiden and Schwann), creation of the doctrine of evolution (Darwin). These achievements not only opened the new perspectives for the future of physiology, but also helped to overcome such misconceptions as vitalism and physiological idealism. The principle of nervosism was growing strong (I. M. Sechenov, I. P. Pavlov, S. P. Botkin, V. M. Bechterev).

The new methods of investigation were elaborated and new apparatuses and devices were created: the direct and indirect calorimeter (Rubner, V. V. Pashutin, Benedict, Atwater), the method of irritation of living tissues with the aid of inductive apparatus (Du Bois-Reymond), kymograph and apparatus for the investigation of blood pressure and blood flow rate (Ludwig), the method of extraction of gases from blood (I. M. Sechenov), the apparatus for pneumatic registration of functions (Marey's capsule), plethysmograph and ergograph (Mosso).

The operative methods were improved (V. A. Basov, Thiry, Vella, Heidenhain, I. P. Pavlov). The greatest achievement of the XIX century physiology was study of the nervous regulation of functions of organs.

Weber brothers discovered the inhibiting effect of vagus nerve and Cyon brothers-increasing the frequency effect of sympathietic nerves on heart activity. I. P. Pavlov established that sympathetic nerve also strengthens heart contractions. Vasoconstrictive (Walter, Claude Bernard) and vasodilative (Claude Bernar and others) innervations were discovered.

The vascular tension center (V. F. Ovsyannicov), the respiratory center (N. A. Mislavsky), the electrical activity of nervous centers (I. M. Sechenov, V. J. Danilevsky) and the trophic

function of nervous system (Magendie, Claude Bernard, Heidenhain, I. P. Pavlov) were studied.

The reflex theory was improved and the functions of different parts of central nervous system were studied in details (Fritsch, Hitzig, Goltz, Munk, V. M. Bechterev, Luciani).

Ivan Mikhailovich Sechenov (1829-1905) discovered the central inhibition. In 1863 he published his work "The Brain Reflexes". I. M. Sechenov stated that all the processes taking place in the brain, including the human thinking, vere of reflex nature. Thus I. M. Sechenov laid the foundation of the physiology of higher nervous activity. This doctrine then was elaborated by I. P. Pavlov.

Ivan Petrovich Pavlov (1849-1936) was the greatest physiologist and exercised an enormous influence on the physiology of the XX century.

There is not a part of physiology which I. P. Pavlov haven't enriched by his investigations and discoveries. He created a well - balanced doctrine of higher nervous activity, studied the types of higher nervous system, the internal inhibition, discovered the conditioned reflexes, the first and second signaling systems, elaborated the fistula method and so on.

I. P. Pavlov stated that the psychical activity was the result of the physiological activity of certain mass of brain.

The XX century physiology is characterized by the conversion from narrow analytical to wide synthetic interpretation of life processes. But the investigations of the functions of not only organs or tissues, but also separate cells and their structural elements were continued.

In the XX century especially such branches of physiology as microphysiology, electro-physiology, endocrinology, the theory of vitamins and the theory or mediators were developing.

The mediators, i. e. the chemical transmitters of nervous impulses, were discovered in 1920 by Loewi and then elaborated by many other scientists (A. F. Samoylov, A. B. Kibyakov, Cannon, Nachmansohn, Dale, Feldberg).

The nature of electrical phenomena (Chagovets, Loeb, Bernstein, Nernst, Arrhenius, Hodgkin, Huxley), the heart activity regularity (Starling, Lewis, Focht), vascular reactions (Hering, Heymans, V. V. Parin), respiratory mechanisms (B. F. Verigo, Barcroft, Haldane, Van Slyke, Kreps), digestion processes (I. P. Pavlov, Y. S. London, K. M. Bykov, Ivy), the functions of kidneys (Cushny, Richards) were profoundly studied.

The great achievement of XX century physiology was the elucidation of the functioning mechanisms of different parts of central nervous system (Sherrington, Magnus, Beritashvili, Fulton). N. I. Vvedenski discovered the parabiosis, A. A. Ukhtomsky- the dominant, Eccles studied the synapses, Magoun and Moruzzi – functions of the reticular formation. P. K. Anokhin formulated the theory of functional systems.

The evolutionary physiology was created. The emotions and motivations are studied intensively (K. V. Sudakov).

In Azerbaijan the first physiology chair was founded in 1920 at medical faculty of Azerbaijan University. At Azerbaijan Medical University the physiology chair was headed by P. J. Rostovtsev, then A. A. Amirov, S. R. Ojagverdizade, G. M. Gahramanov, F. I. Jafarov.

The first director of physiology institute of Azerbaijan Academy of Sciences was academician A. Garayev, then-academician H. Hasanov. The physiology chairs were organized also at Azerbaijan Pedagogical University, Azerbaijan State Institute of Physical Culture and so on.

Lecture 2

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 self-regulating system and reacts to the different changes of environment as the integral whole.

This definition of organism gives us some of its principal features. First of all, 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.

Secondly, 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.

Thirdly, 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 self-regulating 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 well-being 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.

Every change of external environment or the internal state of organism can become a stimulus if its size, speed and duration are enough. Therefore, the irritants are countless. They

can be divided in 3 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.

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.

BLOOD SYSTEM PHYSIOLOGY

Lecture 3

Functions, Physical and Chemical Properties of Blood. Blood Plasma Composition. Physiological Solutions

Following the old tradition "from simple to complex" we begin to study the physiology from the blood system, though we don't regard the blood as the simplest of all systems of organism. The composition of blood, as well as its functions and the significance for organism give not a bit the grounds to think such way. The composition of blood is not yet completely studied and we still find new elements in blood. Up to present we haven't complete understanding of blood clotting process.

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 6-8% 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 (H_2CO_3) and sodium bicarbonate ($NaHCO_3$) 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:

$$HCl + NaHCO_3 = H_2CO_3 + NaCl.$$
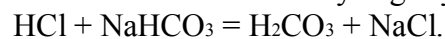
When a strong base, such as sodium hydroxide, is added, the hydroxyl ion of the sodium hydroxide combines with a hydrogen ion from the carbonic acid and forms water. The other product formed is sodium bicarbonate. The result is exchange of the strong base NaOH for the weak base $NaHCO_3$:

$$NaOH + H_2CO_3 — NaHCO_3 + H_2O$$
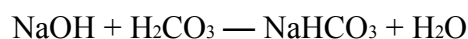
The bicarbonate buffer system is not especially powerful, but it is more important than all the others, because the concentration of each of the two elements of this system can be regulated - carbon dioxide by the respiratory system and the bicarbonate ion by the kidneys. As a result the pH of the blood can be shifted up or down by the respiratory and renal regulatory systems.

The phosphate buffer system is composed of $H_2PO_4^-$ and HPO_4^{--}. It acts in identical manner:

$$HCl + Na_2HPO_4 = NaH_2PO_4 + NaCl$$
$$NaOH + NaH_2PO_4 = Na_2HPO_4 + H_2O$$
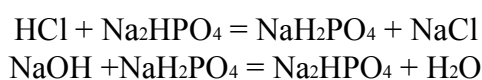
The protein buffer system operates the same way as the bicarbonate buffer system thanks to the amphoteric nature of proteins.

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 non-gaseous (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^+, Ca^{2+}, Mg^{2+}) and anions (Cl^-, HPO_4^{2-}, HCO_3^-) 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 solution animals		
NaCl	0.8	0.6	0.9	0.8
KCl	0.042	0.01	0.042	0.02
CaCl$_2$	0.024	0.01	0.024	0.02
NaHCO$_3$	0.01	0.01	0.02	0.01
MgCl$_2$	-	-	-	0.01
NaH$_2$PO$_4$	-	-	-	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.

Laboratory studies

1. Determination of Hematocrit

The equipment: centrifuge, calibrated tube, scarificator, 5% sodium-citrate solution, spirit, ether, iodine tincture, cotton wool, filter paper.

The blood is brought from the ring finger of man or from blood vessel of animal. The end of the finger is cleared by spirit and ether, then pricked by scarificator. The first drop of blood is wiped by cotton wool (it is not clean). Then the calibrated tube is filled with the blood and centrifuged (700 revolutions per minute). After 1 minute the blood cells are settled and the reading of calibrated tube shows the hematocrit.

2. Determination of the Blood Buffer Properties.

The equipment: 4 beakers, 2 pipettes (5ml), 2 burettes, 10 times diluted blood serum, 0.01 n NaOH, 0.1 n HCl, distilled water, methyl-orange, phenolphthalein.

The buffer properties of blood are demonstrated in two chemical experiments of Friedenthal.

I. Into one beaker 5 ml of distilled water and into the other - 5 ml of blood serum is poured. Into both beakers a drop of methyl-orange is added and titrated by 0.1 n HCl till the stable pink colour. A drop of HCl is enough to obtain the pink colour (the acid reaction) in the beaker with distilled water. But for the same purpose 30-40 drops of HCl are required in the beaker with blood serum and this is 300-400 times more (considering that the blood serum is 10 times diluted) in comparison with the first glass.

II. Into one beaker 5 ml of distilled water and into the other - 5 ml of blood serum is poured. Into both beakers a drop of phenolphthalein is added and titrated by 0.01 n NaOH till weak violet colour. To obtain alkaline reaction in the beaker with blood serum 40-70 times more alkaline solution is required than in other one.

Lecture 4

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 (HCO_3-). 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 HCO_3- and $Cl-$ anions, O_2, Co_2, $H+$, $OH-$. 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 micro-litre-mcl) is 4.5-5 millions (4.5-5 x 10^{12}/litre) and in normal blood of women – 4-4.5 millions in 1 mcl (4-4.5 x 10^{12}/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 6-8 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 O_2 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 (HbO_2). 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 ($HbCO_2$). 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.

Laboratory studies

Count of Erythrocytes

The equipment: Goryayev's accounting camera, the large melangeur, scarificator, 3% NaCl solution, spirit, ether, iodine tincture, cotton wool.

The blood is taken till the mark "0.5" of melangeur and till the mark "101" the 3% NaCl solution is added. Thus, blood is diluted 200 times. After taking out the rubber tube, the melangeur is shaken during 1 minute. 1-2 drops of diluted blood is thrown away and then 1 drop is poured on the middle part of Goryayev's camera which is covered by glass (the blood is placed between the camera and covering glass). This part of the camera is 0.1 mm lower than the side ones. Here the accounting net is drawn. The net consists of 225 (15 x 15) large squares. 25 of them are divided into 16 small squares. Length of the small square's side is 1/20 mm. Thus, volume of the blood on one small square is: 1/20 mm x 1/20 mm x 1/10 mm = 1/4000 mm $_3$.

Erythrocyes are counted under the microscope in 5 large squares which are divided into 16, that is, in 80 small squares. It is recommended to count them in 5 large squares situated along the diagonal.

In order not to count any erythrocyte twice, it is useful to keep Yegorov's rule: only the erythrocytes situated in the small square, on its upper and left sides are counted.

If the number of erythrocytes counted in 5 large squares is marked as "e", then the number of erythrocytes in one large square will be $\dfrac{e}{5}$ and in one small square e $\dfrac{e}{5 \cdot 16}$

Since this number of erythrocytes is found in the $\dfrac{1}{4000}$ mm$_3$ of blood, to determine the number of erythrocytes in 1 mm$_3$ of blood it must be multiplied by 4000. Considering that the blood was diluted 200 times, the result is multiplied by 200, and we have the formula to calculate the number of erythrocytes in 1 mm$_3$ of blood (E):

$$E = \frac{e \cdot 4000 \cdot 200}{5 \cdot 16}$$

After the cancellation: $E = e \cdot 10000$

2. Determinaion of the Hemoglobin Content in the Blood

The equipment: Sahli's hemometer, scarificator, pipettes, micropipette, the glass stick, 0.1 n Hcl solution, spirit, ether, iodine tincture, distilled water, cotton wool.

Into middle test-tube of hemometer 0.1 nHCl is poured till the lower mark (10 and 2). By

special micropipette 20 mm ^{3} blood is added. After 5 minutes the drops of distilled water are poured and by glass stick mixed (the stick must not be taken out of the test tube). When the colour of solution fully corresponds to the standard coloured solutions in the side soldered tubes, its level shows the absolute and relative contents of hemoglobin (on two scales of test-tube).

Lecture 5

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.

Laboratory Studies

1. Calculation of Colour Index.

The colour index (C.I.) is calculated by the following formula:

$$C.\,I. = \frac{Hb}{Hb_n} : \frac{E}{E_n}$$

Hb and E indicate the hemoglobin content of analysed blood and the number of erythrocytes in it. Hbn and En are the same indicis of normal blood (Hbn = 100%, En= 5000000).

If we have established 90% of hemoglobin and 4500000 erythrocytes, then:

$$C.\,I. = \frac{90 \cdot 5000000}{100 \cdot 4500000} = 1.$$

After the cancellation of normal constants we obtain the following simple formula:

$$C.\,I. = \frac{5Hb}{E\ (\text{the first 3 figures})}$$

In our example:

$$C.\,I. = \frac{5 \cdot 90}{450} = 1.$$

The simpler formula is practised in clinics:

$$C.\,I. = \frac{Hb}{2 \times E\ (\text{the first 2 figures})}$$

In our example:

$$C.\,I. = \frac{90}{2 \cdot 45} = 1.$$

When the absolute content of hemoglobin is taken, we have the following formula:

$$C.\,I. = \frac{0.3 \cdot Hb}{E\ (\text{the number of millions})}$$

In our example (90% Hb = 15 gm/dl Hb):

$$C.\ I. = \frac{0.3 \cdot 15}{4.5} = 1.$$

2. Observation of Hemolysis

The equipment: test-tubes, scarificator, 0.85% NaCl solution, 5% sodium citrate solution, distilled water, HCl solution, spirit, ether, iodine tincture, cotton wool.

Into one test-tube the 0.85% NaCl solution is poured, into the second test-tube - the distilled water and into the third one - HCl solution is poured.

In the first test-tube (with the isotonic solution) the blood is not hemolyzed and the blood cells are settled. In the second test-tube the osmotic hemolysis and in the third test-tube the chemical hemolysis is observed.

3. Determination of ESR

The equipment: Panchenkov's apparatus, the watch glass, scarificator, 5% sodium citrate solution, spirit, ether, iodine tincture cotton wool.

Into one of the micropipettes of Panchenkov's apparatus the 5% sodium citrate solution is sucked up to the mark 50 (p) and blown out on the watch glass. Twice the blood is taken from finger up to the mark O (K) of the micropipette, this also is blown out on the watch glass and mixed with the sodium citrate solution. The micropipette is filled with this mixture up to the mark O and is put into the support of the apparatus in the vertical position.

During an hour the blood cells are settled and in the upper part of the micropipette the column of plasma is separated. The higher the ESR - the higher the column of plasma at the top of micropipette. The scale of micropipette shows the ESR in mm/hour.

Lecture 6

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 (α and β) 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 erythrocytes)	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	$\alpha\beta$	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
		αβ	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.
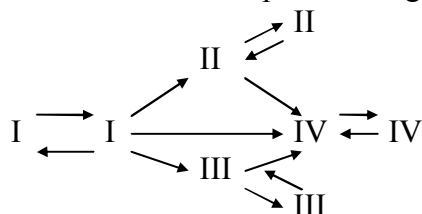
To transfuse precisely the same group is preferable. Because, firstly, when the large quantity of the universal donor's (I group) blood is transfused, for instance, to the recipient of IV group, the donor's agglutinins are not diluted sufficiently and they cause agglutination of recipient's erythrocytes. 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. A_1 is the strongest, but the agglautination 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 post-transfusion complications.

In most instances of erythroblastosis fetalis the mother is rh-negative and the father is Rh-positive. 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.

Laboratory studies

Determination of Blood Groups (blood typing)

The equipment: the II and III group standard blood sera, 2 pipettes, object (flat) glass, glass stick, scarificator, spirit, ether, iodine tincture, cotton wool.

Blood groups are determined by the method of Mosso. On one end of the object glass by a pipette a drop of the II group standard blood serum is poured and by another pipette a drop of the III group serum is poured on the other end of the glass. Beside every drop of standard sera a drop a blood taken from a finger is added and mixed with the drop of serum (by differnt ends of glass

stick). Homogeneous drop of dark pink colour is obtained. If the agglutination occurs, then during 5 minutes the mixture becomes pellucid and the agglutinated erythrocytes form visible dots. Observing the result, the analysed blood is considered as belonging to donor and the agglutinogens of its erythrocytes are taken into account, whereas the II and III group standard sera are considered as belonging to recipient and their agglutinins (II-β, III-α) are taken into account.
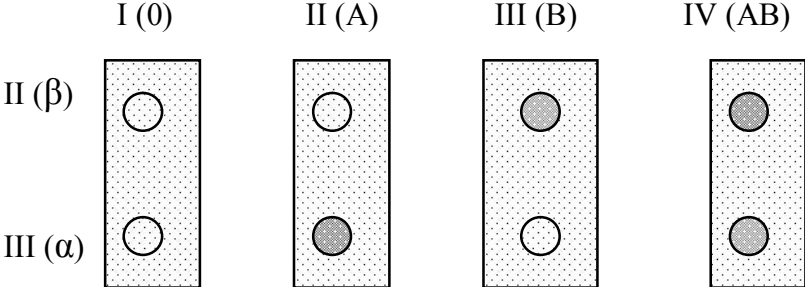
Lecture 7

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 agent 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 mm$_3$) of blood (4-9 x 10$_9$ /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 antibody 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 macro-phages, 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 10_{12} lymphocytes. 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 non-differentiated 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 $0.5 \times 10_9$/litre (500 in 1 mcl) causes the death.

Laboratory studies

Count of the Leukocytes

The equipment: Goryayev's accounting camera, the small melangeur, microscope, scarificator, Thurk's solution (1% acetic acid solution dyed by methylene blue), spirit, ether, iodine tincture, cotton wool.

The blood is taken from finger to the mark "0.5" of melangeur and to the mark "11" the Thurk's solution is added (blood is diluted 20 times). After shaking the melangeur during 1 minute and throwing away 1-2 drops of diluted blood, 1 drop is poured on the Goryayev's camera. The leukocytes are counted under the microscope in 25 large squares (it makes no difference, divided into 16 or not).

If the number of leukocytes counted in 25 large squares is marked as "l", then the number of leukocytes in one large square will be $\frac{1}{25}$, in one small square $\frac{1}{25 \cdot 16}$.

The number of the leukocytes in 1 mcl (1 mm3) of blood will be $\frac{1 \cdot 4000 \cdot 20}{25 \cdot 16}$.

Considering that the blood was diluted 20 times, the result is multiplied by 20 and the formula to calculate the number of leukocytes in 1 mcl of blood (L) will be as following:

$$L = \frac{1 \cdot 4000 \cdot 20}{25 \cdot 16}$$

After the cancellation : $L = 1 \cdot 200$.

Lecture 8

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 (200-400 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 jelly-like clot. There are two main mechanisms by which the hemostasis is achieved: 1) vascular-thrombocytic 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 phase-throbin 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 anti-coagulant 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 ad-sorbs 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 B12 is the extrinsic factor of hemopoiesis. The parietal cells of gastric glands secrete a glycoprotein called intrinsic factor, which combines with vitamin B12 of the food and makes the B12 available 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 re-enter 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.

Laboratory Studies

Determination of the Clotting Time

The equipment: scarificator, capillary tube, the watch glass smeared with paraffin, vaseline oil, spirit, ether, iodine tincture, distilled water, cotton wool.

The most widely used method for determining clotting time belongs to Mas and Magro.

A drop of vaseline oil is poured on the watch glass smeared with paraffin. The blood taken from finger into the capillary tube is added into the drop of vaseline oil. Every 2 minutes the blood is sucked into capillary tube and blown into the drop of vaseline oil until the blood has clotted and to suck it into tube is impossible. By this method the normal clotting time (from the moment when the blood is taken and to the moment when it has been clotted) is about 6-12 minutes (in the temperature 15-20o C).

BLOOD CIRCULATION

Lecture 9

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;

3) 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;

4) the atrioventricular bundle (A- V bundle) or bundle of His, which conducts impulses from the atria into the ventricles;

5) 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- 38о. 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.

Labaratory Studies

1. Observation of Blood Circulation in Web and Tongue Capillarries of Frog

The equipment : frog, microscope, small cork plank with hole, exciccator, 0.6 % NaCl solution, anesthetic ether, cotton wool, pins.

The frog is put into the exsiccator with the anesthetic ether and is made motionless. Then the frog is fastened to the cork plank. The web of one of the hind extremities is stretched over the hole of the plank and fixed by the pins. Under the microscope the blood flow in the capillaries is observed.

In the same way the blood flow in the capillaries of the tongue may be observed.

Taking into consideration the direction of the blood flow, the arteries and veins are distinguished.

2. Ligatures of Stannius

The equipment : frog,small cork plank, scissors, forceps, seconds counter, thread, Ringer solution, pins,

The frog is made motionless by the way of destroying the brain and spinal cord and is fixed on the cork plank on the back. The thoracic cavity is opened and the heart is uncovered. Heart beat rate is counted. Then the thread is put under the venous sinus and tied up between the sinus venous and atria. This is the first ligature of Stannius after which activity of sinus venosus is continued whereas contractions of the atria and ventricle are stopped. This proves that the sinus node generates impulses independently, that is, it is pacemaker, but the atrioventricular node is subordinate.

The second ligature is put between the atria and ventricle.It irritates the atrioventricular node mechanically, and both atria and ventricle begin to contract, though the heart rate is lower. If the second ligature is put slightly higher, only the ventricle contracts, if lower – only atria contract.

The third ligature is put on the lower 1/3 of the ventricle or apex cordis is cut off. It can contract in sluggish way, especially after being stimulated mechanically by the pin. This shows that even the Purkinje fibers have the automatism ability to a certain degree.

3.Graphic Recording Of the Heart Activity

The equipment : the frog, small cork plank, scissors, forceps, cardiograph, kymograph, thread, 0.6% NaCl solution, cotton, wool, pins.

After making the frog motionless it is fixed on the cork plank, the thoracic cavity is opened and the heart is uncovered. The plank is fixed to the cardiograph, the apex cordis is seized by serrifine (the special clip of cardiograph). The contractions of the heart cause the rhythmical movements of the lever which records the cardiogram on the cylindr of kymograph.

In frog cardiogram the systole of atria, the systole of ventricle, the diastole of ventricle and the pause are distinguished.

Lecture 10

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 (V_1 - V_6) 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:

I- the negative terminal of the electrocardiograph is connected to the right arm and the positive terminal to the left arm;

II- the negative termianl of the electrocardiograph is connected to the right arm and the positive terminal to the left leg;

III- 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 V_R lead; when on the left arm - the aV_L lead and when on the left leg- the a V_F lead. These are all similar to the standard limb lead recording except that the recording from a V_R 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:

$$S = 8.22 \sqrt[3]{C} \quad \text{(C -in 0.01 second)}.$$

Bazett's formula:

$$S = 0.37 \sqrt{C} \quad \text{(C - in seconds)}.$$

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	0.05-0.30	0.08-0.10
Q	0 - 0.20	max. 0.03
R	0.60-1.60	max. 0.03
S	0-0.03	max. 0.03
T	0.25-0.50	max. 0.25
Intervals and complexes		
P-Q		12-0.20
QRS		0.06-0.10
QRST		0.30-0.46
S-T		0.10-0.35
R-R		0.70-0.80

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.

Laboratory Studies

Recording of the Electrocardiogram

The equipment: electrocardiograph, electrodes, bandage, the physiological solution, couch.

The electrocardiograph is placed far from the objects which would create an obstacle for its work (alternating current system, transformers and so on). It is earthed. The person lies on the couch. The bandages moistened in the physiological solutions are put on his limbs and on the bandsges the electrodes are tied. Using the coloured conductors of the apparatus the electrodes are connected to the electrocardiograph.

The apparatus is switched on. When the control lamp shines, the ventilator of the apparatus is immediately put in motion. The apparatus is put on calibration regime and in the I lead the potential from the current source (1mV) is recorded. Then the apparatus is switched on working regime and in complete resting state of the person the electrocardiogram is recorded in different leads.

Comparing the obtained electrocardiogram with the calibration lines one can judge about its parameters.

Lecture 11

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 ossilation 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/m$_2$.

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:

$$\frac{100 \cdot 400}{8} = 5000 \text{ ml. This is the cardiac output.}$$

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 non-trained 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.

Laboratory Studies

Auscultation of Heart Sounds

The equipment: stethoscope or phonendoscope.

The first and the second heart sounds are auscultated at resting state of person on the points indicated in the table. Then the person several times sits down and gets up. The heart sounds are once more auscultated. Increase of heart rate and strengthening of heart sounds are observed.

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

Lecture 12

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 activity	The stimulation of the rhythmical fibers	The stimulation of the dynamic fibers	The stimulation of the whole nerve
n. S.	n. S.	n. S.	
	n. V.	n. V.	n. V.
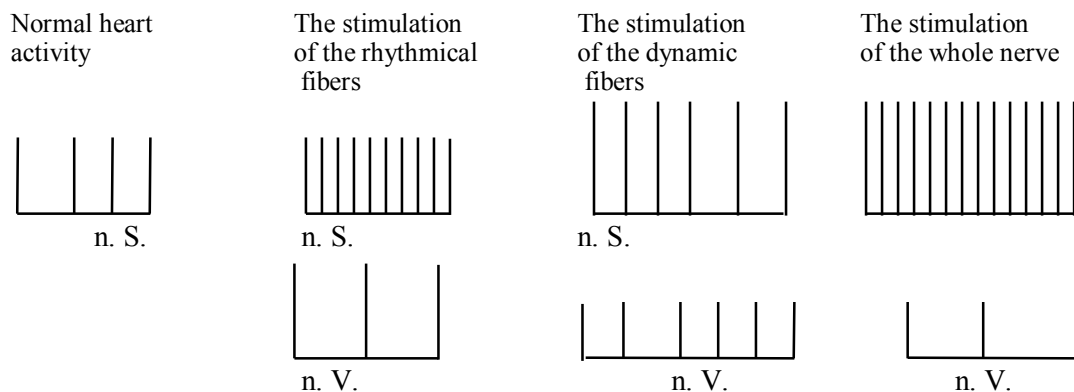
The extracardial nerves exercise their influence on heart activity with the aid of chemical substances called the transmitters or mediators, which are secreted in nerve endings. The parasympathetic mediator is acetylcholine, the sympathetic mediators are adrenaline (epinephrine), noradrenaline (norepinephrine) and others.

Exictestence 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.

Laboratory Studies

Influence of the Frog Vagosympathetic Nerve Fascicle
Stimulation on the Heart Activity

The equipment: frog, cardiograph, electrostimulator, electrodes, the small cork plank, scissors, pincers, pins, the physiological solution, cotton wool.

The frog is made motionless and is fixed on the cork plank. Its chest is widely opened, the heart is released. The vagosympathetic nerve fascicle is ligated and put on the electrodes, the heart is connected to the cardiograph. The cardiogram is recorded before and after the stimulation of vagosympathetic fascicle.

Since the latent period of the vagus nerve is shorter, it is excited first, decreases the heart rate and weakens the heart contractions. Later the sympathetic netve is excited which increases the heart rate and strengthens the heart contractions.

Lecture 13

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.

Laboratory Studies

1. Reflex Influence on Heart Activity (reflex of Holtz, Dagnini - Aschner reflex)

The equipment: frog, the small cork plank, pincers, scissors.

The frog is fixed on cork plank on its back (not destroying its spinal cord). The chest is opened. By the handle of pincers the sudden blow is struck on the stomach. The heart is stopped during a short time. Then the spinal cord is destroyed by the pin and the blow on stomach is repeated. But since the Holtz reflex arch is broken, the heart activity does not change.

The reflex influence on heart activity in human organism is observed by the help of the oculocardiac reflex of Dagnini - Aschner in the above - mentioned way.

2. Effect of Hormones and Electrolyteson Heart Activity
(heart isolation by Schtraub method)

The equipment: frog, cardiograph, kymograph, the small cork plank, pincers, scissors, cannula, guide, pipettes, thread, the Ringer solution for cold - blooded animals, 1 % $CaCl_2$ solution, 1% KCl solution, 0.1 % adrenaline solution, 0.01% acetylcholine solution.

The brain and spinal cord of the frog are destroyed by pin and it is fixed on cork plank on its back. The chest is opened.

The frog aorta has two arches. The right one is ligated and tied. Under the left arch two ligatures are put. Between them the vascular wall is perforated by scissors and the end of the cannula is put into the ventricle through the vessel. The central ligature is tied tightly not to let the cannula from the heart.

To the periphery from the ligatures the aortic arches are cut and the heart is removed from the chest together with the cannula. The cannula is filled with Ringer solution and fixed to the cardiograph's support. The apex cordis is fixed by cardiograph's serrefine. The automatic contractions of heart are recorded on kymograph's cylinder.

After adding several drops of 1% $CaCl_2$ to the Ringer solution in the cannula, the heart rate increases and heart contractions strengthen. When more $CaCl_2$ is added, the heart stops in systole.

Then the solution is removed from the cannula by the pipette and the heart is washed by Ringer solution. When the heart contractions are recovered, in the same way the influence of

KCl, adrenaline and acetylcholine on the heart activity is studied. After studying of the influence of acetylcholine on heart contractions, a drop of blood is added to the Ringer solution in the cannula and the heart activity is recovered. Because acetylcholine is destroyed by blood cholinesterase.

Lecture 14

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 (P_1 -P_2 = P) and inversely proportional to the resistance (R) against the flow of the fluid:

$$Q = \frac{\Delta^P}{R}$$

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:

$$Q = \frac{P}{R}$$

From this equation one can determine 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:

$$R = \frac{P}{Q}$$

Dividing the volumetric velocity by the section area of the vessel one can calculate also the linear velocity of blood flow:

$$V = \frac{Q}{\pi r^2}$$

According to the Poiseuille's law:

$$Q = \frac{\pi P r^4}{8\eta l}$$

In this formula Q is the blood flow volumetric velocity, Δ^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:

$$R = \frac{8\eta l}{\pi r^4}$$

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:

$$R = R_1 + R_2 + R_3 + ... R_n$$

When the tubes are connected in parallel, their total resistance is calculated by the following formula:

$$R = \frac{1}{1/R_1 + 1/R_2 + 1/R_3 + ... + 1/R_n}$$

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 cm$_2$) is more than that of aorta (2.5 cm$_2$).

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 110-125 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

$$R = \frac{8\eta l}{\pi r^4}$$

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 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.

Laboratory Studies

Measuring of the Blood Pressure of Man

The equipment: sphygmomanometer, phonendoscope or stethoscope.

The blood pressure is measured by above - mentioned methods of Riva-Rocci and Korotkov.

Lecture 15

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.

The 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 m$_2$), 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 (P_{hc}) 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:

$V = K[(P_{hc} + P_{ot}) - (P_{ht} + P_{oc})]$ (+V) shows filtration and (-V) - reabsorption.

The average values of above - mentioned pressures are given in the following table.

Capillaries	Pressures (mm Hg)			
	hydrostatic		oncotic	
	in capillaries	in tissues	in capillaries	in tissues
	P_{hc}	P_{ht}	P_{ot}	P_{oc}
Arterial part	32.5	3	25	4.5
Venous part	17.5			

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.

In the investigations carried out by the corresponding member of the Academy of Sciences of Azerbaijan Republic, professorY. J. Mamedov at the pathophysiology chair of the Azerbaijan Medical University named after N. Narimanov, the coagulation factors of protein origin that are in blood plasma, were found also in the lymph. Quantitative changes of these factors in blood plasma were accompanied by their changes in the same direction in lymph. These experiments prove that plasma proteins may pass from the capillaries into intercellular space and from there into lymphatic vessels.

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.

RESPIRATION

Lecture 16

External Respiration. Gaseous Exchange in Lungs.
Transport of Gases in the Blood. Gaseous Exchange in Tissues

Respiration is the totality of the processes providing oxygen to the tissues and removing of carbon dioxide. Respiration includes the following major processes:

1) external respiration or pulmonary ventilation - the inflow and outflow of air between the atmosphere and alveoli of lungs;

2) diffusion of oxygen and carbon dioxide between the alveoli and the blood;

3) transport of oxygen and carbon dioxide in the blood to and from the cells;

4) diffusion of oxygen and carbon dioxide between the blood and tissues;

5) internal respiration or cell respiration- consumption of oxygen by tissues and excretion of carbon dioxide.

The first four processes are studied by the physiology, the internal respiration - by biochemistry.

Respiratory cycle consists of inspiration and expiration.

Inspiration is the active process which is realized by the contraction of the inspiratory muscles (diaphragm and external intercostals muscles). As a result of oblique direction of external intercostals muscles the distance from the attachment point of ribs to the vertebral column is longer for lower ribs than that of upper ones and accordingly the moment of lower lever is larger than that of upper one. Therefore, when the external intercostals muscles are contracted, the ribs rise and the sagittal size of chest increases. Besides, when the ribs are rised, they rotate a little and the frontal size of the chest also increases. The mechanism of the rise of the ribs is demonstrated on the action model of ribs.

When the diaphragm is contracted its cupola becomes flat and the vertical size of chest increases. This is demonstrated on the Donders model.

So, during the inspiration first the volume of thoracic cavity increases, the pressure in the pleural cavity decreases and then the atmospheric air enters the lungs by the respiratory tracts and causes the lung expansion.

Depending on the principal participation of the intercostals muscles or diaphragm in respiration its three types are distinguished: 1) costal or thoracal type, 2) diaphragmatic or abdominal type, 3) mixed type.

In the hard inspiration besides these muscles, some subsidiary respiratory muscles take part: scalene muscles, pectoral muscles, anterior denticulated muscle, trapezoid muscle and so on.

The normal quiet expiration in the ordinary state of organism is passive process and it is realized owing to the elasticity energy accumulated during the preceding inspiration. When the inspiration is over and the inspiratory muscles are relaxed:

1) the ribs go down under the influence of their own gravity and thanks to the elasticity power of costal cartilages which were deformed during the inspiration;

2) the cupola of diaphragm rise, because the abdominal wall and organs of abdominal cavity which were displaced during the inspiration, return to their ordinary position.

So, during the expiration the volume of thoracic cavity decreases, the pressure in the pleu-

ral cavity increases, the extended pulmonary tissues are tightened and the air leaves the lungs.

But the intensive expiration is the active process and requires the contraction of internal intercostal muscles, the muscles of abdominal wall and so on.

Thus, the direct cause of the expansion and collapse of lungs is the change of the pleural pressure, that is, the pressure in the narrow space between the visceral pleura and the parietal pleura.

The considerable part of the atmospheric pressure is spent on overcoming of elastic draught of lungs. Therefore, the pressure in the pleural cavity is lower than atmospheric pressure. This is called the negative pressure. During the expiration the pressure in the pleural cavity is -3 mm Hg. During the inspiration it becomes even more lower, i.e. - 6 mm Hg, and this creates the sucking power.

The elastic draught of lungs is due to the following factors:

1) the surface tension of the liquid film covering the internal surface of alveoli;

2) elasticity of alveolar walls tissue caused by the elastic fibers;

3) tonus of bronchial muscles.

The internal surface of the alveoli is covered by surfactant - a surface active agent, which is secreted by special surfactant-secreting epithelial cells called type II alveolar epithelial cells. During the expiration surfactant reduces the surface tension and prevents the atelectasis (complete collapse) of some alveoli and excessive extension of other ones.

The surfactant formation is stimulated by parasympathetic effects and it is suppessed when vagus nerves are cut.

When the chest or pulmonary tissue are wounded the atmospheric air enters the pleural cavity. This is called pneumothorax. There are three types of pneumothorax:

1. The closed pneumothorax-some amount of air enters the pleural cavity and loses its connection with atmospheric air. The lung is partly collapsed, but its ventilation continues. Later the air is absorbed from the pleural cavity and the lung expands. The degree of respiratory disturbance depends on the amount of the air which has entered the pleural cavity and displacement of the mediastinum organs.

Sometimes the closed pneumothorax is applied for the therapeutic purpose (to collapse the diseased lobe of the lung and allow it to rest and recover).

2. The open pneumothorax- during the inspiration and expiration the air freely enters the pleural cavity and goes out. The disturbance of the respiratory function is more serious than that of during the closed pneumothorax and it depends on the size of the hole.

3. The valvular (tension) pneumothorax - is most dangerous of all types of the pneumothorax. Because the air is always entering the pleural cavity and cannot go out. More air is accumulated in the pleural cavity-more seriously the pulmonary function is disturbed and at last the lungs are, completely collapsed and are not able to fulfil their function.

A simple method for studying pulmonary ventilation is to record the volume movement of air into and out of the lungs, a process called spirometry. A typical spirometer consists of a drum inverted over a chamber of water and counterbalanced by a weight. A tube connects the mouth with the gas chamber formed in the drum. When one breathes in and out of the chamber the drum rises and falls, and an appropriate recording is made on a moving sheet of paper.

Four volumes and four capacities of the air in the lungs are distinguished. The pulmonary volumes are the following:

1. The tidal volume (about 500 ml) is the volume of air inspired or expired with each normal breath.

2. The inspiratory reserve volume (3000 ml) is the extra volume of air that can be inspired over and beyond the normal tidal volume.

3. The expiratory reserve volume (1100 ml) is the extra amount of air that can be expired by forceful expiration after the end of a normal tidal expiration.

4. The residual volume (1200 ml) is the volume of air still remaining in the lungs after the most forceful expiration.

The pulmonary capacities are following combinations of the above mentioned volumes together:

1. The aspiratory capacity (3500 ml) equals the tidal volume plus the aspiratory reserve volume (the amount of air that a person can breathe beginning at the normal expiratory level and distending the lungs to the maximum amount).

2. The functional residual capacity (2300 ml) equals the expiratory reserve volume plus the residual volume (the amount of air remaining in the lungs at the end of the normal expiration).

3. The vital capacity (4600 ml) equals the aspiratory reserve volume plus the tidal volume plus the expiratory reserve volume (the maximum amount of air that a person can expel from the lungs after first filling the lungs to their maximum extent and then expiring to the maximum extent).

4. The total lung capacity (5800 ml) is equal to the vital capacity plus the residual volume (the maximum volume to which the lungs can be expended with the greatest possible aspiratory effort).

All pulmonary volumes and capacities are about 20-25% less in women than in men and greater in large and athletic persons than in small and asthenia persons.

Since the air in the residual volume of the lungs cannot be expired into the pyrometer, it cannot be used in a direct way to measure the functional residual capacity. Therefore, to measure this important index, the pyrometer is used in an indirect manner, usually by means of a helium dilution method.

A pyrometer of known volume is filled with air mixed with helium at a known concentration. After normal expire (when the remaining volume in the lungs is exactly equal to the functional residual capacity) the person immediately begins to breathe from the pyrometer, and the gases of the pyrometer begin to mix with the gases of the lungs. The helium becomes diluted by the functional residual capacity gases and this index can be calculated using the following formula:

$$\mathrm{FRC} = \left(\frac{\mathrm{Ci}_{\mathrm{He}}}{\mathrm{Cf}_{\mathrm{He}}} - 1 \right) \mathrm{Ve}_{\mathrm{sper}}$$

In this formula FRC is functional residual capacity, $\mathrm{Ci}_{\mathrm{te}}$ - initial concentration of helium in the Spirometer, $\mathrm{Cf}_{\mathrm{He}}$ -final concentration of helium in the spirometer, $\mathrm{Vi}_{\mathrm{spir}}$-initial volume of the spirometer.

The pulmonary ventilation is determined by the volume of the air which is inspired and expired in time unit. Usually the minute respiratory volume is measured. The minute respiratory volume is the total amount of fresh air moved into the respiratory passages each minute; this is equal to the tidal volume times the respiratory rate. Since the tidal volume is approximately 500 ml, and the normal respiratory rate is about 16 breathes per minute, the minute respiratory volume averages about 8 liters per minute.

A person can occasionally live for short periods of time with a minute respiratory volume as low as 1.5 liters per minute and with a respiratory rate as low as 2-4 breaths per minute.

During the physical work the respiratory volume rises to 30-50 liters per minute.

Some of the air that a person breathes never reaches the gas exchange areas but goes to fill respiratory passages where gas exchange does not occur. This air is called dead space air (150 ml). Therefore, to have more exact information about the effectiveness of pulmonary ventilation the alveolar ventilation also must be studied.

Alveolar ventilation per minute (V_A) is the total volume of fresh air entering the alveoli (and other adjacent gas exchange areas) each minute:

$$V_A = (V_T - V_D) \cdot F$$

V_T - is the tidal volume, V_D - the dead space volume, F - the frequency of respiration per minute.

In our example of norm, when the pulmonary ventilation is equal to 8 liters, the alveolar ventilation will be: (500 ml - 150 ml) x 16 = 5.6 liters.

The alveolar ventilation can differ considerably whereas, the pulmonary ventilation is the same. For instance if the tidal volume is 250 ml and the respiratory rate - 32 per minute, the pulmonary ventilation will be as above (250 ml x 32 = 8 liters), but the alveolar ventilation - almost twice less: (250 ml - 150 ml) x 32 = 3.2 liters.

In the majority of the respiratory passageways the gaseous exchange does not occur, but they are necessary for the normal respiration. Passing through these ways,, the inspired air is moistened, warmed, cleared from the dust and microorganisms. Especially in the nasal passages these particles stick to the mucus which contains the bactericidal substance lysozyme. The mucus is gradually moved owing to the activity of the ciliated epithelium.

Irritation of receptors of nasopharynx, larynx and trachea by dust or accumulated mucus causes cough, that of nasal cavity - sneezing. The cough and sneezing centers are located in the medulla oblongata.

Lumen of bronchi and bronchioles depend on number of factors. The sympathetic nerve fibers as well as norepinephrine and epinephrine cause dilatation of the bronchial tree, whereas the parasympathetic (vagus) nerves as well as acetylcholine cause constriction.

In ordinary conditions we breathe by atmospheric air the composition of which is relatively constant. In the alveolar air the oxygen is least of all and the carbon dioxide - most of all. The alveolar air differs not only from the inspired air, but also from the expired air. Because on its way off the expired air is mixed with the air of the dead space.

The gas contents (in per cents) of the atmospheric, alveolar and expired airs are shown in the table.

Air	O_2	CO_2	N_2 and inert gases	H_2O
Atmospheric	20.84	0.04	79.62	0.50
Alveolar	13.6	5.3	74.9	6.2
Expired	15.7	3.6	74.5	6.2

Gaseous exchange between the alveolar air and the pulmonary blood occurs through the membranes of all the terminal portions of lungs. These membranes are collectively known as the respiratory membrane, also called the pulmonary membrane.

Although the overall thickness of the respiratory membrane in some areas is as little as 0.2 mcm (it averages about 0.6 mcm), it consists of the large number of layers:

1. A layer of fluid lining the alveolus and containing surfactant (it reduces the alveolar fluid's surface tension).

2. The alveolar epithelium comprised of very thin epithelial cells.

3. An epithelial basement membrane.

4. A very thin interstitial space between the alveolar epithelium and the capillary membrane.

5. A capillary basement membrane that in many places fuses with the epithelial basement membrane.

6. The capillary endothelial membrane.

Since there are 300-400 million pulmonary alveoli, the total surface area of the respiratory membrane is approximately 50-100 sq. m in the normal adult.

The total quantity of blood in the capillaries of the lung at any given instant is 60-140 ml. If one imagines this small amount of blood spread over above-mentioned surface it is easy to understand the rapidity of respiratory exchange of gases.

Since the average diameter of the pulmonery capillaries is very small (about 5 mcm) the

erythrocytes must actually squeeze through them. Therefore, their membrane touches the capillary wall so that oxygen and carbon dioxide need not pass through large amounts of plasma diffusing between the alveolus and erythrocytes.

The gaseous exchange in lungs is realized as a result of diffusion of oxygen from the alveolar air into the blood (about 500 liters in a day) and the carbon dioxide in the opposite direction (about 430 liters in a day). The diffusion occurs owing to the partial pressure difference of these gases in the alveolar air and their pressure in the blood.

In the mixture of gases the rate of diffusion of each of these gases is directly proportional to the preasure caused by this gas alone, which is called the partial pressure of the gas.

For instance, let us fancy that the atmospheric air with its total pressure of 760 mm Hg consists of only 79% nitrogen and 21% oxygen. Since each gas contributes to the total pressure in direct proportion to its concentration, 79% of the 760 mm Hg is caused by nitrogen (about 600 mm Hg) and 21% by oxygen (about 160 mm Hg). Thus, the partial pressure of nitrogen in the mixture is 600 mm Hg and that of oxygen - 160 mm Hg.

The partial pressures of the individual gases in a mixture are designated by the symbols P_{O_2}, P_{CO_2} etc.

The pressures of the separate dissolved gases are designated similarly as for the partial pressures of the gases in the gaseous state, i.e., P_{O_2}, P_{CO_2} etc.

When air enters the respiratory passage-ways, water immediately evaporates from the surfaces of these passages and humidifies the air. The pressure that the water molecules exert is called the vapor pressure of the water. At normal body temperature the vapor pressure of the water as well as the partial pressure of the water vapor in the gas mixture (P_{H_2O}) is 47 mm Hg.

The partial pressures (in mm Hg) of respiratory gases (at sea level) as they enter and leave the lungs, are shown in the table.

Air	O_2	C_{O_2}	N2 and inert gases	H_2O
Atmospheric	159	0.3	597	3.7
Alveolar	104	40	569	47
Expired	120	27	566	47

In the blood the gases are in the state of solution or in the chemically bound state. Only the molecules of the dissolved (free) gases take part in the diffusion.

The amount of the gas dissolved in the fluid depends on the nature of the gas itself, its volume and pressure on the fluid, the composition and temperature of the fluid. Higher the pressure of this gas and lower the temperature - more gas is dissolved in the fluid.

The partial pressure of oxygen and carbon dioxide in alveolar air is the power forcing these gases to diffuse into the blood through the respiratory membrane. The power forcing the dissolved gas to pass into the gaseous mixture is the tension of the gas in the fluid. Thus, in the balanced state the tension of the gas in the fluid is equal to its partial pressure upon the fluid. If the partial pressure of the gas is higher than its tension, the gas will dissolve. When the tension of the gas is higher than its partial pressure, the gas will come out of the solution into the gaseous mixture.

Ability of the respiratory membrane to exchange a gas between the alveoli and the pulmonary blood is expressed in quantative terms by its diffusing capacity which is defined as the volume of a gas that diffuses through the membrane each minute for a pressure difference of 1 mm Hg. All the factors affecting diffusion through the respiratory membrane can affect the diffusing capacity.

The diffusion capacity for oxygen under resting conditions averages 21 ml/min. mm Hg; during the cinditions greatly increasing pulmonary blood flow and alveolar ventilation, the diffusion capacity for oxygen increases to about 65 ml/min. mm Hg.

Owing to the higher dissolubility of carbon dioxide, a diffusion capacity for it is 20-25 times more than that of for oxygen: 400-450 ml/min. mm Hg under resting conditions and 1200-1300 ml/min. mm Hg during exercise.

The P_{O_2} of the gaseous oxygen in the alveolus averages 104 mm Hg, whereas the P_{O_2} of the venous blood entering the capillary is only 40 mm Hg (while passing through the peripheral tissues, the blood loses a large amount of its oxygen). So, the initial pressure difference causing oxygen to diffuse into the pulmonary caplliary is 64 mm Hg.

The P_{CO_2} of the venous blood entering the pulmonary capillaries equals 45 mm Hg, whereas P_{CO_2} in the alveolar air is 40 mm Hg. So, only 5 mm Hg pressure difference causes all the required carbon dioxide diffusion out of the pulmonary capillaries into the aveoli. Such rapid (in 0.7 sec) removal of carbon dioxide from the venous blood into tee alveolar air when the pressure difference is so small, is explained by the high diffusion capacity of lungs for this gas.

The ratio between the alveolar ventilation (V_A) and the blood flow through lesser circulation or alveolar capillaries perfusion (Q) is of great significance for the gaseous exchange in the lungs. But even normally to some extent, and especially in many pulmonary diseases, some areas of the lungs are well ventilated but have almost no blood flow, whereas other areas may have excellent blood flow but little or no ventilation. Therefore, the ventilation-perfusion ratio (V_A/Q) is determined. The normal ventilation-perfusion ratio is equal to 0.8:

$$V_A/Q = \left(\frac{\text{Alveolar ventilation per minute}}{\text{Pulmonary blood flow per minute}} \right) = \frac{4 \text{ liters}}{5 \text{ liters}} \ 0.8$$

When ventilation of some of the alveoli is great but the alveolar blood flow is low, there is then far more available oxygen in the alveoli than can be transported away from the alveoli by flowing blood. So, the ventilation of these alveoli is wasted. Since the ventilation of the anatomical dead space areas of the respiratory passageways is also wasted, the sum of these two types of wasted ventilation is called the physiological dead space.

Ventilation of alveoli in the area of apex pulmonis is less effective than those in the base of the lungs. On the whole more tensile outside zone of the pulmonary tissues is much better ventilated than the least tensile inner zone in the area of the root of the lung.

Rather small quantity of oxygen and carbon dioxide are transported in the blood in free (dissolved) state. Their main amounts are transported in the bound state.

Oxygen is transported in the state of oxyhemoglobin. In body temperature in each 100 ml of blood only 0.3 ml of oxygen is dissolved. The oxygen dissolved in blood plasma of lesser circulation capillaries diffuse into the erythrocytes and it is at once combined with the hemoglobin to form oxyhemoglobin. Conversion of hemoglobin into oxyhemoglobin is determined by the tension of dissolved oxygen and this process finds its expression in the oxygen-hemoglobin dissociation curve. More the tension of oxygen dissolved in the blood-more oxyhemoglobin is formed. The curve has S-like shape.

In the interval of 10-40 mm Hg of oxygen tension (usual for the tissues of organism) the ox hemoglobin level rises especially rapidly reaching 75%. This part of the curve is steep. After 60 mm Hg, when the saturation of hemoglobin by oxygen reaches 90%, the sloping part of the curve begins and further it becomes almost flat.

A number of different factors can shift the dissociation curve to the left or to the right, i.e., facilitate formation of oxyhemoglobin or return of oxygen.

When the blood becomes slightly acidic the oxygen - hemoglobin dissociation curve shifts to the right. Besides the decreased pH, the increased carbon dioxide concentration increased blood temperature, increased 2,3 - diphosphoglycerate shift the curve to the right. Because all these situations are connected with the intensive metabolism and require the increase of oxygen supply. For instance, in exercise these factors shift the oxygen - hemoglobin dissociation curve of the muscle capillary blood considerably to the right.

Presence of large quantities of fetal hemoglobin in the blood shifts the dissociation curve to the left. This is important for oxygen delivery to the tissues under the hypoxic conditions in which the fetus exists.

So, shift of the oxygen - hemoglobin dissociation curve by changes in the blood CO_2 and hydrogen ions has a very significant effect in enhancing oxygenation of blood in the lungs and then again in enhancing release of oxygen from the blood in the tissues. This is called the Bohr Effect.

The maximum amount of oxygen which the blood can bind when hemoglobin is completely saturated by oxygen, is called the oxygen capacity of blood. It depends on the hemoglobin content of blood.

The blood of a normal person contains approximately 15 grams of hemoglobin in each 100 milliliters of blood, and each gram of hemoglobin can bind with a maximum of about 1.34 milliliters of oxygen (1.39 ml when the hemoglobin is chemically pure, but this is reduced by impurities such as methemoglobin). So, the hemoglobin in 100 ml of blood can combine (when it is 100% saturated) 20 ml of oxygen (20 volumes per cent).

Carbon dioxide is transported in blood in the state of physical solution (7 per cent), in the carbohemoglobin (23 per cent) but mainly (70 per cent) in the form of the carbonic acid salts.

Inside the erythrocytes is an enzyme called carbonic anhydrate. Depending on the tension of carbon dioxide carbonic anhydrate catalyses formation of carbonic acid (in the tissue capillaries) as well as it's splitting to carbon dioxide and water (in the pulmonary capillaries), accelerating the rate of this reaction in both directions 5000-20000-fold.

The carbon dioxide that is continuously formed in cells and diffuses into the blood of tissue capillaries, reacts with water to form carbonic acid (mainly in erythrocytes). Part of carbon dioxide molecules combines with hemoglobin to form carbohemoglobin. Therefore, the carbon dioxide tension in the erythrocytes is not high and it continues to diffuse into erythrocytes. The HCO_3^- ions concentration in erythrocytes is increased (as a result of carbonic acid dissociation) and many of the bicarbonate ions diffuse into the plasma, while chloride ions diffuse into the erythrocytes to take their place. Their negative charges are balanced by K+ ions. In plasma $NaHCO_3$ is increased.

As a result of ions accumulation in the erythrocytes the osmotic pressure in them increases and therefore, the volume of erythrocytes in the greater circulation capillaries is slightly augmented.

Simultaneously oxyhemoglobin gives back oxygen and hemoglobin binds the released H+ ions of carbonic acid to form the reduced hemoglobin (H_{Hb}). Carbon dioxide reacts directly with hemoglobin to form the compound carbaminohemoglobin (CO_2H_{Hb}).

In the capillaries of lesser circulation, where the tension of carbon dioxide is low, carbaminohemoglobin is spitted, carbohemoglobin also gives back the carbon dioxide which diffuses into plasma and then into the alveolar air.

Simultaneously oxygen diffuses from the alveolar air into plasma and then into erythrocytes to form oxyhemoglobin.

When the arterial blood reaches the peripheral tissues, its Po_2 is still 95 mm Hg. The Po_2 in the interstitial fluid averages only 40 mm Hg. The normal intracellular Po_2 ranges from as low as 5 mm Hg to as high as 40 mm Hg, averaging 23 mm Hg. Because only 1 to 3 mm Hg of oxygen pressure is normally required for full support of the metabolic processes of the cell, even this low cellular Po_2 provides a considerable safety factor.

So, oxygen diffuses by the gradient (95-40-23 mm Hg) from the blood into the interstitial fluid and then into the cells.

The total quantity of oxygen bound with hemoglobin in normal arterial blood (which is 97% saturated) is approximately 19.4 milliliters per deciliter of blood. On passing through the

tissue capillaries, this amount is reduced to 14.4 milliliters. Thus, under normal conditions about 5 milliliters of oxygen is transported to the tissues by each deciliter of blood.

In hard exercise the muscle cells utilize oxygen at a rapid rate and only 4.4 ml of oxygen remains found with the hemoglobin in each deciliter of blood. Thus, 15 ml of oxygen is transported by each 100 ml of blood.

The percentage of the oxygen that blood gives up as it passes through the tissue capillaries, is called the utilization coefficient. The normal value for this is 25-35%:

$$\frac{(19.4 - 14.4) \cdot 100}{19.4} \approx 25.8\%$$

During strenuous exercise the utilization coefficient in the entire body can increase up to 75-85%:

$$\frac{(19.4 - 4.4) \cdot 100}{19.4} \approx 77.3\%$$

When oxygen is used by the cells most of it becomes carbon dioxide, and this increases the intracellular P_{CO_2} which is about 46 mm Hg. Interstitial P_{CO_2} is about 45 mm Hg. P_{CO_2} of the arterial blood entering the tissues is 40 mm Hg. So, carbon dioxide diffuses by the gradient (46-45-40 mm Hg) from the cells into the interstitial fluid and then into the blood of tissues capillaries.

Laboratory Studies

1. The Donders Model

The equipment: The Donders model.

The model suggested by Donders to demonstrate the role of diaphragm in the act of inspiration consists of wide glass bottle, the bottom of which is replaced by rubber membrane. Into the bottle the trachea with the lungs of rabbit or rat is placed. Its opening is closed by cork in which there are two holes. Through these holes two glass tubes pass. One of them connects the trachea with the atmospheric air and another one connects the cavity of bottle by the water manometer indicating the pressure in it. If one pulls the membrane, it stretches, the volume of air in the bottle increases, the manometer shows fall of the pressure in it. Under the influence of atmospheric pressure the atmospheric air enters the lungs and expands them. When the membrane is let go, the volume of the air in the bottle decreases, the pressure rises and part of the air goes out of lungs through the glass tube.

2. The Action Model of Ribs

The equipment: frog, electro stimulator, support, the mobile wooden frame, scissors, pincers, electrodes, pins.

The action model of ribs consists of the mobile wooden frame fastened to the vertical support. The nerve-muscle preparation from hind limbs of frog is fixed into the frame obliquely in the direction of external intercostals muscles. The horizontal sides of the frame imitate the two neighbor ribs, one of vertical sides fastened to the support - the vertebral column and the free vertical (anterior) side - the breast bone.

When the preparation is stimulated, the muscles contract and lift the frame. That side of frame which imitate the breast bone, moves forward. This demonstrates the mechanism of increase of chest's sagittal size.

3. Pneumography

The equipment: Pneumography, polygraph (capsule of Marey), kymograph.

The pneumograph is inflated around the chest and connected with Marey capsule. Respiratory movements of thoracic wall change the pressure of air in the pneumograph, these fluctuations of pressure are received by the capsule and cause corresponding movements of lever which records pneumogram on the drum of the kymograph.

Then the pneumogram is recorded in different states of organism (physical work, respiratory standstill and so on).

4. Measuring of Vital Capacity

The equipment: spirometer, spirit, cotton wool.

After first filling his lungs to their maximum extent with the atmospheric air the person expires to the maximum extent into the chamber of the apparatus through the mouthpiece. The floating drum rises and the scale shows the vital capacity.

Then the compounds of vital capacity are measured.

5. Determination of Minute Respiratory Volume

The equipment: The rubberized sac of Douglas, gas-meter, gas-mask, the offered rubber tube with the three-passage tap, spirit, cotton wool.

The person puts on the mask and breathes normally during 5 minutes. All this time he inspires from the atmospheric air, but the expired air is accumulated in the sac which is connected with the mask by the tube.

Then the sac is disconnected from the mask and connected with the gas-meter. All its contents are let pass through gas-meter and so, the volume of the gas which passed through the lungs is determined. Dividing the result by 5 one can calculate the minute respiratory volume. Then tying up the sac on the back of the person who runs or jumps during 1 minute, the minute respiratory volume during the physical work is determined.

Lecture 17

Regulation of Respiration.
Pecularities of Breathing under Different Conditions.
Respiratory Defence Reflexes. Artificial Respiration

The nervous system adjusts the rate of aveolar ventilation almost exactly to the demands of the body so that the arterial blood oxygen pressure and carbon dioxide pressure are hardly altered even during strenuous exercise and most other types of respiratory stress.

After separation of the brain from the spinal cord on the level of the upper cervical segments the respiratory movements stop. But when the section is made on the level of lower cervical segments, the respiratory activity of the diaphragm is preserved, but that of intercostal muscles - ceases. Because the motoneurons, by the axons of which the diaphragm is innervated, are localized in the anterior horns of III-IV cervical segments of spinal cord, and the motoneurons of intercostal muscles are in the thoracic segments. Together with the interneurons taking part in the coordination of contractions, these motoneurons form the cerebrospinal center of respiartion.

After section of brain stem between the midbrain and the pons (decerebration) the breathing in the resting state does not change essentailly. After separation of the pons from the medulla oblongata the respiratory rhythm may be preserved, but will differ from the normal rhythm. Consequently, the central mechanisms, controlling the respiratory movements, are localized in the medulla oblongata and pons and the major structures of respiratory center are in the medulla oblongata. The destruction of this center causes complete cessation of the periodical contractions of respiratory muscles.

The respiratory center is composed of several widely despersed groups of neurons located bilaterally in the medulla oblongata and pons. It is divided into three major collections of neurons: 1) a dorsal respiratory group, located in the dorsal portion of the medulla, which mainly causes inspiration, 2) a ventral respiratory group, located in the ventrolateral part of the medulla which can cause either expiration or inspiration, depending upon which neurons in the group are stimulated, 3) the pneumotaxic center, located dorsally in the superior portion of the pons, which helps to control both the rate and pattern of breathing.

The dorsal respiratory group of neurons plays the fundamental role in the control of respiration. This group extends most of the lenght of the medulla. Either all or most of its neurons are located within the nucleus of the tractus solitarius, though additional neurons in the adjacent reticular substance of the medulla probably also play important roles in respiratory control. The nucleus of the tractus solitarius is also the sensory termination of both the vagal and glossopharyngeal nerves, which transmit sensory signals into the respiratory center from the peripheral chemoreceptors, the baroreceptors and several different types of receptors in lungs.

The basic rhythm of respiration is generated mainly in the dorsal respiratory group of neurons. Even when all the peripheral nerves entering the medulla are sectioned and the brain stem is transected both above and below the medulla, this group of neurons still emits repetitive bursts of inspiratory action potentials.

The nervous signal that is transmitted to the inspiratory muscles is not an instantaneous burst of action potentials - it begins very weakly at first and increases steadily for about 2 seconds. It abruptly ceases for approximately the next 3 seconds, then begins again for still

another cycle. Thus, the inspiratory signal is said to be a ramp signal.

The pneumotaxic center transmits impulses continuously to the inspiratory area to control the "switch-off" point of the inspiratory ramp, thus controlling the duration of the filling phase of the lung cycle. When the pneumataxic signals are strong, inspiration might last for as little as 0.5 seconds; but when weak, for as long as 5 or more seconds, thus filling the lungs with a great excess of air.

So, the function of the pneumotaxic center is primarily to limit inspiration. But this has a secondary effect of increasing the rate of breathing. Because limitation of inspiration also shortens expiration and the entire period of respiration. Thus, a strong pneumotaxic signal can increase the respiration rate up to 30-40 breaths per minute, whereas a weak pneumotaxic signal may reduce the rate to only a few breaths per minute.

The neurons of the ventral respiratory group remain almost totally inactive during normal quiet respiration. Therefore, normal quiet breathing is caused only be repetitive inspiratory signals from the dorsal respiratory group transmitted mainly to the diaphragm, and expiration results from elastic recoil of the lungs and thoracic cage.

When the respiratory drive for increased pulmonary ventilation becomes greater than normal, respiratory signals then spill over into the ventral respiratory neurons from the basic oscillating mechanism of the dorsal respiratory area. As a consequence, the ventral respiratory area then does contribute its share to the respiratory drive as well.

The neurons in the ventral group are especially important in providing the powerful expiratory signals to the abdominal muscles during expiration. Thus, this area operates more or less as an overdrive mechanism when high levels of pulmonary ventilation are required.

There is another center in the lower part of the pons, called the apneustic center. It operates in association with the pneumotaxic center to control the depth of inspiration.

When the vagus nerves to the medulla have been sectioned and when the connections from the pneumotaxic center have also been blocked by transecting the pons in its midregion, the apneustic center of the lower pons sends signals to the dorsal respiratory group of neurons that prevent the "switch off" of the inspiratory ramp signal. Therefore, the lungs become almost completely filled with air, and only occasional short expiratory gasps occur.

In addition to the neural mechanisms operating entirely within the brain stem, reflex signals from the periphery also help to control respiration. In the walls of the bronchi and bronchioles throughout the lungs most important stretch receptors are located. They transmit signals through the vagi into the dorsal respiratory group of neurons when the lungs become overstretched. These signals affect inspiration in much the same way as signals from the pneumotaxic center; that is, when the lungs become overly inflated, the stretch reflectors activate an appropriate feedback response that "switches off" the inspiratory ramp and thus stops further inspiration. This is called the Hering-Breuer inflation reflex. This reflex as well as signals from the pneumotaxic center, increases the rate of respiration.

In human beings this reflex is not activated until the tidal volume increases to greater than 1.5 litres and therefore, it appears to be mainly a protective mechanism.

Simpler, activity of the respiratory center may be described as the following. Under the influence of carbon dioxide on the respiratory center via chemoreceptors the inspiratory center is excited. The impulses are transmitted to motoneurons innervating respiratory muscles and inspiration occurs. At the same time impulses from the inspiratory center are transmitted to the pneumotaxic center and from there-to the expiratory center. Expiration is stimulated and inspiration is ceased by impulses transmitted from the expiratory center to the inspiratory center. Such a movement of impulses in a circle is called reverberation.

The expiratory center is excited (besides impuses coming from the pneumotaxic center) also by reflex way under the influence of impulses conducted by vagus nerves from stretched pulmonary alveoli. This is an example of reliability of the brain. After cutting of vagus nerves

the expiratory center is excited only by impulses coming from the pneumotaxic center - breathing is not stopped, though becomes rarer and deeper. The same effect is observed after cutting of brain stem between pneumotaxic center and expiratory center when the expiratory center is excited only by impulses coming through vagus narves.

Since the ultimate goal of respiration is to maintain proper concentrations of oxygen, carbon dioxide and hydrogen ions in the tissues, it is fortunate that respiratory activity is highly responsive to chages in each of these.

The normal tension of carbon dioxide in the blood is called normocapnia, the increased tension-hypercapnia, the decreased tension-hypocapnia. The normal content of oxygen in the tissues of organism is called normoxia, the increased oxygen tension-hyperoxia, oxygen deficiency in the organism and tissues-hypoxia, oxygen deficiency in the blood-hypoxemia. Asphyxia is the state, when hypercapnia and hypoxia exist simultaneously.

The normal (quiet) breathing in resting state is called eupnea. Hypercapnia as well as acidosis are followed by hyperpnea - increase of pulmonary ventilation purposeful to the excretion of carbon dioxide surplus from the organism. Hypocapnia and alkalosis result in decrease of ventilation and then the respiratory standstill - apnea. During severe asphyxia the breathing becomes maximally deep and it is realized by the help of the subsidiary muscles of respiration. Such a breath is called dyspnea.

On the whole the normal gas content of the blood is maintained by the principle of negative feedback: hypercapnia causes intensification of the respiratory center activity and increse of pulmonary ventilation and hypocapnia results in respiratory center activity weakening and decrease of ventilation.

Using the cross circulation method, Fredericq demonstrated that the respiratory center activity depends on the composition of the blood entering the brain by the carotid arteries. The carotid arteries and jugular veins of two dogs were connected in such a way that after this operation one dog's head was supplied by the second dog's blood and vice versa. When the trachea of one dog was squeezed to cause asphyxia, hyperpnea developed in another dog. But in the first dog, despite the increase of carbon dioxide tension in arterial blood and decrease of oxygen tension, apnea was observed. Because to its head the blood from the body of the second dog was flowing in which as a result of hyperventilation carbon dioxide tension was decreased.

Carbon dioxide, hydrogen ions and moderate hypoxia cause the intensification of breathing acting on the special chemoreceptors. There are two groups of chemoreceptors, regulating the respiration: central (medullary) and peripheral (arterial) receptors.

Exess carbon dioxide or hydrogen ions stimulate mainly the respiratory center itself, causing greatly increased strength of both the inspiratory and expiratory signals to the respiratory muscles.

Oxygen does not have a significant direct effect on the respiratory center of the brain in controlling respiration. It acts on peripheral chemoreceptors located in the carotid and aortic bodies, and these in turn transmit apropriate nervous impulses to the respiratory center for control of respiration.

It is believed that none of above-mentioned three areas of the respiratory center are affected directly by changes in blood carbon dioxide or hydrogen ion concentration. Instead, an additional neuronal area, a very sensitive chemosensitive area is located bilaterally lying less than 1 mm beneath the ventral surface of medulla. This area is highly sensitive to changes in either blood P_{CO_2} or hydrogen ion concentration, and it in turn excites the other portions of the respiratory center.

The sensory neurons in the chemosensitive area are especially excited by hydrogen ions, but they do not easily cross either the blood-brain barrier or the blood - cerebrospinal fluid barrier.

Though carbon dioxide has very little direct effect to stimulate the neurons in the

chemosensitive area, it has a very potent indirect effect: it reacts with the water of the tissues to form carbonic acid. This in turn dissociates into hydrogen and bicarbonate ions; the hydrogen ions then have a potent direct stimulatory effect.

Carbon dioxide passes through both barriers almost as if they did not exist. Consequently whenever the blood P_{CO_2} increases, so also does the P_{CO_2} of both the interstitial fluid of the medulla and of the cerebrospinal fluid. In both of these fluids the carbon dioxide immediately reacts with the water to form hydrogen ions. So, more hydrogen ions are released into the respiratory, chemosensitive sensory area when the blood carbon dioxide concentration increases than when the blood hydrogen ion concentration increases and therefore, respiratory center activity is affected considerably more by changes in blood carbon dioxide than by changes in blood hydrogen ions.

Special chemoreceptors are located in several areas outside the brain (carotid bodies, aortic bodies etc.) and are especially important for detecting changes in oxygen in the blood, although they also respond to changes in carbon dioxide and hydrogen ion concentrations. The chemoreceptors transmit nervous signals to the respiratory center to help regulate respiratory activity.

Changes in arterial oxygen concentration have no direct effect on the respiratory center itself, but when the oxygen concentration in the arterial blood falls below normal, the chemoreceptors become strongly stimulated. An increase in either carbon dioxide or hydrogen ion concentration also excites the chemoreceptors and in this way indirectly increases respiratory activity. But the direct effects of both these factors on the respiratory center itself are so much more powerful than their effects mediated through the chemoreceptors (about seven times as powerful) that for most practical purposes the indirect effects through the chemoreceptors do not need to be considered.

Yet there is one difference between the peripheral and central effects of carbon dioxide: the peripheral stimulation of the chemoreceptors occurs as much as five times as rapidly as central stimulation, so that the peripheral chemoreceptors might increase the rapidity of response to carbon dioxide at the onset of exercise.

There are also other factors that affect respiration. The epithelium of the trachea, bronchi and bronchioles is supplied with sensory nerve endings (irritant receptors) which are stimulated by irritants that enter the respiratory airways. These cause coughing and sneezing, and also bronchial constriction in such diseases as asthma and emphysema.

Some sensory nerve endings occur in the alveolar walls in juxtaposition to the pulmonary capillaries (whence comes the name "J receptors"). They are stimulated when irritant chemicals are injected into the pulmonary blood and they are also excited when the pulmonary capillaries become engorged with blood or when pulmonary edema occurs in such conditions as congestive heart failure. Excitation of J receptors gives the person a feeling of dyspnea.

The role of pleura receptors in the regulation of normal breathing is not great. The stretch receptors and chemoreceptors exercising a significant influence on the respiratory center activity were not revealed in pleura. In pleurisy when the layers of pleura are inflamed and rough, each respiratory movement irritates their receptors (especially those of parietal pleura) and therefore, the respiration becomes painful.

The receptors of breathing passages (cold ceptors, mechanoreceptors, chemoreceptors, olfactory ceptors), the proprioceptors of respiratory muscles, arterial pressoreceptors also, when stimulated, exercise an influence on the respiratory center activity. For instance, rise of arterial pressure results in the intensive irritation of the carotid sinus and aortic arch pressoreceptors, and simultaneously with the depressor reflex the slight inhibittion of respiratory center activity and the decrease of ventilation occurs. The fall of arterial pressure, in the contrary, causes the insignificant intensification of pulmonary ventilation.

Practically every behavioural act of organism (even such psychical processes as thinking, attention, emotions) is followed by the changes in the breathing. Therefore, regulation of

breathing provides two groups of processes: 1) maintenance of constancy of arterial blood gaseous composition or homeostatic regulation - is realized by the respiretory center; 2) processes adapting respiration to changing conditions of the environment and life activity of the organism or the behavioural regulation - is realized by the cerebral hemispheres and brain cortex. The significant role in this regulation belongs to limbic system, subcortical structures, striopallidal system, hypothalamus, brain stem reticular formation.

The hypothalamus centers play a significant role in the regulation of breathing during behavioural acts. As a result of these centers influence on the respiratory center the intensification of breathing occurs during the defence reactions of organism (emotional excitation, painful irritation, physical work). Heat centers of hypothalamus provide increase of respiration rate when the body temperature has been risen.

Different changes in the breathing may be caused by stimulation of most areas of cortex. At the same time the most significant fluctuations of the breathing were observed during the stimulation of the somatosensory and orbital zones. Removal of cerebral cortex is followed by increase of respiratory rate and indicis of pulmonary ventilation. Consequently, the tonic inhibiting influence of cerebral cortex on the respiratory center activity is predominating.

From the standpoint of adaptation the significant changes of respiratory are realized by means of conditioned reflexes. For instance, metronome blows were combined with inspiration of the air with increased carbon dioxide concentration. After several such combinations the metronome blows became a conditioned stimulant and caused increase of pulmonary ventilation.

Thanks to conditioned reflex changes the forward (priority) control of the respiration is realized: the compitition has not begin yet, but the respiratory system of the sportsman is already prepared to fulfil the increased loading.

Respiration may be controlled voluntarily. One can hyperventilate or hypoventilate to such an extent that serious derangements in Po_2, Pco_2 and pH can occur in the blood. One can voluntarily delay his breathing during 40-60 seconds or, quite the reverse, for a short time increase pulmonary ventilation up to 170 litres per minute. The voluntary control of respiration is widely used during the speech, singing, playing the musical wind-instruments etc. The nervous pathway for voluntary control passes directly from the cortex and other higher centers downward through the corticospinal tract to the spinal neurons that drive the respiratory muscles.

An abnormality of respiration called periodic breathing occurs in a number of different disease conditions. The person breathes deeply for a short interval of time and then breathes slightly or not at all for an additional interval, the cycle repeating itself over and over again.

The most common type of periodic breathing, Cheyne-Stokes breathing, is characterrized by slowly waxing and waning respiration, occuring over and over again approximately every 40-60 seconds. The main cause of periodic breathing is decrease of extability of respiratory center neurons resulted from hypoxia or influences from the higher centers of brain. Hypocapnia also promotes the Cheyne-Stokes breathing. The beginning and intensification of breathing after the pause are connected with excitation of carotid sinus chemoreceptors caused by oxygen deficiency. When the degree of hypoxemia decreases (as a result of intensive pulmonary venti-lation), the respiration is weakened and temporarily stoppped. When the carbon dioxide tension in the blood increases, the respiration appears anew and gradually becomes more intensive.

During the physical loading the muscles need a large amount of oxygen. A human organism in resting state requires 250-350 ml oxygen per minute, when walking - up to 2.5 litres per minute and during excessive heavy physical work - up to 4 litres per minute. Simultaneously increases the formation of carbon dioxide in the muscles and sour products of metbolism which must be removed from the organism. The oxygen supply of the organism in such situation is reached by combined effort of respiration and circulation.

The pulmonary ventilation increases in proportion to the power expenditure of the orga-nism and may reach up to 120-150 litres per minute (10-20 folds of the norm). Heart rate increa-

ses up to 150-200 per minute, systolic volume - to 200 ml, cardiac output - up to 25-30 litres.

Thanks to the blood from depots rich in erythrocytes, the oxygen capacity of blood is increased. The oxygen supply of working muscles is increased significantly also owing to increase of dissociation of oxyhemoglobin as a result of very low oxygen tension, pH, increase of carbon dioxide tension and temperature.

At great altitudes man (parachutists, pilots, mountain-climbers) is exposed to the influence of decreased atmospheric pressure, the main consequence of which is hypoxia developing as a result of low partial pressure of the oxygen in the air.

At 2.5-5 km upon the sea level the pulmonary ventilation is increased (resulted from the stimulation of carotid chemoreceptors). Simultaneously arterial pressure is rised and heart rate is increased. These reactions partly compensate the decreased partial pressure of oxygen.

The increased pulmonary ventilation at a great altitude leads to decrease of the carbon dioxide partial pressure in the alveolar air and its removal from the blood. Therefore, under the condition of decreased atmospheric pressure hypoxia is combined with hypocapnia.

At the 4-5 km high altitude sicknes or mountain sickness (or aviator's sickness or hypobaropathy) develops: weakness, cyanosis, increase of heart rate, arterial pressure, headache, shallow breathing. At the altitude of more than 7 km loss of consciousness and serious disorders of respiration and blood circulation, dangerous for the life, may begin.

The breathing of pure oxygen through the mask permits to preserve the normal capacity for work even at 11-12 km. The flights into the stratosphere are possible only in the hermetic cabins or space suits.

The prolonged stay in the condition of low pressure, the life in the mountinous regions is followed by acclimatization to the oxygen deficiency which is connected with the following factors: 1) intensification of erythropoiesis; 2) increase of oxygen capacity of blood; 3) increase of pulmonary ventilation; 4) shift of the oxygen-hemoglobin dissociation curve to the right caused by the increased 2,3 diphosphoglycerate in the erythrocytes; 5) increase of the density and length of capillaries in the tissues; 6) increase of the stability of the cells (especially neurons) to the hypoxia.

During diving and caisson works man is exposed to the influence of increased atmospheric pressure. When human beings descend beneath the sea, the pressure around him increases tremendously - 1atmosphere in each 10 m, that is to say, in the depth of 90 m 10 atmospheres exercise influence on him.

In these cinditions a large amount of gases (including oxygen and nitrogen) is dissolved in the blood. Increase of oxygen partial pressure may cause the oxygen toxicity which is followed by convulsions.

If a diver has been beneath the sea long enough that large amounts of nitrogen have dissolved in his body and then suddenly comes back to the surface of the sea, significant quantities of nitrogen bubbles can develop in his body fluids either intracellularly or extracellularly, and these can cause minor or serious damage in almost any area of the body, depending on the number of bubbles formed. The gas embolism is developing. This is decompression sickness which is called also: compressed air sickness, bends diver's paralysis, dysbarism, caisson disease.

Most of the symptoms of decompression sickness are caused by gas bubbles blocking blood vessels in the different tissues. Tissue ischemia and sometimes tissue death are the result.

In most persons the symptoms are pain in the joints and muscles of the legs or arms. In some persons nervous system symptoms occur, ranging from dizziness to paralysis or collapse and unconsciousness. Finally, some persons develop "the chokes", caused by massive numbers of microbubbles plugging the capillaries of the lungs. This is characterrized by serious shortness of breath, often followed by severe pulmonary edema and occasionally death.

The sick man must be recompressed immediately to a deep level. Then decompresssion is carried out over a time period several times as long as the usual decompression period.

In very deep dives helium is used in the gas mixture instead of nitrogen because it has only one-fifth the narcotic effect of nitrogen, only about half as much volume of helium dissolves in the body tissues as nitrogen and the low density of helium keeps the airway resistance for breathing at a minimum.

Finally, the maximum speed of decompresion must be established.

The intense oxidizing properties of high pressure oxygen (hyperbaric oxygen) has very valuable therapeutic effects in several important clinical conditions. Therefore, in many medical centers large pressure tanks are available into which patients can be placed and treated with hyperbaric oxygen.

The respiratory defence reflexes are the cough reflex and the sneeze reflex. Both the coughing center and the sneezing center are localized in the medulla oblongata.

The bronchi, the trachea, especially the larynx are so sensitive to light touch that excessive amounts of any foreign matter or any other cause of irritation initiates the cough reflex. Afferent impulses pass from the respiratory passages mainly through the vagus nerves to the medulla. Then the following effects are caused. About 2.5 litres of air is inspired. The epiglottis closes and the vocal cords shut tightly to entrap the air within the lungs. The abdominal muscles as well as other expiratory muscles (such as the internal intercostales) contract forcefully. The pressure in the lungs rises to as high as 100 mm Hg or more. The vocal cords and the epiglottis suddenly open widely so that air under pressure in the lungs explodes outward. The rapidly moving air carries with it any foreign matter that is present in the bronchi or trachea.

The initiating stimulus of the sneezing reflex is irritation in the nasal passage ways, the afferent impulses pass in the fifth nerve to the medulla, where the reflex is triggered. A series of reactions similar to those for the cough reflex takes place. The uvula is depressed so that large amounts of air pass rapidly through the nose, thus helping clear the nasal passages of foreign matter.

In some cases, when cessation of the respiratory center activity results in the respiratory standstill, it is necessary to apply the artificial respiration. There are three methods of the artificial respiration :

Rhythmical pumping of the air into the lungs through respiratory tracts. This is done by the help of the resuscitation apparatus, pumps or directly (" from the mouth into the mouth").

Rhythmical squeezing and expansion of the thoracic cavity (imitation of its natural movements) by the hand or using the apparatus " iron lungs".

Rhythmical electrical stimulation of the respiratory muscles.

The resuscitators and tank respirators are applied.

DIGESTION

Lecture 18

Significance of Digestion and Methods of Investigation of Digestive Tract Functions. Secretion of Saliva. Chewing. Swallowing. Gastric Digestion. Emptying of theStomach. Vomiting

The digestive system provides such physical and chemical processing of the food, after which the nutritive matters could be absorbed into the blood and assimilated by the organism.

The physical processing of food consists of its mechanical changes - crushing, intermixing, dissolving. The chemical processing consists of successive stages of hydrolytic splitting of proteins, fats, carbohydrates by hydrolyzing enzymes (protease, lipase, carbohydrase). The enzymes are produced by the digestive glands and enter the digestive tract in the saliva, gastric, pancreatic, intestinal juices.

Amount and correlation of the enzymes in the secretion of digestive glands correspond to the peculiarities of the food. As if the digestive tract is the conveyor, gradually converting nutritive matters into monomers (proteins - into amino acids, carbohydrates - into monosaccharides, fats - into monoglycerides, glyserin and fatty acids). These can be absorved into the blood and lymph and used by the cells of organism. Water, mineral salts and some simple organic compounds of the food enter the blood unchanged.

Digestive system fulfils the following main functions:

1. The secretory function - production of digestive juices (saliva, gastric, pancreatic, intestinal juices, bile) by glandular cells.

2. The motor functions - chewing (mastication), swallowing (deglutition), movement of the food along the digestive tract and throwing away of the undigested residues - is realized by the musculature of the digestive apparatus.

3. The absorptive function is fulfilled by the mucous membrane of stomach, small and large intestines.

4. The excretory function - excretion of some metabolism products (biliary pigments), heavy metal salts from the organism.

Intracellular and extracellular (distant and contact) digestion are distinguished. Intracellular digestion consists of hydrolysis of nutritive matters in cells by the way of phagocytosis or pinocytosis (in the leukocytes and lymphoreticulohistiocytic system cells). In distant (cavitary) digestion the enzymes effect on the nutritive matters in the gastrointestinal tract, that is, the digestion is realized far from the place where the enzymes were formed. For instance, the enzymes of saliva act in the oral cavity and stomach, the pancreatic enzymes - in the small intestine cavity.

The contract or parietal (or membranaceous) digestion is realized by the enzymes, fixed on the cell membrane, on the boundary of the extracellular and intracellular media. The structure, on which the enzymes are fixed, is glycocalyx of small intestine (reticular formation from the processes of the membrane of microvilli). Just here is realized membrane digestion which is the continuation of the cavitary digestion in the stomach and small intestine.

The digestive system activity is regulated by nervous and humoral mechanisms. The

nervous regulation of the digestive functions is realized by the digestive centers by the way of the unconditioned and conditioned reflexes. The efferent pathways of these reflexes are formed by the sympathetic and parasympathetic nervous fibers. Besides the long reflex arches, which are closed in the brain and spinal cord centers, there are short ones which are closed in the peripheral extramural and intramural ganglia of the vegetative nervous system.

Since the activity of the sympathetic part of the vegetative nervous system is increased during emotions and stress situations when the activity of gastrointestinal tract is not needed and it is even undesirable, the sympathetic nerves inhibit both the secretory and motor functions of all the digestive organs. So, the secretory nerves of digestive system are parasympathetic nerves. Vagus nerve excites both secretory and motor activity of all digestive organs.

The appearance and smell of the food, the time and condition of its reception excite digestive glands by the way of the conditioned reflexes. Reception of the food irritates the oral cavity receptors and evokes the unconditioned reflexes, intensifying the digestive glands juice secretion. Such reflex influences are especially expressed in the upper part of the digestive tract. Father participation of true reflexes in the digestive functions regulation is decreased. So, the most marked are the reflex effects on the salivary, glands, then on the stomach and less - on the pancreas.

Less the significance of the reflex mechanisms of regulation - more that of the humoral mechanisms, especially of hormones which are formed in special endocrine cells of the mucous membrane of the gastrointestinal tract and pancreas. These are called the gastrointestinal hormones. They belong to the peptides. In the small and large intestine the role of the local mechanisms of regulation is significant.

Thus, there is a gradient of the distribution of the nervous and humoral regulatory mechanisms of the gastrointestinal tract. But the activity of one organ may be regulated by several mechanisms.

The local mechanical and chemical irritants influence by the way of peripheral reflexes, as well as through the digestive tract hormones. The chemical stimulants of the nerve endings in the gastrointestinal tract are acids and alkalies, products of the hydrolysis of the nutritive matters. They are brought to the digestive glands by blood flow and excite them directly or via the biogenic amines. Histamine and serotonin are important humoral regulators of the digestive organs.

In the humoral regulation of the digestive organs activity a significant role belongs to the gastrointestinal hormones. They exercise plural influences on the functions of the gastrointestinal tract and some other systems, metabolism of the whole organism. They effect on the secretion of the ferments, motor activity of the gastrointestinal tract, absorption of the water, electrolytes and nutritive matters, proliferative activity of the mucous membrane, functional activity of endocrine cells of gastrointestinal tract and some endocrine glands, cardiovascular system activity etc.

For instance, gastrin potentiates secretion of stomach, motilin-motility of the stomach and small intestine, enkephaline inhibits secretion of enzymes and so forth.

Several gastrointestinal peptide-hormones are revealed also in different structures of the brain. Some of them (vasoactive intestinal peptide, somatostat, enkephaline, the substance P) are released in the vegetative nerve endings which innervate gastrointestinal tract. Such nerve fibers are called peptidergic fibers.

The intestinal hormones take part not only in the regulation of the digestive organs activity, but also in the metabolism.

Efferent nervous and hormonal influences on the digestive organs cause three types of effects: functional, vasomotor and trophic.

Two phases of the digestive glands secretion are distinguished: 1) complex reflex phase - is realized by the help of the conditioned and unconditioned reflexes; 2) nervous - chemical phase - is realized by the neurohumoral mechanisms. These phases are interconnected.

The starting and correcting regulatory mechanisms are distinguished. The correcting

mechanisms play a significant role in adjusting the quantity and properties of the digestive secretion to the amount and pecularities of the gastric and enteric contents.

The surgical methods of investigation of the digestive organs functions in chronic experiments were improved by I. P. Pavlov.

To get saliva Pavlov suggested the method of chronic salivary fistula. The excretory duct of parotid or submandibular gland is cut, brought out through the hole made in the skin and is sewn to it. On the animal with such a chronic salivary fistula the salivation may be observed for years.

The gastric juice was first got by Basov who created the "artificial entrance into the stomach", that is, introduced a fistula into the stomach. But the juice that was obtained by this method was mixed with the food. Therefore, to get the pure gastric juice the method of "sham feeding" was offered by Pavlov: in the dog with the gastric fistula the gastroesophagotomy was made. The ends of the severed esophagus were sewn to the skin of the neck. Such animal can eat hour after hour, but the food falls out of the peripheral opening of the severed esophagus. The gastric juice is secreted by the reflex way and the pure juice is obtained through the fistula. But since the food does not enter the stomach the gastric juice secretion by the humoral way is disturbed.

The method of isolated stomach by Heidenhain permits to obtain the gastric juice by humoral way. From the greater curvature of the stomach the triangle is cut out and after putting the stitches in a wound the isolated part is sewn to the abdominal wall and a fistula is put into it. So, the small stomach is formed which is isolated from the large stomach, but preserves its blood supply. Therefore, though the food do not enter the small stomach, during the digestion the juice is secreted also in the small stomach by the humoral way. But in the course of the operation the nerves of the stomach are cut and the gastric juice secretion by the reflex way is disturbed.

The isolated small stomach by the method of Pavlov permits to observe the gastric secretion both by humoral and reflex ways. Because the section is made in such way that the innervation of stomach is preserved: the greater curvature is cut till the nerve and then only the mucous membrane is cut. The upper and lower edges of the wound are sewn separately to recover the stomach and to form a small stomach.

To get the bile Pavlov suggested to take out the common bile duct and sew it to the skin.

The enteric secretion is investigated on the isolated piece of small intestine by the methods of Thiry, Vella and Pavlov.

Thiry firmly sewed one end of the isolated piece of intestine and the other end sewed to the abdominal wall. Vella sewed both ends to the abdominal wall. But Pavlov connected both ends to form a circle and making an opening sewed it to the abdominal wall.

London's method of angiostomy and Abel's method of vividiffusion are used to study the absorption. In angiostomy cannula is introduced into the blood vessel through which the blood is obtained. In vividiffusion cannulas are introduced into the central and peripheral ends of the portal vein and they are connected with collodium tubes dipped into warm saline solution. Some substances, such as amino acids and glucose, diffuse through the collodium from blood into the saline solution.

To study the human digestive system activity the special methods are applied. By the method of masticatiography the chewing is investigated. By the help of the special capsule it is possible to collect the saliva separately from the parotid, submandibular and sublingual glands.

The secretory activity of the gastrointestinal tract is studied by the way of introducing the stomach sound or duodenal tube.

In radiotelemetry the special radiopills are swallowed which consist of electromagnetic vibrations generator, power supply and sensing element. They help to obtain an information about the temperature, pressure and pH in the stomach or intestine.

Electrogastrography is the method of recording of the bioelectric potentials generated by

the gastric muscles. Its modifications are used for recording of the motor activity of the small and large intestine and gallbladder.

X-ray methods are widely used to study the motor activity of the digestive organs. The methods of endoscopy permit to examine the mucouse membrane of stomach, initial part of the intestine, openings of the excretory ducts and take a small pieces of mucouse membrane (biopsy) for the histological and biochemical investigation.

The processes of hydrolysis and absorption are investigated by the help of the marked proteins, fats etc.

The processing of the food begins in the oral cavity where it remains on an average 15-18 seconds. Here the food is reduced to fragments, moistened by saliva, its gustatory properties are analysed and the initial hydrolysis of some nutritive matters begin.

Food irritates the gustatory, tactile, thermal receptors and by reflex way excites the secretion of salivary, gastric and pancreatic glands, motor activity of stomach, moving of the bile into duodenum. Irritation of oral cavity receptors plays a significant role in realization of chewing and swallowing.

At the initial stage of the digestion the role of saliva is significant. The principal glands of salivation are the parotid, submandibular, sublingual glands, there are also many small buccal glands.

The daily secretion of saliva normally ranges between 800 and 1500 milliliters.

Saliva contains two major types of protein secretion: 1) a serous secretion containing ptyalin (an α-amylase), which is an enzyme for digesting starches; 2) mucous secretion containing mucin for lubricating purposes. The parotid glands secrete entirely the serous type. The submandibular and sublingual glands secrete both the serous type and mucus, that is, they are the mixed glands. The buccal glands secrete only mucus.

Under basal conditions about 0.5 ml/min of saliva, almost entirely of mucous type, is secreted all the time except during sleep. This secretion plays an exceedingly important role in maintaining healthy oral tissues. The flow of saliva helps to wash away the pathogenic bacteria, as well as the food particles that provide their metabolic support. The saliva contains several factors destroying bacteria (thiocyanate ions, proteolytic enzymes, lysozyme). Often saliva contains significant amount of protein antibodies that can destroy oral bacteria, including those that cause dental caries.

Saliva has a pH between 6.0 and 7.4, a favourable range for the digestive action of ptyaline. Its specific gravity is 1.001-1.017. Saliva contains especially large quantities of potassium and bicarbonate ions, proteins, amino acids, carbohydrates, urea, ammonia, creatine.

Saliva is rich by enzymes. But α-amylase is significant which hydrolyses carbohydrates. Its effect continues in stomach till the sour gastric juice penetrates the food. The second important ferment of the saliva is maltase. So, in the oral cavity only carbohydrates are subjected to the chemical processing.

Saliva contains kallikrein which takes part in the forming of kinins. Kinins dilate the blood vessels and this way promote the blood supply of salivary glands as well as other glands during the meal.

As far back as in the last century Ludwig demonstrated that secretion of the saliva was continued even when the pressure in the salivary duct was higher than that of in the afferent artery of the salivary gland. This means that salivation cannot be explained by the filtration theory. The following facts argue that secretion of the saliva is the result of activity of the glandular cells.

During the abundant salivation requirement of the salivary gland cells in the oxygen is increased 2-3 times in comparison with resting state. Temperature of the gland is increased. Concentration of some substances (for example iodine) is significantly higher in the saliva than in the blood and tissues of the gland. In resting state in the salivary gland cells a great amount of

secretion granules are accumulated. During the salivation they move in cells and are exuded into the ducts of the glands. After abundant salivation quantity of secretion granules in the cells is sharply decreased.

Regulatory mechanisms adapt the enzyme composition and properties of saliva to the quantity and quality of food. Signals from the oral cavity receptors are transmitted to the central nervous system by afferent fibers of trigeminal, facial, glossopharyngeal and vagus nerves.

Salivary glands are controlled mainly by parasympatheic nervous signals from the salivatory nuclei which are located approximately at the juncture of the medulla oblongata and pons and are excited by both taste and tactile stimuli from the tongue and other areas of the mouth. Salivation occurs during 1-3 seconds after the food is taken. But if the stimulation is weak, this latent period may be as longer as 20-30 seconds.

Salivation can be stimulated or inhibited also by impulses arriving into the salivatory nuclei from higher centers of the central nervous system. For instance, when a person smells or eats favourite foods, salivation is greater than when disliked food is smelled or eaten. The appetite area of the brain, which partially regulates these effects, is located in close proximity to the parasympathetic centers of the anterior hypothalamus, and it functions to a great extent in response to signals from the taste and smell areas of the central cerebral cortex or amygdala.

Salivation also occurs in response to reflexes originating in the stomach and upper intestines, particularly when very irritating foods are swallowed or when a person nauseates because of some gastrointestinal abnormality. The swallowed saliva helps to remove the irritating factor in the gastrointestinal tract by diluting or neutralizing the irritating substances.

Sympathetic stimulation can also increase salivation a moderate amount, but much less so than does parasympathetic stimulation. The sympathetic nerves originate from the superior cervical ganglia and then travel along the blood vessels, to the salivary glands.

When the parasympathetic nerve fibers are stimulated a large amount of watery saliva is secreted, but the stimulation of sympathetic fibers causes secretion of small amount of thick saliva.

In the parasympathetic nerve endings, stimulating salivation acetylcholine is secreted as a mediator. It has a local effect, because in blood and tissues there is the enzyme cholinesterase which destroys acetylcholine.

If activity of cholinesterase is suppressed by eserine (physostigmine) then acetylcholine is not destroyed. It enters the blood and exercises its influence also on other organs. Therefore, if chorda tympani, coming up to one salivary gland, is stimulated in such an animal, secretion is observed also in other salivary glands.

Atropine and similar drugs (homatropine, scopolamine) block the action of acetylcholine on the muscarinic type of cholinergic effector organs. Therefore, under the influence of atropine the salivation is stopped.

In sympathetic nerve endings norepinephrine is secreted.

Salivation may be inhibited by reflex way. For instance, when the sciatic nerve is stimulated or the intestinal loops are drawn out of the abdominal cavity, the painful stimulation causes the reflex inhibition of the salivation.

The salivation is controlled by cerebral cortex. Appearance or smell of the food which once was eaten by the man or animal causes secretion of saliva by the conditioned reflex way.

The mechanical processing of food in the oral cavity is realized owing to the chewing. The anterior teeth (incisors) provide a strong cutting action and the posterior teeth (molars) - a grinding action. All the jaw muscle working together can close the teeth with a force as great as 25 kg on the incisors and 90 kg on the molars.

The chewing process is controlled by nuclei in the brain stem. Stimulation of the reticular formation near the brain stem centers can cause cintinual rhythmic chewing movements. Stimulation of areas of the hypothalamus, amygdala cerebral cortex (near the sensory areas for

taste and smell) also can cause chewing.

The chewing reflex is realized in the following way. Presence of a bolus of food in mouth causes reflex inhibition of the muscles of mastication, which allows the lower jaw to drop. The drop in turn inititates a stretch reflex of the jaw muscles that leads to rebound contraction. This automatically raises the jaw to cause closure of the teeth, but it also compresses the bolus again against the linings of the mouth, which inhibits the jaw muscles once again, allowing the jaw to drop and rebound another time.

Moistened with the saliva food after being masticated throughly forms a slippery bolus which is moved to the back of the tongue, and the swallowing reflex begins.

Swallowing is a complex coordinated and complicated mechanism, principally because the pharynx most of the time subserves several other functions besides swallowing and is converted for only a few seconds at a time into a tract for propulsion of food. It is especially important that respiration not be compromised because of swallowing.

The swallowing can be divided into three stages:

1) the voluntary stage - initiates the swallowing process;

2) the pharyngeal stage - is involuntary and constitutes the passage of food through the pharynx into the esophagus;

3) the esophageal stage - is also involuntary and promotes passage of food from the pharynx to the stomach.

By pressure of the tongue upward and backward against the palate, the food is voluntarily squeezed or rolled posteriorly into the pharynx. From here on the process of swallowing becomes automatic and ordinarily cannot be stopped.

As the bolus of food enters the pharynx, it stimulates receptor areas all around the opening of the pharynx, and impulses from these areas are transmitted through the sensory portions of the trigeminal and glossopharyngeal nerves into a region of the medulla oblongata closely associated with the tractus solitarius, which receives essentially all sensory impulses from the mouth. The areas in the medulla oblongata and lower pons that control swallowing are collectively called the deglutition or swallowing center.

The motor impulses from the swallowing center to the pharynx and upper esophagus that cause swallowing are transmitted by trigeminal, glossopharyngeal, vagus, hypoglossal and a few of the superior cervical nerves. These impulses initiate a series of automatic pharyngeal muscular contractions:

1. The soft palate is pulled upward and closes the posterior nares to prevent reflux of food into the nasal cavities.

2. The palatopharyngeal folds on either side of the pharynx are pulled medially to approximate each other and form a sagittal slit through which the food must past into the posterior pharynx. So, any large object is impeded to pass through the pharynx into the esophagus.

3. The vocal cords of the larynx are strongly approximated. The larynx is pulled upward and anteriorly by the neck muscles, the epiglottis swings backward over the opening of the larynx. Both effects prevent passage of food into the trachea.

4. The upward movement of the larynx also enlarges the opening of the esophagus. The upper esophageal sphincter or the pharyngoesophageal sphincter relaxes, allowing food to move from the posterior pharynx into the upper esophagus. Between swallows this sphincter remains strongly contracted, preventing air from going into the esophagus during respiration.

5. At the same time the entire muscular wall of the pharynx contracts, beginning in the superior part of the pharynx and spreading downwards as a rapid peristaltic wave over the middle and inferior pharyngeal muscles and thence into the esophagus, which propels the food into the esophagus.

So, at the pharyngeal stage of swallowing during 1-2 seconds the trachea is closed, the esophagus is opened and a fast peristaltic wave originating in the pharynx forces the bolus of

food into the upper esophagus.

The esophagus functions primarily to conduct food from the pharynx to the stomach. The musculature of the pharynx and the upper quarter of the esophagus is striated muscle. Therefore, the preistaltic waves in these regions are controlled only by skeletal nerve impulses in the glosspharyngeal and vagus nerves. In the lower two thirds of the esophagus the musculature is smooth, this portion of the esophagus is also strongly controlled by the vagus nerves. But when the vagus nerves to the esophagus are sectioned, the myenteric nerve plexus of the esophagus becomes excitable enough after several days to cause strong secondary peristaltic waves even without support from the vagal reflexes.

The esophagus exhibits two types of peristaltic movements:

1. Primary peristalsis - is a continuation of the peristaltic wave that begins in the pharynx and spreads into the esophagus during the pharyngeal stage of swallowing. This wave passes all the way from the pharynx to the stomach in approximately 8-10 seconds.

2. If the primary peristaltic wave fails to move into the stomach all the food that has entered the esophagus, secondary peristaltic waves result from distention of the esophagus by the retained food, and they continue until all the food has emptied into the stomach.

At the lower end of the esophagus the esophageal circular muscle is slightly thickened and functions as a lower esophageal sphincter or gastroesophageal spincter. It normally remains tonically constricted. When a peristaltic swallowing wave passes down the esophagus, this sphincter is relaxed ahead of peristaltic wave and allows easy propulsion of the swalowed food into the stomach. Rarely the sphincter does not relax satisfactorily, resulting in a condition called achalasia.

The esophageal mucosa (except in its lower eighth) is not capable of resisting for long the digestive action of gastric secretions which are highly acidic and contain many proteolytic enzymes. The tonic constriction of the lower esophageal sphincter helps to prevent significant reflux of stomach contents into the esophagus. Valvelike mechanism of short portion of the esophagus that lies immediately beneath the diaphragm before reaching the stomach, is another factor, preventing reflux.

In the stomach the food is deposited, it is subjected to the mechanical and chemical processing and evacuated into the duodenum. The gastric juice exercises antibacterial action. The stomach takes part also in the hemopoiesis - Castle's intrinsic factor is produced in the stomach.

The entire surface of the stomach is lined by mucus secreting cells. In addition, mucosa has the oxyntic (acid-forming) or gastric and pyloric glands.

The oxyntic glands comprise the proximal 80% of the stomach (the body and fundus). A typical oxyntic gland is composed of three different types of cells: the mucous neck cells, secreting mainly mucus and some pepsinogen, the peptic or chief cells, secreting mainly pepsinogen and parietal or oxyntic cells, secreting hydrochloric acid and intrinsic factor.

There are no parietal cells in the pylorus and therefore, the pyloric secretion is alkaline. The pyloric glands secrete mainly mucus for protection of the pyloric mucosa, some pepsinogen and the hormone gastrin.

In the stomach 2-2.5 litres of gastric juice is secreted in a day. Its reaction is acid (pH=1.5-1.8). The hydrochloric acid of the gastric juice:

1) causes denaturation and swelling of proteins, this way promoting their splitting by pepsins;

2) activates pepsinogens;

3) creates necessary acidic medium for pepsins to split the proteins;

4) takes part in antibacterial action of the gastric juice;

5) takes part in regulation of the digestive system activity (the intensification or inhibition of the stomach activity by nervous mechanisms and gastrointestinal hormones depends on pH of the gastric contents).

The chief enzyme of the gastric juice is pepsin which splits the proteins to the polypeptides. Several different types of pepsinogen are secreted by the peptic and mucous cells of the gastric glands (all of them perform the same functions). As soon as they come in contact with hydrochloric acid, they are immediately activated to form pepsin.

Another fraction of pepsins is called gastricsin.

Chymosin, as well as pepsin, coagulates the milk, that is, converts the water-soluble caseinogen into insoluble casein.

Small quantities of other enzymes are also secreted in the stomach juice: gastric lipase, gastric amylase and gelatinase. Gastric lipase is of little importance in adults. Gastric amylase plays also very minor role in digestion of starches. Gelatinase helps to liquefy some of the proteoglycans in meat.

Mucoids are important components of gastric juice. The mucus contains mucoids and protects the mucous membrane of stomach from mechanical and chemical irritations. The gastromucoproteid (Castle's intrinsic factor) belongs to mucoids.

Character of the food determines not only the volume and duration of the secretion, but also acidity of the juice and content of pepsin in it. The experiments on the dogs with the isolated small stomach by the method of Pavlov revealed that the bread (carbohydrates), meat (proteins) and milk (fats) evoke different secretion from the quantitative and qualitative point of view. More juice was secreted and its acidity was higher after using the meat, but the duration of secretion was longer and the juice was rich in enzymes when the bread was used. The fats after several hours of their reception suppressed the gastric juice secretion. Character of diet influences on the quantity and quality of the gastric juice in the same direction. The long (30-40 days) using of the food rich in carbohydrates (bread, vegetables) decreases the secretion. When the diet is rich in proteins (during 30-60 days) the secretion is increased.

Increase and decrease of the gastric secretion are called accordingly the hypersecretion and hyposecretion, the increase and decrease of its acidity-hyperacidity and hypoacidity.

Correspondence of the gastric juice to pecularities of the food is reached thanks to the nervous and humoral mechanisms of regulation. The gastric juice secretion is stimulated by parasympathetic nervous fibers (vagus nerve). In the nerve endings acetylcholine is secreted. Vagotomy (dissection of vagus nerves) leads to decrease of gastric juice secretion.

Sympathetic nerves inhibit secretion of gastric juice. But the sympathetic effect combined with the factors stimulating the gastric glands, cause secretion of the gastric juice rich in pepsin.

The basic neurotransmitters and hormones that directly stimulate gastric juice secretion are acetylcholine, gastrin, histamine. Acetylcholine excites secretion by all of the secretory cell types in the gastric glands including secretion of pepsinogen by the peptic cells, hydrochloric acid by the parietal cells, mucus by the mucus cells and gastrin by the gastrin cells. Both gastrin and histamine stimulate very strongly the secretion of acid by the parietal cells but have much less effect in stimulating the other cells.

A few other substances also stimulate (more slightly) the gastric secretory cells (amino acids, caffeine and possibly alcohol). The products of the digestion of the proteins which are absorbed into the blood also excite the gastric secretion.

Bombesin and motilin intensify gastric glands secretion. Secretin and cholecystokinin-pancreozymin inhibit secretion of hydrochloric acid, but they increase secretion of the pepsin.

Some interstitial hormones (gastric inhibitory peptide, vasoactive intestinal polypeptide, neurotensin, somatostatin, enterogastrone, bulbogastrone, serotonin) inhibit secretion of hydrochloric acid. They are released in the cells of the mucous membrane of intensine under the influence of the digestion products of the nutritive matters and especially that of fats.

Increased duodenum contents acidity inhibits secretion of the hydrochloric acid by the reflex way and by the help of the duodenal hormones. This is one of the self-regulation mechanisms.

Several factors inhibit the gastric secretion. The rich (fatty) food entering the duodenum inhibits the gastric glands secretion. This effect is explained partly by reflex action but mainly by formation of the enterogastrone in the duodenum. Similar hormones are revealed in the pylorus (gastrone) and urine (urogastrone).

Formation of enterogastrone was proved by Ivy who established that injection of pure extract of intestinal mucous membrane into the blood decreases the gastric juice secretion. Enterogastrone is transported by blood into the gastric glands and inhibits their secretion.

Passage of large amounts of hydrochloric acid into the duodenum also suppresses the gastric secretion.

Emotions inhibit the gastric secretion. This is explained by excitation of the sympathetic part of the vegetative nervous system and secretion of its mediator epinephrine (adrenaline). The same is the mechanism of the gastric secretion inhibition under the painful stimulation.

Suggestion under hypnosis of the unpleasant taste of the food decreased the secretion. In the experiment of sham feeding of the dog at the peak of the gastric juice secretion a cat was demonstrated to the dog and the secretion was quite stopped.

Gastric secretion occurs in three phases:

1) cephalic phase;

2) gastric phase;

3) intestinal phase.

The cephalic or complex reflex phase includes the gastric juice secretion by conditioned and unconditioned reflex ways. This phase begins by the conditioned reflexes, that is, even before the food enters the stomach or while it is being eaten. It results from the sight, smell of the food or thought about it. The greater the appetite, the more intense is the stimulation.

Neurogenic signals causing the caphalic phase of secretion can originate in the cerebral cortex or in the appetite centers of the amygdala or hypothalamus. They are transmitted through the dorsal motor nuclei of the vagi to the stomach. This phase of secretion normally accounts for less than one fifth of the gastric secretion associated with eating a meal.

The gastric juice secreted at the sight, smell of the food during chewing and swallowing was called the appetite juice. Not only the sight and smell of the food, but the sounds connected with the preparation to the meal (rattle of plates, cutlery) also cause the gastric juice secretion by the conditioned reflex way.

Some experiments demonstrate the existence of the cephalic phase of the gastric secretion. During the sham feeding of the dogs with esophagotomy after 5-10 minutes secretion of the gastric juice begins, though the food never enters the stomach.

Demonstration of meat to the cubs of several months which never ate the meat, did not cause the gastric secretion. But after feeding them even once by the meat, during such demonstration the gastric juice was secreted. This experiment proves that gastric juice secretion caused by sight and smell of the food is of conditioned reflex character.

When food enters the stomach, it excites the long vagovagal reflexes, the local enteric reflexes and the gastrin mechanism, which in turn cause secretion of gastric juice that continues through the several hours that the food remains in the stomach.

The gastric phase of secretion accounts for at least two thirds of the total gastric secretion associated with eating a meal and therefore, accounts for most of the total daily gastric secretion of about 1500 milliliters.

Existence of the gastric phase of the gastric secretion was proved in the experiment when the meat was put into the stomach of the dog through the fistula. This action caused the gastric juice secretion though the oral cavity receptors were not irritated by the food.

Releasing of the gastrin in the gastric phase is intensified also by the products of hydrolysis of proteins, amino acids and extractive matters of the meat and vegetables.

So, when the food enters the stomach the gastric secretion is excited by the mechanical as

well as chemical (humoral) stimulations.

Existence of the chemical stimulants of the gastric secretion in the blood was demonstated in the following experiment. At the peak of the gastric secretion from the artery of the dog the blood was taken and injected into the vein of the second dog, the gastric glands of which were in resting state. After the injection the gastric secretion was observed in the second dog.

When the food enters the intestine, the secretion of gastric glands is excited mainly by the chemical stimulations (the intestinal phase).

The presence of food in the upper portion of the small intestine, particularly in the duodenum, can cause the stomach to secrete small amounts of gastric juice. This is due partly to the small amounts of the gastrin (enterogastrin) that are also released by the duodenal mucosa in response to distention or chemical stimuli of the same type as those that stimulate the stomach gastrin mechanism. In addition, amino acids absorbed into the blood, as well as several other hormones or reflexes, play minor roles in causing secretion of gastric juice.

Although chyme stimulates gastric secretion during the intestinal phase of secretion, it often inhibits secretion during the gastric phase.

The motor functions of the stomach are the following:

1) storage of large amounts of food until it can be accomodated in the duodenum;

2) mixing of this food with gastric secretions until it forms a semifluid mixture called chyme;

3) emptying of the food from the stomach into the small intestine at a rate suitable for proper digestion and absorption by the small intestine.

To study the motor functions of the stomach the bulb is introduced into the stomach and is connected with the Marey's capsule or manometer through the rubber tube. The contractions of the stomach change the pressure in the capsule and these changes are recorded on the drum of the kymograph. Three types of the waves of the gastric contractions are recorded:

I - The simple monophase waves of low amplitude (5-8 mm Hg) and the duration of each wave - 5-20 seconds;

II - also simple, but more prolonged (12-60 seconds) waves with comparatively higher amplitude;

III - complex slow waves of large amplitude (35-50 mm Hg in the fundus and 80-100 mm Hg in the pylorus).

The waves of the I and II types maintain the gastric tonus and the certain pressure in its cavity, promote the mixing of the food with the gastric juice. These weak peristaltic constrictor waves, also called the stomach mixing waves, move toward the antrum along the stomach wall. They are initiated by the basic electrical rhythm (BER) consisting of "slow waves" that occur spontaneously in the stomach wall.

The slow waves, moving down the stomach, not only cause the secretions to mix with the outer portions of the stored food but also provide weak propulsion to move the food toward the antrum. When the stomach is full these mixing contractions usually begin near the midpoint of the stomach; but as the stomach empties, the contractions become stronger and also originate farther back up the stomach wall thus propelling the last vestiges of stored food into the stomach antrum. then when completely empty, the stomach becomes mainly quiescent until new food enters.

The waves of the III type are characteristic of the pylorus and they are of the propulsive character. They take part in evacuation of the gastric contents into duodenum.

Thus, on the whole, there are two types of the gastric contractions:

A- the phase contractions of peristaltic character of short duration (3 contractions per minute);

B- the tonic contractions of propulsive charactar of considerably long duration, but more frequent (6-7 per minute).

Besides the peristaltic contractions that occur when food is present in the stomach, another type of intense contractions, called hunger contractions, often occurs when the stomach has been

empty for a long time. These are rhythmical peristaltic contractions in the body of the stomach. But when they become extremely strong, they often fuse together to cause a continuing tetanic contraction lasting 2-3 minutes.

Hunger contractions are most intense in young healthy persons with high degrees of gastrointestinal tonus. They are greatly increased by a low level of blood sugar.

Sometimes during the hunger contractions the person feels a pain in the pit of the stomach (hunger pangs). Hunger pangs usually do not begin until 12-24 hours after the last ingestion of food. In starvation they reach their greatest intensity in 3-4 days and then gradually weaken in succeeding days.

Hunger contractions are often associated with a feeling of hunger and therefore are perhaps an important means by which the alimentary tract intensifies the animal drive to acquire food when a person is in a state of incipient starvation.

The gastric motility regulation is realized by the nervous and humoral mechanisms. The impulses conducted by the efferent fibers of vagus nerve intensify the gastric motility, that is, they increase the frequency and strength of the contractions, accelerate peristalsis and evacuation of the gastric contents.

But vagus nerve also takes part in the receptive relaxation of the stomach and inhibition of its motility under the influence of products of hydrolysis of fats in duodenum.

Impulses conducted by sympathetic nerves inhibit the gastric motility. They decrease frequency and strength of contractions and velocity of spreading of the peristaltic wave along the stomach.

The parasympathetic and sympathetic influences on the gastric motility are changed by reflex way as a result of the stimulation of the receptors of the oral cavity, esophagus, stomach, duodenum, small and large intestines. Their reflex arches are closed on different levels of the central nervous system, in the peripheral sympathetic nodes, in the intramural ganglia.

The gastrointestinal hormones are of great significance in the regulation of the gastric motility. Gastrin, motilin, serotonin and insulin strengthen the gastric motility, whereas secretin, cholecystokinin-pancreozymin, gastric inhibitory peptide (GIP), vasoactive intestinal polypeptide, bulbogastrone, enterogastrone inhibit it.

Mixed food remains in the stomach 6-10 hours. Fatty food is evacuated more slowly, but the food rich of carbohydrates is evacuated more rapidly. Liquids begin to pass into the intestine as soon as they enter the stomach.

Until quite recently the activity of the pyloric sphincter was considered to be the most important factor determining the velocity of stomach emptying. Realy, the opening of this sphincter provides the evacuation and its closing stops the evacuation. But experiments on animals and observations on persons after removal of the pyloric sphincter or pylorus revealed that the evacuation time of the gastric contents is near to that of the unoperated animals and people. These facts permit to come to a conclusion that evacuation of food from the stomach is conditioned more by strong contractions of all the musculature of the stomach, especially of its pyloric part, than by opening of the sphincter.

When pyloric tone is normal each strong antral peristaltic wave forces several milliliters of chyme into the the duodenum. Thus, the peristaltic waves provide a pumping action that is frequently called the " pyloric pump".

The rate at which the stomach empties is regulated by signals both from the stomach and from the duodenum. The stomach signals (nervous signals caused by distention of the stomach by food and gastrin released from the antral mucosa in response to the presence of food in the stomach) mainly increase pyloric pumping force and at the same time slightly inhibit the pyloris, thus promoting stomach emptying.

Signals from the duodenum depress the pyloric pump and increase pyloric tone. In general, when an excess volume of chyme enters the duodenum, strong negative feedback signals

(nervous and hormonal) depress the pyloric pump and enhance pyloric sphincter tone.

When food enters the duodenum, multiple nervous reflexes are initiated from the duodenum wall that pass back to the stomach and slow or even stop stomach emptying if the volume of chyme in the duodenum has become too much. The following factors can excite the enterogastric reflexes:

1) degree of distention of duodenum;

2) presence of irritation of the duodenal mucosa;

3) degree of acidity of the duodenal chyme;

4) degree of osmolality of the chyme;

5) presence of certain breakdown products (especially of proteins and fats) in the chyme.

Whenever the pH of the chyme in the duodenum falls below approximately 3, 5-4, the reflexes frequently block entirely further release of acidic stomach contents into the duodenum until the duodenal chyme can be neutralized by pancreatic and other secretions.

Vomiting is the reflex act of protective significance. It is the means by which the gastrointestinal tract rids itself of its contents when almost any part of the upper gastrointestinal tract becomes excessively irritated, overdistended or overexcitable. Impulses are transmitted by both vagal and sympathetic afferents to the bilateral vomiting center in the medulla oblongata. Appropriate motor reactions are then instituted to cause the vomiting act. The motor impulses that cause the vomiting are transmitted from the vomiting center through the trigeminal, facial, glossopharyngeal, vagus, hypoglossal nerves to the upper gastrointestinal tract and through the spinal nerves to the diaphragm and abdominal muscles.

In the early stages of excessive gastrointestinal irritation or overdistention (often many minutes before vomiting) antiperistalsis begins to occur. The antiperistalsis may begin as far down in the intestinal tract as the ileum and the antiperistaltic wave travels backward up the intestine. This process can push the intestinal contents all the way back to the duodenum and stomach. Distention of these upper portions of the gastrointestinal tract (especially the duodenum) becomes the exciting factor that initiates the actual vomiting act. During the vomiting strong intrinsic contractions occur in both the duodenum and the stomach along with beginning relaxation of the lower esophageal sphincter, thus allowing the vomitus to begin moving into the esophagus. From here a specific vomiting act involving the abdominal muscles expels the vomitus to the exterior.

When the vomiting center is sufficiently stimulated the first effects are: 1) a deep breath; 2) raising of the hyoid bone and the larynx to pull the upper esophageal sphincter open; 3) closing of the glottis; 4) lifting of the soft palate to close the posterior nares.

Next comes a strong downward contraction of the diaphragm along with simultaneous contraction of all the abdominal wall muscles. This squeezes the stomach between the two sets of muscles, building the intragastric pressure to a high level. Finally, the lower esophageal spincter relaxes completely, allowing expulsion of the gastric contents upward through the esophagus.

Vomiting can be caused also by nervous signals arising in areas of the brain outside the vomiting center, especially in a small area located bilaterally on the floor of the fourth ventricle and called the chemoreceptor trigger zone. Electrical stimulation of this area or administration of certain drugs (apomorphine, morphine, some of the digitalis derivates) directly stimulating it, initiate vomiting. Destruction of this area blocks this type of vomiting but does not block vomiting resulting from irritative stimuli in the gastrointestinal tract itself.

Rapidly changing directions of motion of the body cause some people to vomit: the motion stimulates the receptors of the labyrinth and impulses are transmitted by way of the vestibular nuclei into the cerebellum, then to the chemoreceptor trigger zone and finally to the vomiting center.

Various psychic stimuli (disquieting scents, noisome odours), stimulation of certain areas

of the hypothalamus can also cause vomiting.

Laboratory Studies

1. Effect of Neostigmine Methylsulfate and Atropine on Salivation

The equipment: rabbit, syringe, 0.05% neostygmine methylsulfate solution, 0.1% atropine sulfate solution.

Into the auricular vein of rabbit 0.05% neostigmine metylsulfate solution is injected (counting 0.3 - 0.4 ml per 1 kg of the animal's body mass). 30-60 seconds later neostigmine methylsulfate exercises its influence. The animal begins to tremble and sometimes falls, its pupil narrows and heart activity weakens. The intensive salivation is observed. After 20-30 seconds 1 ml of 0.1% atropine sulfate solution is injected into the auricular vein. 1-1.5 minutes later the initial state of the animal is restored. The salivation stops.

(The experiment was suggested by A. Kh. Aliyev from the physiology chair of Azerbaijan Medical University).

2. Observation of Frog Ciliated Epithelium Movements

The equipment: frog, the small cork plank, scissors, pincers, seconds counter, 0.6% NaCl solution, adrenaline solution (1×10^{-6} - 1×10^{-9}), acetylcholine solution (1×10^{-6} - 1×10^{-9}), eye pipette, pins, cotton wool.

The frog is made motionless (destroying its brain and spinal cord) and fixed on the cork plank. The thoracic cavity is opened and the esophagus is dessected beginning from the mouth side to the end. It is fixed by pins and washed by the physiological solution. The velocity of the movement of small piece of cork along the esophagus is determined. The same is done after the influence of adrenaline and acetylcholine.

Lecture 19

Duodenal Digestion. Pancreatic Secretion. Secretion of Bile. Digestion in Small and Large Intestines. Defecation

Food is subjected to the action of pancreatic juice, bile and intestinal juice in duodenum. Reaction of duodenal contents on an empty stomach is weak alkaline. When the portions of acidic gastric contents are evacuated into duodenum, its contents become acidic. But soon the hydrochloric acid is neutralized by the bile, pancreatic juice and the juice of duodenal glands. The reaction is changed and action of gastric pepsin stops.

Higher the duodenal contents acidity - more the secretion of pancreatic juice and the bile,and more sharply is delayed evacuation of the gastric contents into the duodenum. And simultaneously the duodenal contents passes into the small intestine more slowly.

In the hydrolysis of the nutritive matters in duodenum the pancreatic juice is of great significance.

Pancreas is a large compound gland. In addition to secreting insulin by the islets of Langerhans in the pancreas, digestive enzymes also are secreted by the pancreatic acini, and large volumes of sodium bicarbonate solution are secreted both by small ductules and larger ducts leading from the acini. The combined product then flows through a long pancreatic duct that joins the hepatic duct immediately before it empties into the duodenum through the sphincter of Oddi.

In experiment the pancreatic juice is got by the method of chronic fistula. The area of the duodenal wall, where the opening of the pancreatic duct is located, is excised and sewn to the skin.

In a day 1.5-2 litres of pancreatic juice is secreted. Its reaction is alkaline (pH-7.8- 8.4).

Pancreatic juice contains enzymes for digesting all three major types of food: proteins carbohydrates and fats. It also contains large quantities of bicarbonate ions, which play an important role in neutralizing the acid chyme emptied by the stomach into the duodenum.

The more important of proteolytic enzymes are trypsin, chymotrypsin and carboxypo-lypeptidase. There are also several elastases and nucleases which are of less importance.

The trypsin and chymotrypsin split whole and partially digested proteins into peptides of various sizes. Carboxypolypeptidase splits the peptides into the individual amino acids, thus completing the digestion of much of proteins.

The pancreatic amylase hydrolyses starches, glycogen and most other carbohydrates (except cellulose) to form disaccharides and a few trisaccharides.

The pancreatic lipase is capable of hydrolysing neutral fat into fatty acids and monoglycerids. Cholesterol esterase causes hydrolysis of cholesterol esters. Phospholipase splits fatty acids from phospholipides.

When synthesized in the pancreatic cells, the proteolytic enzymes are in the inactive forms of trypsinogen, chymotrypsinogen and procarboxypolipeptidase. These become activated only after they are secreted into the intestinal tract. Trypsinogen is activated by enterokinase which is secreted by the intestinal mucosa when chyme comes in contact with it. Trypsinogen can be activated also autocatalytically by trypsin that has already been formed. Chymotrypsinogen is activated by trypsin to form chymotrypsin and procarboxypolypeptidase is activated in a similar way.

It is important for the proteolytic enzymes of the pancreatic juice not become activated until they have been secreted into the intestine, for the trypsin and other enzymes would digest the pancreas itself. Fortunately, the same cells that secrete the proteolytic enzymes into the acini of the pancreas secrete simultaneously trypsin inhibitor.

Pancreatic juice is secreted most abundantly in response to the presence of chyme in the upper portions of the small intestine, and the characteristics of the pancreatic juice are determined to some extent by the types of food in the chyme.

Carbohydrates cause increase of amylase secretion, proteins-secretion of trypsin and chymotrypsin and fats that of lipase. The long use of the same food causes corresponding changes in the character of the pancreatic secretion.

Dynamics of the pancreatic secretion in some degree repeats the curve of the gastric secretion and this is due to the close connection between their functions and community of the control mechanisms.

Pancreatic secretion occurs in three phases, the same as for gastric secretion: the cephalic phase, the gastric phase and the intestinal phase.

During the cephalic phase the same nervous signals that cause secretion in the stomach also cause acetylcholine release by the vagal nerve endings in the pancreas. This causes moderate amount of enzymes to be secreted into the pancreatic acini.

During the gastric phase the nervous stimulation of enzyme secretion continues. In addition, the large quantities of gastrin formed in the stomach stimulate still more enzyme secretion.

After chyme enters the small intestine, pancreatic secretion becomes copious, mainly in response to the hormone secretion. In addition, cholecystokinin causes still much more increase in the secretion of enzymes.

So, four basic stimuli are important in causing pancreatic secretion: acetylcholine, gastrin, cholecystokinin (CCK) and secretin. When all the different stimuli of pancreatic secretion occur at once, the secretion is far greater than the sum of the secretions caused by each one separately, that is, various stimuli multiply or potentiate each other.

The pancreatic secretion is stimulated also by serotonin, insulin, bombesin, bile acid salts, and it is inhibited by glucagon, calcitonin, gastric inhibitory peptide, somatostatin, vasoactive intestinal polypeptide.

Besides the humoral factors the pancreatic secretion is regulated by nervous mechanisms. Stimulation of vagus nerve causes secretion of small amount of pancreatic juice rich by enzymes. The sympathetic nerves inhibit the secretory activity of pancreas.

Nervous control is realized by the conditioned and unconditioned reflex way.

In duodenal digestion the bile plays a diverse role. The liver secretes between 600 and 1200 ml bile a day. Bile serves two important functions. First, it plays a very important role in fat digestion and absorption. Second, bile serves as a means for excretion of several important waste products from the blood (bilirubin, cholesterol).

Bile acids help to emulsify the large fat particles of the food into many minute particles that can be attacked by the lipases secreted in pancreatic juice. They aid in the transport and absorption of digested fat end products to and through the intestinal mucosal membrane.

The bile increases acitivty of the pancreatic and intestinal enzymes, especially that of lipase.

As a stimulant of cholopoiesis (bile production), bile secretion, motor and secretory activity of the small intestine, the bile fulfils also the regulative function. It can stop the gastric digestion. The bile has also bacteriostatic properties.

The bile plays a great role in the absorption from intestine of the liposoluble vitamins, cholesterol, amino acids, calcium salts.

Secretion of the bile by liver cells is the continuous process, but it enters the duodenum

periodecally, during the meal. Out of this period the bile is stored in the gallbladder until needed in the duodenum. Here it is concentrated and slightly changes its composition. Therefore, the hepatic bile (C-bile), cystic bile (B-bile) and duodenal bile (A-bile) are distinguished.

Although the maximum volume of the gallbladder is only 20-60 milliliters, 450 milliliters of the bile (12 hours' bile secretion) can be stored in it. Because water, sodium, chloride and most other small electrolytes are continually absorbed by the gallbladder mucose, concentrating other bile constituents, including the bile salts, cholesterol, lecithin, bilirubin. Bile is normally concentrated 5-fold, but it can be concentrated up to a maximum of 12-20-fold.

pH of the bile is 7.3-8.0. When the pellucid hepatic bile of golden yellow colour is concentrated in the gallbladder and mucin is added to it the cystic bile is formed. It is darker and more viscous, its pH is 6.0-7.0.

The bile salts account for about half of the total solutes of bile, but also secreted or excerted in large concentrations are biliary pigments (bilirubin, biliverdin), cholesterol, fatty acids, lecithin, the usual electrolytes of plasma (Na_+, K_+, Ca_{2+}, Cl_-, HCO_3_-).

The biliary pigments are the final products of decomposition of the hemoglobin which are excreted by liver. The main human biliary pigment bilirubin which determines the colour of hepatic bile, is of red-yellow colour. Biliverdin is green.

The precursor of the bile salts is cholesterol, which is either supplied in the diet or synthesized in the liver cells and then converted to cholic acid or chenodeoxycholic acid. These acids then combine with glycine and taurine to form glyco-and tauro-conjugated bile acids. Their salts are secreted in the bile.The bile salts have two important actions in the intestinal tract. First, they fulfil the emulsifying or detergent function. Second, more important, bile salts help in the absorption of fatty acids, monoglycerids, cholesterol and other lipids from the intestinal tract.

Conditioned reflex influences and unconditioned reflexes, i.e. irritation of the gastrointestinal tract receptors (the act of eating) stimulate secretion of the bile. Irritation of vagus nerve intensifies the bile formation.

Humoral stimulants of bile formation are: the bile itself, secretin, glucagon, gastrin, cholecystokinin - pancreozymin.

When food begins to be digested in the upper gastrointestinal tract, the gallbladder also begins to empty, especially when fatty foods enter the duodenum. The basic cause of the emptying is rhythmic contracions of the wall of the gallbladder, but effective emptying also requires simultaneous relaxation of the sphincter of Oddi that guards exit of the common bile duct into the duodenum.

Cholecystokinin is the most potent stimulus for causing the gallbladder contractions. The gallbladder is also stimulated by cholinergic nerve fibers both the vagi and the enteric nervous system.

Glucagon, bombesin, calcitonin, vasoactive intestinal polypeptide inhibit contractions of gallbladder.

In the first few centimeters of the duodenum, where the pancreatic juice and bile empty into the duodenum, Brunner glands are located. They secrete mucus which protects the duodenal wall from digestion by the gastric juice.

Brunner's glands are inhibited by sympathetic stimulation which leaves the duodenal bulb unprotected. This is one of the factors that cause this area to be the site of peptic ulcers in about 50% of the cases.

On the entire surface of the small intestine crypts of Liberkuhn are located. The intestinal secretions are formed by the epithelial cells in these crypts.

The intestinal juice contains more than 20 different enzymes which take part in digestion: enterokinase, some peptidases, amylase, lactase, saccharase, lipase, phospholipase, phosphatase, nuclease.

The most important means for regulating small intestinal secretion are various local

nervous reflexes, especially reflexes initiated by tactile or irritative stimuli. Secretion in the small intestine occurs simply in response to the presence of chyme in the intestine.

Some of the same hormones that promote secretion elswhere in the gastrointestinal tract (especially secretin and cholecystokinin) increase also small intestinal secretion.

The chemical stimulants of the small intestine are products of the digestion of the nutritive matters, pancreatic juice hydrochloric acid etc.

Movements of the small intestine, as elswhere in the gastrointestinal tract, can be divided into mixing and propulsive contractions. But essentially all movements of the small intestine cause some degree of both mixing and propulsion.

Several types of contractions are distinguished: the rhythmical segmentation, the pendulum-like, peristaltic, antiperistaltic, tonic contractions.

The contractions of small intestine occur as a result of the coordinated movements of the longitudinal (external) and transversal or circulatory (internal) layers of the smooth muscle fibers.

When a portion of the small intestine becomes distended with chyme, the stretch of the intestinal wall elicits localized concentric contractions spaced at intervals along the intestine. The longitudinal length of each one of the contractions is only about 1 cm, so that each set of contractions causes segmentation of the small intestine, dividing the intestine into spaced segments that have the appearence of a chain of sausages. As one set of segmentation cont-ractions relaxes, a new set begins, but the contractions this time occur at new points between the previous contractions. These segmentation contractions "chop" the chyme 8-12 times a minute, in this way promoting progressive mixing of the solid food particles with the secretions of the small intestine.

The segmentation contractions become exceedingly weak when the excitatory activity of the enteric nervous system is blocked by atropine. This means that these contractions are not really effective without background excitation by the enteric nervous system, especially by the myenteric plexis.

During the pendulum-like contractions the chyme is moved forward and backward.

The peristaltic waves propel the chyme through small intestine. These can occur in any part of the small intestine, and they move analward at a velocity of 0.5-2 cm/sec, much faster in the proximal intestine and much slower in the terminal intestine.

Peristaltic activity of the small intestine is greatly increased after a meal. This is caused partly by the beginning entry of chyme into the duodenom but also by gastroenteric reflex that is initiated by distention of the stomach and conducted principally through the myenteric plexus from the stomach down along the wall of the small intestine.

The small intestine motility is regulated by nervous and humoral mechanisms. Great is the role of the myogenic mechanisms based on the automatism of the smooth muscles.

The intramural neurons provide the coordinated contractions of the intestine. They are influenced by the extramural, parasympathetic and sympathetic nervous mechanisms as well as the humoral factors.

The parasympathetic nervous fibers chiefly excite the small intestine contractions, whereas the sympathetic fibers inhibit them.

Stimulation of the nuclei of the anterior and intermediate areas of hypothalamus mainly excite the motility of stomach, small and large intestines. The cerebral cortex influences the intestinal motility chiefly through hypothalamus and limbic system.

Role of the second signal system in the regulation of motlity of the intestine is significant. It is demonstrated by the fact that a talk or a mere thought about the tasty food intensifies the motility of the intestine, whereas the negative attitude to the food results in inhibition of the motility. It is inhibited also under the influence of anger, fear and pain. But sometimes during certain strong emotions, for example, fear, the violent peristalsis is observed. Prof. J. H. Tagdisi

explains this "nervous diarrhaea" by the fact that usually fear forces the individual to run away, and to make this task easy, organism tries to reduce its weight.

There are some reflex influences from different parts of the gastrointestinal tract on the motor apparatus of the small intestine, the arches of which are closed in the central nervous system or in the ganglia of the vegatative nervous system. The esophagoenteric and gastroenteric reflexes excite, the enteroenteric reflexes excite or inhibit and the rectoenteric reflexes inhibit the motility of small intestine.

So, influences from the proximal parts of the gastrointestinal tract are exciting and those from the distal parts - inhibiting.

Several hormonal factors also affect the intestinal motility. Vasopressin, oxytocin, brady-kinin, serotonin, histamine, gastrin, motilin, cholecystokinin - pancreozymin enhance intestinal motility. Secretin and glucagon inhibit small intestinal motility.

The intestinal motility depends on the physical and chemical properties of the chyme. The rough food intensifies it.

From the small intestine portions of chyme pass into the large intestine through the ileocecal sphincter.

A principal function of the ileocecal valve is to prevent backflow of fecal contents from the colon into the small intestine. The lips of the ileocecal valve protrude into the lumen of the cecum and therefore are forcefully closed when any excess pressure builds up in the cecum and tries to push the cecal contents backwards. The ileocecal sphincter normally remains mildly constricted and slows the emptying of ileal contents into the cecum except immediately after a meal, when a gastroileal reflex intensifies the peristalsis in the ileum. Gastrin also increases ileal contractions and relaxes the ileocecal sphincter.

The mucosa of the large intestine, like that of the small intestine, is lined with crypts of Lieberkuhn, but in this mucosa, unlike that of the small intestine, there are no villi. Also, the epithelial cells contain almost no enzymes. Instead, they are lined almost entirely by mucous cells that secrete only mucus.

The large intestine juice contains only a small amount of alkaline phosphatase, cathepsins, peptidase, lipase, amylase and nuclease. Therefore, the chemical processing of the food in the large intestine is insignificant.

The secretion in the large intestine is conditioned by local mechanisms. The mechanical irritation increases the secretion 8-10 times.

From the small intestine about 400g of chyme passes into the large intestine a day. Here the water is absorbed intensively and gradually the chyme is converted into the fecal masses (approximately 150-250 g a day).

The large intestine contains a great amount of microorganisms. The bacterial flora of the gastrointestinal tract is the necessary condition of the life. The intestinal microflora takes part in the final decomposition of the remainders of the undigested food, inhibition of the pathogenic microbes, synthesis of some vitamins (K and B) and enzymes, in the metabolism. The bacterial enzymes split the cellulose fibers.

The digestion process in human organism continues 1-3 days, most of this time is used for the movement of the remainders of the food along the large intestine.

The principal functions of the colon are: absorption of water and electrolytes from the chyme and storage of fecal matter until it can be expelled.

The proximal half of the colon is concerned principally with absorption and the distal half- with storage. Since intense movements are not required for these functions, the movements of the colon are normally sluggish. Yet in a sluggish manner, the movements still have characteristic similar to those of the small intestine and can be divided into mixing and propulsive movements.

In the same manner that segmentation movements occur in the small intestine, large

circular constrictions also occur in the large intestine. At the same time, the longitudinal muscle of the colon, which is aggregated into three longitudinal strips (teneal coli), contract. These combined contractions of the circular and longitudinal smooth muscle cause the unstimulated portion of the large intestine to bulge outward into baglike sacs called haustrations. The haustral contractions provide a minor amount of forward propultion of the colonic contents.

Peristaltic waves of the type seen in the small intestine only rarely occur in most parts of the colon. Instead, most propulsion occurs by the slow analward movement of haustral contractions and mass movements.

A mass movement is a modified type of peristalsis. First, a constrictive ring occurs at a distended or irritated point in the colon (usually in the transverse colon) and then rapidly the 20 or more centimeters of colon distal to the constriction lose their haustrations and contract as a unit, forcing the fecal material in this segment en masse down the colon. The whole series of mass movements persist usually for only 10 minutes to half an hour, and they will then return a half day or even a day later.

Automatism of the large intestine is weaker than that of small intestine.

The large intestine has intramural innervation as well as extramural innervation which is realized by parasympathetic (vagus nerve) and sympathetic parts of the vegetative nervous system.

Role of the local mechanical and chemical irritations in the stimulation of the large intestine motility is significant.

The large intestine motility is intensified during the meal by conditioned and unconditioned reflex way when esophagus, stomach and duodenum are irritated by the food.

Serotonin, adrenaline, glucagon inhibit the large intestine motility. It is inhibited also when the rectal mechanoreceptors are irritated.

Thanks to the existence of a sharp angulation and a weak functional sphincter at the juncture between the sigmoid and the rectum, most of the time the rectum is empty of feces. Continual dribble of fecal matter through the anus is prevented by tonic constriction of the internal and external anal sphincters. The external sphincter is composed of striated voluntary muscles which are controlled by somatic nerve fibers, therefore it is under voluntary, conscious control.

When a mass movement forces feces into the rectum, the desire for defecation is normally initiated, including reflex contraction of the rectum and relaxation of the anal sphincters.

Defecation is initiated by defecation reflexes. One of them is an intrinsic reflex mediated by the local enteric nervous system. But it is weak and to be effective in causing defecation it usually must be fortified by a parasympathetic defecation reflex that involves the sacral segments of the spinal cord.

When the nerve endings in the rectum are stimulated, signals are transmitted into the spinal cord and thence reflexly back to the descending colon, sigmoid, rectum and anus by the way of parasympathetic nerve fibers in the pelvic nerves. These parasympathetic signals greatly intensify the peristaltic waves as well as relaxing the internal anal sphincter and thus convert the weak intrinsic defecation reflex into a powerful process of defecation that is sometimes effective in emptying the large bowel in one movement all the way from the splenic flexure of the colon to the anus.

The afferent signals entering the spinal cord initiate also other effects, such as taking a deep breath, closure of the glottis, contraction of the abdominal wall muscles to force the fecal contents of the colon downward, and at the same time cause the pelvic floor to extend downward and pull outward on the anal ring to evaginate the feces. Aside from the duodenocolic, gastrocolic, gastroileal, enterogastric and defecation reflexes, several other reflexes exist which inhibit gastrointestinal activity. These are peritoneointestinal, renointestinal, vesicointestinal and somatointestinal reflexes. All of them are initiated by sensory signals that pass to the prevertebral

sympathetic ganglia or to the spinal cord and then are transmitted through the sympathetic nervous system back to the gut.

Lecture 20

Absorption in the Gastrointestinal Tract.
Functions of Liver. Hunger and Satiety

Proteins, carbohydrates and fats first are digested into small enough compounds and then the digestive end products as well as water, electrolytes and vitamins are absorved.

To study the absorption the method of the marked compounds (isotopes) is applied.

Transport of micromolecules from the gastrointestinal tract cavity into internal environment of the organism may be of 3 types: passive transport, facilitated diffusion and active transport.

Passive transport includes diffusion, filtration and osmose. It is realized according to concentration, osmotic and electrochemical gradients of the substances which are transported.

Faciliated diffusion is possible by the help of the special membrane carriers.

Active transport is the transference of the substances through the membrane against concentration, osmotic and electrochemical gradients with the expenditure of energy and with the particioation of the special systems (mobile carriers, transport membrane canals).

Absorption is realized all along the gastrointestinal tract, but its intensity is different in different parts of this tract.

Practically there is almost no absorption in the oral cavity. Because the food remains here for a short time and the monomer products of the hydrolysis of the nutritive matters are not formed yet. In oral cavity only a small amount of alcohol is absorbed.

Stomach is also a poor absorptive area of the gastrointestinal tract because it lacks the villus-type of absorptive membrane and the junctions between epithelial cells are tight ones. Only a few highly lipid-soluble substances, such as alcohol and some drugs like aspirin, can be absorbed in small quantities.

The contents of the duodenum leave it rapidly and here also the absorption is realized in the jejunum and ileum.

In the absorptive surface of the intestinal mucosa there are many folds which increase the surface area of the absorptive mucosa about threefold.

Millions of small villi are located over the entire surface of the small intestine. They lie very close to each other and their presence on the mucosal surface enhances the absorptive area another ten-fold. Finally, each intestinal epithelial cell is characterized by a brush border, consisting of about 600 microvilli. This increases the surface area exposed to the intestinal materials anothee 20-fold.

Thus, combination of the folds, the villi and the microvilli increases the absorptive area of the mucosa about 600 - fold, making a tremendous total area of about 250 squire meters for the entire small intestine.

Absorption is complicated physiological process which results passage of different nutritive matters through the epithelial membrane of the intestinal wall into blood and lymph. Thanks to one-sided permeability of the intestinal epithlium, this substances do not pass in the opposite direction. Only some ions, such as Na + and Cl- can pass in both directions.

In absorption the processes of filtration, osmose and diffusion are of importance. But absorption is not the simple process of filtration, osmose or diffusion. It is the physiological function of the intestinal epithelium.

Role of filtration in the process of absorption is confirmed by the fact that the absorption depends on the hydrostatic pressure created in the intestine by contraction of smooth muscle fibers of the intestinal wall. Rise of the pressure up to 8-10 mm Hg accelerates absorption of sodium chloride two-fold. But if the pressure is rised up to 80-100 mm Hg, then the absorption is stopped as a result of the squeezing of the villi and blood vessels of the intestinal wall.

Absorption of water from the hypotonic solutions can be explained by the laws of the osmose and diffusion.

But many facts testify that the intestinal epithelium is not only a semipermeable membrane, but an organ realizing the absorption as its physiological function.

When the solution of glucose of less concentration than that of in blood is injected into the intestine, the glucose is absorbed against the gradient.

When the isotonic solution of the sodium chloride is injected into the intestine, the salt is absorbed more rapidly than the water and the intestinal contents become hypotonic.

The fact that poisons suppress the absorption testifies that it is a physiologucal function of the living tissue connected with the metabolism. This is confirmed also by the fact that absorption depends on the temperature and blood supply.

Absorption of substances in the small intestine depends also on the contraction of its villi, when their lymphatic vessels are constricted and lymph is squeezed out. The local mechanical irritation of villi intensifies their contractions. The chemical influences on the mucous membrane (peptides, some amino acids, glucose, extractive substances, bile acids) also cause contractions of the villi.

The blood of sated animal when transfused to the hungry one, intensifies the contractions of villi. This indicates the significant role of the humoral factors, among their number, of villikinin, which is formed in the mucous membrane of the duodenum and jejunum when the acid gastric contents enters the intestine. Absorption of the nutritive substances in the large intestine is not great, because they are already absorbed in the small intestine. In larhe intestine absorption of water is significant, and this is important in formation of the feces. Clucose, amino acids and other easily absorbed substances also may be absorbd in little amounts. The use of nutrient enema (introduction of the easily assimilable nutritive matters into rectum) is based on this property.

From the gastrointestinal tract into the internal environment of the organism mainly the monomers of the nutritive substances and ions are absorbed.

All of the carbohydrates are absorbed in the form of monosaccharides, only a small fraction (1%) - as disaccharides.

Little carbohydrate absorption results from simple diffusion, for the pores of the mucosa, through which diffusion occurs, are essentially impermeable to water - soluble solutes with molecular weights greater than 100.

Transport of the most of monosaccharides through the intestinal membrane can occur against large concentration gradients and therefore requires an active source of energy.

Glucose and galactose transport either ceases or is greatly reduced wherever active sodium transport is blocked. The reason is that the energy required for transport of these monosac-charides is provided seconrarily by the sodium transport system. Although a carrier protein for transport of glucose (as well as galactose) is present in the brush border of the epithelial cell, it will not transport the glucose molecule in the absence of sodium transport.

This explanation is called the sodium co-transport theory for glucose transport; it is also called secondary active transport of glucose.

Transport of fructose is slightly different from that of most other monosaccharides. It is not blocked by some of the same metabolic poisons (phlorhizin) and it does not require metabolic energy for transport, even though it does require a specific carrier. It is transported by facilitated diffusion rather than active transport. Also, it is partly converted into glucose inside the epithelial

cell before entering the portal blood.

The parasympathetic nerves intensify and sympathetic nerves inhibit absorption of carbohydrates.

Absorption of glucose is strengthened by the hormones of adrenal glands, pituitary body, thyroid gland and pnacreas, as well as by serotonin and acetylcholine. Histamine andsomatostatin inhibit this process.

Absorbed in the intestine, monosaccharides enter the liver by the portal vein system. Its considerable part is delayed here and is converted into glycogen.

More than 99% of the final protein digestive products that are absorbed are individual amino acids, with only rare absorption of peptides.

Both the method of angiostomy by London and the method of vividiffusion by Abel demonstrate that at the peak of the digestion of food rich of proteins content of amino acids in the blood of portal vein is sharply increased.

The energy for most of this transport is supplied by a sodium co-transport mechanism. This is called secondary active transport of the amino acids or peptides.

A few amino acids are transported by a process of facilitated diffusion.

When fed by the animal proteins, 95-99% of them is digested and absorbed, but of vegetable proteins - only 75-80% is absorbed.

Fats are digested to form monoglycerides and free fatty acids; both of these end products become dissolved in the central lipid portion of the bile acid micelles. These micelles are soluble in the chyme. In this form the monoglycerides and the fatty acids are carried to the surfaces of the microvilli, diffuse first into the local fluids and then immediately through the epithelial membrane. This leaves the bile acid micelles still in the chyme. They diffuse back through the chyme and absorb still more monoglycerides and fatty acids similarly carrying them to the epithelial cells. Thus, the bile acids perform a "ferrying" function. In the presence of bile acids about 97% of the fat is absorbed, whereas in their absence only 50-60% is absorbed.

After entering the epithelial cells, the fatty acids and monoglycerides are taken up by the smooth endoplasmic reticulum and are mainly recombined to form new triglycerides.

Triglycerides aggregate within the endoplasmic reticulum into globules along with cholesterol and phospholipids. Small of β-lipoprotein coat part of the surface of each globule. In this form the globule diffuses to the side of the epithelial cell and is excreted by the process of cellular exocytosis into the space between the cells; from there it passes into the lymph. These globules are then called chylomicrons.

Between 80 and 90 per cent of all fat absorbed from the gut is absorbed in this manner and is transported to the blood by the way of the thoracic lymph in the form of chylomicrons.

Small quantities of short chain fatty acids, such as those from butter-fat, are absorbed directly into the portal blood. Because these fatty acids are more water-soluble and mostly are not reconverted into triglycerides by the endoplasmic reticulum.

Absorption of fats is intensified by the parasympathetic influences and slowed down by sympathetic influences. It is intensified also by the hormones of the adrenal cortex, thyroid gland, pituitary body as well as by the duodenal hormones (secretin and cholecystokinin / pancreozymin).

The total quantity of fluid that must be absorbed each day is equal to the ingested fluid (1,5 litres) plus that secreted in the various gastrointestinal secretions (about 7 litres). The considerable part of this is absorbed in the small intestine, leaving only 1.5 litres to pass through the ileocecal valve into the colon each day.

Water is transported through the intestinal membrane entirely by the process of diffusion and this diffusion obeys the usual laws of osmosis.

But water can be transported in the opposite direction from the plasma into the chyme (especially when hyperosmotic solutions are discharged from the stomach into the duodenum).

As dissolved substances are absorbed from the lumen of the gut into the blood, the absorption tends to decrease the osmotic pressure of the chyme. But water diffuses so readily through the intestinal membrane that it almost instantaneously follows the absorbed substances into the blood.

20-30 grams of sodium are secreted into the intestinal secretions each day. In addition, the normal person eats 5-8 grams of sodium each day. Thus, small intestine must absorb 25-35 grams of sodium each day, which is equal to about 1/7 of all the sodium present in the body. Less than 0.5% of the intestinal sodium is lost in the feces each day.

The sodium plays an important role in the absorption of sugars and amino acids.

The motive power for the sodium absorption is provided by active transport of sodium from inside the epithelial cells through the basal and side walls of these cells into the intercellular spaces. Obeying the usual laws of active transport, this process requires energy and is catalyzed by appropriate ATP-ase carrier enzymes in the cell membrane.

Part of the sodium is absorbed along with chloride ions that are passively "dragged" along by the positive electrical charges of the sodium ion. Other sodium ions are absorbed while either potassium or hydrogen ions are transported in the opposite direction in exchange for the sodium ions.

The active transport of sodium reduces its concentration inside the cell and sodium moves down an electrochemical gradient from the chyme through the brush border of the epithelial cell into the epithelial cell cytoplasm.

During dehydration of the organism large amounts of aldosterone are secreted by adrenal glands. The excess aldosterone enhances all the enzyme and transport mechanisms for all aspects of sodium absorption by the intestinal epithelial cells. The increased sodium absorption causes secondary increase also in absorption of chloride ions, water and some other substances.

The bicarbonate ion is absorbed in indirect way.. When sodium ions are absorbed, moderate amounts of hydrogen ions are secreted into the lumen of the gut. They combine with the bicarbonate ions to form carbonic acid which then dissociates to form H_2O and CO_2. The water remains as part of the chyme in the intestines, but the carbon dioxide is readily absorbed into the blood and subsequently expired through the lungs.

Calcium ions are actively absorbed, especially from the duodenum, and calcium ion absorption is exactly controlled in relation to the need of the body for calcium. The important factors controlling calcium absorption are parathyroid hormone and vitamin D. The parathyroid hormone activates vitamin D in the kidneys and the activated vitamin D enhances calcium absorption.

Iron ions are also actively absorbed from the small intestine. Potassium, magnesium, phosphate and other ions can also be actively absorbed through the mucosa.

In general, the monovalent ions are absorbed with ease and in great quantities, whereas bivalent ions are absorbed in small amounts (fortunately, they are needed by body just in small quantiies).

Practically all the blood from the gastrointestinal tract enters the liver by the portal vein system. Small amount of poisonous substances enters from the intestine into the liver. In the liver they are converted into nontoxic products by the way of oxidation, reduction, methilation, acetylation and conjucation with other substances.

As a matter of fact, liver is the physiological barrier between the internal and external environments of the organism, that is, between blood and gastrointestinal tract.

The barrier function of the liver is demonstrated by the method of Ecc. The portal vein is ligated and connected with the vena cava inferior. After this operation the blood from the intestine passes by the liver and the products of the decomposition of the proteins, which are usually detoxicated in the liver, poison the organism. This leads to the death.

The liver fulfils also many other vital functions. It is called the biochemical laboratory of

the organism.

The basic functions of the liver can be divided into its vascular functions for storage of blood, its metabolic functions concerned with the majority of the metabolic systems and its secretory and excretory functions that are responsible for forming the bile.

Liver is the organ of hemopoieses in the intrauterine period.

Liver is depot of blood, antianemia factor, minerals (iron, copper), vitamins. It takes part in the metabolism of proteins carbohydrates, fats, water. Some hormones are destroyed in liver. Liver takes part in the temperature control.

Hunger and thirst are congenital motivations, that is, congenital reactions - drives, directed to satisfaction of the vital needs of the organism. They force the individual to ceratin purposeful activity leading to removal of the state which caused it.

The term hunger means a craving for food and it is associated with a number of objective sensations. For instance, in a person who has not had food for many hours, the stomach undergoes intense rhytmic contractions called hunger contractions. These cause a tight or gnawing feeling in the pit of the stomach and sometimes actually cause pain called hunger pangs.

But even after the stomach is completely removed, the physical sensations of hunger still occur and craving for food still makes the person search for an adequate food supply.

The term appetite is often used in the same sense as hunger except that it usually implies desire for specific types of food instead of food in general. Appetite helps a person choose the quality of food to eat.

Satiety is the opposite of hunger. It means a feeling of fulfilment in the quest for food. Satiety usually results from a filling meal, particularly when the person's nutritional storage depots, the adipose tissue and glycogen stores are already filled.

The sense of hunger occurs periodically, every 1-1.5 hours, and lasts 15-20 minutes. It manifests itself by unpleasant sensations in the area of the stomach which are often followed by the nausea, feeling of general weakness.

Usually the hunger occurs when the stomach is empty. But disturbances of function of some cerebral centers causes the pathological voracity called bulimia.

Apperance of hunger, that is, according sensations and certain activity of the organism occur as a result of the exciting of broad region of the central nervous system which is designated as alimentary center. This center's function is regulation of the alimentary behaviour, i.e., getting and taking of foodand coordination of the activity of the gastrointestinal tract as a whole.

In the regulation of the alimentary behaviour hypothalamus plays an important role. This was studied by the way of electrical stimulation and destruction of hypothalamus nuclei in experiments.

Stimulation of the lateral hypothalamus forces an animal to eat voraciously, which is called hyperphagia. When the ventromedial nuclei of hypothalamus are stimulated, complete satiety occurs, and even in the presence of highly appetizing food the animal will still refuse to eat. This is aphagia.

Destructive lesions of the two areas cause results exactly opposite to those caused by stimulation. That is, ventromedial lesions cause voracious and continued eating until the animal becomes extremely obese, sometimes as large as four times normal size. Lesions of the lateral nuclei on the two sides of the hypothalamus cause complete lack of desire for food and progressive inanition of the animal.

Thus, the lateral nuclei of the hypothalamus may be called hunger center or feeding center and the ventromedial nuclei of the hypothalamus - satiety center.

The feeding center operates by directly exciting the emotional drive to search for food (while also stimulating other emotional drives as well). It is believed that the satiety center

opeates primarily by inhibiting the feeding center.

The actual mechanisms of feeding are controlled by ceters in the brain stem. If the brain is sectioned below hypothalamus but above the mesencephalon, the animal can still perform tha basic mechanical features of the feeding process (salivate, lick its lips, chew, swallow). The function of the hypothalamus in feeding is to excite the lower centers to activity and to control the quantity of food intake.

The centers, higher than the hypothalamus also play important role in the control of feeding, particularly in the control of appetite. These include limbic system, especially the amygdala and the prefrontal cortex, which are closely coupled with the hypothalamus. Hypothalamus nuclei "adjust" the higher centers accordingly.

Some areas of amygdala greatly increase feeding whereas others inhibit it. Besides, stimulation of some areas of the amygdala elicits the mechanical act of feeding.

The most important effect of destruction of the amygdala on both sides is a "psychic blindness" in the choice of foods, when the mechanism of appetite control of the type and quality of food is lost.

Regulation of food may be divided into:

1) nutritional or long-term regulation which is concerned primarily with long-term mainterance of normal quantities of nutrient stores in the body;

2) alimentary or short-term regulation which is concerned primarily with preventing over-eating at the time of each meal.

The feeding control mechanisms of the body are geared to its nutritional status. Some of the nutritional factors that control the degree of activity of the feeding center are the following.

Decrease in blood glucose concentration causes hunger. This fact has led to the glucostatic theory of hunger and feeding regulation. The same effect for blood amino acids concentrations and blood concentration of break-down products of lipids (keto acids and some fatty acids) has led to the aminostatic and lipostatic theories. That is, when the availability of any of the three major types of food decreases, the animal automatically increases its feeding, which returns the blood metabolite concentrations back toward normal.

Neurophysiological studies have also substantiated the glucostatic, aminostatic and lipostatic theories.

There is interaction within the hypothalamus between the temperature-regulating system and the food intake-regulating system. When an animal is exposed to cold, it tends to overeat and when exposed to heat, it tends to undereat. It is important because by increased food intake in the cold animal increases its metabolic rate.

As a summary of long-term regulation we can make the following general statement. When the nutrient stores of the body fall below normal, the feeding center of the hypothalamus becomes highly active and the person exhibits increased hunger,. When the nutrient stores are abundant, the person loses the hunger and develops a state of satiety.

Above-mentioned nutritional feedback mechanisms take an hour or several hours before enough quantities of the nutritional factors are absorbed into the blood to cause the necessary inhibition of eating. But it is important that the person not overeat and even that he eat an amount of blood that approximates his nutritional needs. Different types of signals are important for this puprose:

1. When gastrointestinal tract (especially stomach and duodenum) becomes filled and distended, inhibitory signals are transmitted mainly by the way of vagi to suppress the feeding center, thereby reducting the desire for food.

2. The gastrointestinal hormone cholecystokinin, released mainly in response to fat entering the duodenum, has a strong direct effect on the feeding center to reduce further eating. Besides, the presence of food in stomach and duodenum causes the pancreas to secrete significant quantities of glucagon and insulin, both of which also suppress the hypothalamic

feeding center.

3. When a person with an esophageal fistula is fed large quantities of food, even though this food is immediately lost again to the exterior, the degree of hunger is decreased after a reasonable quantity of food has passed through the mouth. This effect occurs despite the fact that the gastrointestinal tract does not become the least bit filled. Therefore, it is postulated that various "oral factors" relating to feeding, such as chewing, salivation, swallowing and tasting, "meter" the food as it passes through the mouth, and after a certain amount has passed, the hypothalamic feeding center becomes inhibited. But the inhibition caused by this mechanism is considerably less intense and less lasting (only 20-40 minutes) than is the inhibition caused by gastrointestinal filling.

It is important to have both long-term and short-term regulatory systems for feeding. The long-term regulatory system, which includes all the metabolite feedback mechanisms, helps to maintain constant stores of nutrients in the tissues, preveting these from becoming too low or too high.

The short-term regulatory stimuli make the individual eat smaller quantities at a time, thus allowing food to pass through the gastrointestinal tract at a steadier pace so that its digestive and absorptive mechanisms can work at more optimal rates rather than becoming exessively overburdened only when the food is needed. They prevent from eating amounts of food at each meal that would be too much for the metabolic storage systems once the food has all been absorbed.

Influences of blood composition on the nervous centers related to the alimentary behaviour was demonstrated in the experiments where the electrical activity of the different areas of the alimentary center was recorded. During the hunger in the ventromedical nuclei of the hypothalamus (satiety center) the low activity was recorded, but in the lateral nuclei (feeding center) the activity was somewhat increased. In such state of organism in the prefrontal cortex the reaction of activation was recorded which testifies that these parts of the brain are excited.

After the intravenous injection of glucose the electrical activity was decreased in lateral nuclei and slighly increased in the ventromedial nuclei of hypothalamus. In the prefrontal cortex the slow waves of higher amplitude appeared which were characteristic of fed-up animal in resting state.

The same effect was observed after infusion of the blood of the sated animal to the hungry animal.

Laboratory Studies

1. Observation of Intestinal Absorption

The equipment: rabbit (cat or rat), set of surgical instruments, supports, seconds counter, graduated glass tubes, clamps, gause, napkins, NaCl solutions (5%, 1.5%, 0.9%), 0.005% sodium-fluoride solution.

By the way of chirurgical operation on the anesthetized animal part of small intestine (10-15 cm) is isolated, but its nervous and vascular connections are preserved. Then graduated tubes are introduced into both ends of the isolated intestine and fixed to the supports in vertical position. It is washed and filled with isotonic NaCl solution. After 5 minutes the amount of the absorbed solution is measured. The experiment is repeated with hypotonic and hypertonic solutions. Addition of NaF to these solutions leads to decrease of absorption velocity.

2. Observation of Alimentary Behaviour of Rabbit

The equipment: rabbit or cat with electrodes implanted in the lateral hypothalamus area, electrostimulator.

The sated animal does not respond to the food. Then through implanted electrodes the lateral hypothalamus area is stimulated using electrostimulator. The sated animal acts as if it is hungry, that is, it begins to eat with greediness. When the stimulation is stopped, the animal rejects the food.

3. Recording of Brain Electric Activity during Hunger and Satiation

The equipment: the cat with the elctrodes implanted in the frontal lobe of cerebral cortex, electroencephalograph, 40% glucose solution.

The brain electrical activity of the hungry animal is recorded. Then slowly 20 ml of 40% glucose is injected into the vein. During 15-30 minutes the brain electrical activity is recorded.

METABOLISM. TEMPERATURE EGULATION

Lecture 21

Metabolism

Metabolism is the most important function of living organism and characteristic sign of the life. As a result of metabolism the cellular structures are continuously formed, renewed and destroyed, different chemical compounds are synthesized and destroyed. When the chemical compounds are splitted, their potential energy is released and converted into the kinetic (mainly thermal and mechanical, partly-electrical) energy.

To compensate the power expenditures of the organism, preserve the body mass and satisfy the requirements of growth the feeding provides proteins, fats, carbohydrates, vitamins, mineral salts and water according to the needs of the organism.

Excretory organs provide the clearence of the body from the end products which are formed when different substances are splitted.

The main place among the organic elements belongs to proteins. They make more than 50% of dry mass of the cell. The proteins fulfil a number of most important biological functions. All the totality of the metabolism in the organism (breathing digestion, excretion) is provided by the activity of enzymes which are proteins. All the motor functions of the organism are also provided by interaction of contractile proteins (actin and myosin).

Proteins entering with the food fulfil the plastic and energetic functions, that is, they form different structural components of the cell and provide organism by the energy which is released during the splitting of proteins.

In the tissues the proteins are continuously disintegrated and synthesized, and therefore, the proteins of the organism are always renewed. The renewal of the proteins of the liver, mucous membrane of the intestine and other internal organs and blood plasma is more rapid, then come the proteins of the cells of the brain, heart, sexual glands and more slower is the renewal of proteins of muscles, skin and especially of the supporting tissues (tendons, bones, cartilages).

From 20 amino acids which are in the proteins, 12 may be synthesized in the organism. They are called the replaceable amino acids. The other 8 amino acids cannot be synthesized in the organism, and they are called nonreplaceable amino acids. The nonreplaceable amino acids of human organism are: leucine, isoleucine, valine, methionine, lysine, threonine, phenylalanine, tryptophan.

The long life and normal state of the organism is not possible even if one of the nonreplaceable amino acids is absent in the food. Without the nonreplaceable amino acids synthesis of proteins is sharply disturbed and the negative nitrogen balance develops, the growth of the organism stops, the body mass is decreased.

The proteins which contain all set of necessary amino acids in ratio providing normal process of the synthesis, are biologically complete proteins. The proteins which do not contain some of amino acids or contain them in little amounts are incomplete proteins. Biologically most valuable proteins are those of meat, eggs, fish, caviare, milk. The proteins of maize, wheat, barley are incomplete proteins.

The human food must contain no less than 30 % of complete proteins. Practically it is important that two incomplete proteins, one of which do not contain some amino acids and

other- another ones, together can provide the needs of the organism.

The ratio of the amount of nitrogen received by organism in the food to that of excreted from the organism is called the nitrogen balance. Since the main source of the nitrogen in the organism is protein, by the nitrogen balance one can judge about the amounts, of the proteins, received by the organism and destroyed in it. The amount of the nitrogen received by the food differs from that of assimilated by organism, because part of the nitrogen is lost in feces.

Protein contains 16% of nitrogen, that is, 1 gramme of nitrogen is contained in 6.25 grammes of the protein. So, when the amount of the assimilated nitrogen is known, one can easily calculate the quantity of the protein assimilated by the organism, multiplying the amount of the nitrogen by 6.25. The assimilated nitrogen is calculated by the difference of nitrogen content in the food and feces.

In adult persons during the adequate diet the amount of the nitrogen introduced into the organism and that of excreted from the organism are equal. This state is called the nitrogen equilibrium.

If more nitrogen is received and less excreted, the nitrogen balance becomes positive. The stable nitrogen balance is observed during the increased body mass (growth of the organism, pregnancy, recovery after severe disease, intensive sports training causing increase of the musculature mass). In these conditions retention of nitrogen is observed, that is, nitrogen is delayed in the organism.

If the amount of the excreted nitrogen exceeds that of received by the organism, the nitrogen balance is negative. The negative nitrogen balance is observed during the protein deprivation as well as in the cases when organism does not receive some amino acids, necessary for the synthesis of proteins.

Disintegration of the proteins in the organism when the proteins are absent in the food but other nutritive matters are introduced in sufficient amounts, reflects the minimum expenditures that are connected with the basic vital processes. These minimal expenditures of proteins in the resting state of the organism when calculated for 1 kg of body mass, are called amortization coefficient.

The amortization coefficient for adult person is equal to 0.028-0.075 g of nitrogen for 1 kg of body mass in a day.

During the protein deficiency the body mass is gradually decreased, even if the organism receives sufficient amounts of the fats, carbohydrates, mineral salts, vitamins and water. Because the expenditure of the tissue proteins which are minimal in this condition and equal to the amortization coefficient, are not compensated. Therefore, the long protein deprivation, as well as complete starvation (fasting) leads to the death. In particular, the growing organisms bear the protein deficiency severely.

Some hormones realize the neuroendocrine regulation of the protein metabolism.

During the growth of the organism somatotropic hormone of pituitary body stimulates increase of the mass of all organs and tissues. In adult persons it provides the process of protein synthesis.

Hormones of thyroid gland-thyroxin and triiodothyronine in certain concentrations stimulate synthesis of proteins and this way activate growth, development and differentiation of tissues and organs.

The hormones of adrenal cortex-the glucocorticoids (hydrocortisone, corticosterone) intensify decomposition of proteins in tissues, especially in the muscular and lymphoid tissues. But in the liver they stimulate synthesis of proteins.

Fats and lipoids (phosphatides, sterols, cerebrosides etc.) are important for their plastic and power functions. The plastic role of lipides is determined by the fact that they are in the cell membrane. Their power role is also great. The heat value of lipides is twice more than that of carbohydrates or proteins.

The fats of the human and animal organism are the triglycerides of the oleic, palmitic, stearic and other higher fatty acids.

Most of the reserve fat in the organism is in adipose (fatty) tissue which is in subcutaneous fat, around some internal organs (for instances, perinephric fat) and in some organs (for example, in liver and muscles).

The total content of the fat in organism is in average 0-20% of body mass and in pathological obesity may reach even 50%.

The quantity of reserve fat depends on character of the feeding, quantity of food, sex, age, the constitutional peculiarities of organism. But the quantity of protoplasmatic fat is stable and constant.

Absorbed from the intestine the fat enters chiefly the lymph and in less amounts-directly the blood.

In the experiments when the animals were given the marked fats containing carbon and hydrogen isotopes, it was demonstrated that the fats absorbed in the intestine, enter directly the adipose tissue which is the fatty depot. The fat from here may pass into the blood and entering the tissues, it is used as power material. Role of liver in fat metabolism is significant.

The fat of different animals and even the fat of different organs differ by their chemical composition, physical and chemical properties. Accumulated in the body fat has specific properties of that animal, but the specific properties of fats are incomparably less marked than that of proteins.

Abundant feeding for a long time by the same type of fat may change composition of the fat that is accumulated in the organism. For instance, the properties of subcutaneous fat of the polynesians, using a large amounts of coconut oil, approximate to the oil of coconuts.

When the fats are absent in the food, but it is rich of carbohydrates, the fat may be synthesized from them in the organism.

Some unsaturated fatty acids (linolic, linolenic, arachidonic acids) are nonreplaceable, that is, they are not formed in the human or animal organism from other fatty acids. But these acids are necessary for normal vital activity. Besides, some vitamins are liposoluble and their absorption requires existence of fats. Therefore, deprivation of fats for a long time causes severe pathological disturbances in the organism.

The process of lipogenesis, the accumulation and mobilization of fats are regulated by nervous, endocrine and tissue mechanisms. They are closely connected with carbohydrate metabolism. Rise of glucose concentration in blood decreases the decomposition of triglycerides and activates their synthesis. But decrease of glucose concentration inhibits synthesis of tryglycerides and intensifies their splitting.

Thus, the intercommunication of fat and carbohydrate metabolisms is directed to providing of power wants of organism.

Hormones of adrenal medulla (adrenaline, norepinephrine), the somatotropic hormone of pituitary body and the thyroid gland hormone thyroxin have a marked fat mobilizing action.

Hormones of adrenal cortex-glucocorticoids and pancreatic hormone insulin inhibit mobilization of fats.

There are direct nervous influences on the fat metabolism. The parasympathetic nerves promote adiposis. But the sympathetic nerves inhibit the synthesis of triglycerides and intensify their splitting. For instance, after cutting of celiac nerve on one side of the starving cat, to the end of the starvation more perirenal fat remains on the denervated side than on other side.

The nervous influences on the fat metabolism are controlled by hypothalamus. When the ventromedial nuclei of hypothalamus are destroyed, appetite is increased and this leads to the adiposis. Stimulation of the ventromedial nuclei on the contrary, causes loss of appetite and emaciation.

Phosphatides and sterols are in the cell structures. The nervous tissue is especially rich of

phosphatides.

Phosphatides are synthesized in the intestinal wall and liver. The liver is depot of some phosphatides (lecithin).

Sterols are of great physiological significance. For example, cholesterol is present in the cell membrane. It is the source for formation of bile acids, hormones of adrenal cortex and sexual glands. A great importance is attached to cholesterol in the origin and development of some diseases and especially of atherosclerosis.

Some sterols of food (for instance, vitamin D) are physiologically very active.

The main role of carbohydrates is determined by their power function. The blood glucose is the immediate source of energy in organism. Rapidity of its splitting and oxidation and possibility of its rapid extraction from the depot provide the urgent mobilization of power resources in the case of power expenditure, emotional excitement, intensive muscular work and so on.

The blood glucose level (4.4 -6.7 mmol/l or 80-120 mg%) is the most important homeostatic constant of organism. Significant decrease of blood glucose concentration leads to the development of hypoglycemic coma, whereas the significant increase of this concentration results in the hyperglycemic coma. The central nervous system is particularly sensitive to decrease of the glucose concentration in blood.

Absorbed in the intestine, glucose enters the blood and it is transported into the liver. Here from glucose the glycogen is synthesized. When the isolated liver is perfused by the glucose solution the glycogen content in liver tissue is increased.

Amount of glycogen in the liver can reach 150-200 grammes. This is the reserve carbohydrates.

If a great amount of glucose enters the gastrointestinal tract and blood glucose content is considerably increased, this alimentary hypoglycemia causes also the glucosuria, i.e., the glucose is excreted in urine. This occurs when blood glucose content is more than 8.9-10 mmol/l (160-180 mg%).

In absolute absence of carbohydrates in food they are formed in the organism from the products of splitting of fats and proteins.

Decrease of blood glucose causes splitting of glycogen in the liver and the glucose enters the blood. Such mobilization of glycogen provides the relative constancy of blood glucose content. Glycogen is accumulated also in the muscles.

The carbohydrate metabolism is regulated by the principle of negative feedback and the main parameter is maintenance of the blood glucose content within the limits of 4.4-6.7 mmol/l. Changes of glucose content in the blood is perceived by the glucoreceptors in liver blood vessels and cells of ventromedial hypothalamus. Some areas of central nervous system take part in the regulation of the carbohydrate metabolism.

In 1849 Claude Bernard demonstrated that puncture of medulla oblongata in the area of the bottom of the fourth ventricle of the brain causes hyperglycemia, that is, increase of blood glucose content. Stimulation of hypothalamus may cause the same effect. The regulative influences of hypothalamus are realized by the vegetative nerves and humoral way including the endocrine glands.

In carbohydrate metabolism the role of insulin is significant. Insulin is hormone of β-cells of pancreatic island. It causes increase of blood glucose content and intensifies the glycogen formation in liver. The insulin deficit leads to the stable hyperglycemia and glucosuria, and the diabetes mellitus develops.

Some hormones cause increase of blood glucose content. These "contra-insular" hormones are produced in the α-cells of pancreatic island (glucagon), adrenal medulla (adrenalin), adrenal cortex (glucocorticoids), pituitary gland (somatotropic hormone), thyroid gland (thyroxin).

60% of body mass in adults and 70% that of newborns consists of water. Water is the

medium where the metabolic processes are realized in cells, tissues and organs. Continuous entering of the water into the organism is one of the main conditions of the vital activity.

The basic mass of water (71%) in the organism is the intracellular water in the composition of the cell protoplasm. The extracellular water is in the tissue (interstitial) fluid (21%) and blood plasma (8%).

The daily water balance of organism is 2.2-2.8 litres:

drinked - 1.5 litres;

in the food - 0.6-0.9 litres;

formed in the oxidation processes-0.3-0.4 litres.

Excreted:

by urine - 1.5 litres;

by sweat - 0.4-0.6 litres;

by the expired air - 0.35-0.4 litres;

by feces - 0.1-0.15 litres.

The normal balance of mineral substances is also important. Sodium, chlorine, calcium, phosphorus, sulfur, potassium, iron, iodine and other macroelements are necessary for normal vital activity organism.

The daily balance of sodium is 4-5 g (10-12.5 g NaCl), of calcium - 3-4 g, of potassium - 2-3g, of phosphorus -1-2 g, of iron -10-30 mg.

The mineral substances which compose less than 0.001% of body mass are called microelements or trace elements (manganese, zinc, copper, molybdenum, cobalt etc.). In spite of such insignificant content in the organism, the trace elements fulfill vital functions.

In the regulation of water and salt metabolism hormones of adrenal cortex (mineralocorticoids) and pituitary body (vasopressin) are significant. The mineralocorticoids cause delay of the sodium in the organism and increase excretion of potassium. Vasopressin decreases excretion of water by kidneys. Need of organism for salts is expressed in salt appetite, its need for water - in the sensation of thirst.

Sensation of thirst occurs when not enough water enters the organism or organism loses large amounts of water and also when surplus quantity of salts enter the organism. This sensation forces the individual to drink a water and thus, promotes the maintenance of normal level of water and electrolyte balance in organism.

The sensation of thirst has a compound mechanism consisting of central and peripheral parts. When content of water in organism is decreased, osmoreceptors are excited. These receptors are sensitive to increase of osmotic pressure and they are located in hypothalamus as well as in some internal organs. Salivation is decreased, dryness in mouth and throat occurs.

An area called the thirst center is located in the lateral hypothalamus. The hypothalamus regulates body water in two separate ways: 1) by creating the sensation of thirst, which makes an individual drink water; 2) by controlling the excretion of water into the urine.

In the brain there is a drinking center similar to that of alimentary center.

Vitamins are not characterized by the community of the chemical nature and they are not significant for their plastic or power properties. These are organic compounds needed in small quantities for operation of normal metabolism and they cannot be manufactured in the cells of the body. Frequently the vitamins are components of the enzyme molecules.

Sources of vitamins are food-products of vegetable or animal origin where they are in ready form or as provitamins. From provitamins the vitamins are formed in organism. Absence of any vitamin causes the diseased state called avitaminosis. The vitamin insufficiency is called hypovitaminosis. These states may be developed not only when the vitamins are absent in the food, but also when they are not absorbed in the gastrointestinal tract.

Amounts of vitamins required daily vary considerably depending on such factors as body size, rate of growth, amount of exercise, pregnancy and so on.

The vitamins are divided into two groups: I- water-soluble vitamins (B, C, P), II-liposoluble vitamins (A, D, E, K).

Vitamins are stored to a slight extent in all cells. But some of them are stored to a major extent in the liver. For instance, the quantity of vitamin A stored in the liver may be sufficient to maintain a person without any intake of vitamin A for up to 10 months and the quantity of vitamin D stored in the liver is sufficient to maintain a person for 2-4 months without any additional intake of this vitamin.

The storage of most water-soluble vitamins is relatively slight. For instance, when a person's diet is deficient in vitamin B compounds, clinical symptoms of the deficiency can be recognized within a few days (except for vitamin B_{12} which can last in the liver for a year or longer). Absence of vitamin C can cause symptoms within a few weeks and can cause death from scurvy in 20-30 weeks.

Mechanisms of regulation play significant role in adaptation of metabolic processes to the functional state and requirements of the organism in healthy body and in pathology.

Rapid and protracted mechanisms of regulation of metabolism are distinguished. The rapid mechanisms cause momentary changes in metabolism. They are connected with the rate of passing of substances through cell memrane and the change of activity of enzymes. The protracted mechanisms cause long and steady changes in metabolism. They are connected with increase of number of enzymes in cells.

Metabolism is regulated by intracellular and extracellular mechanisms. Intracellular mechanisms are formed in the cells and influence activity and number of enzymes. Extracellular mechanisms link up metabolic processes in different tissues and organs. There are special receptors (proteins) in effector cells which perceive influence of these mechanisms (a kind of biological antennas). Some of these receptors are situated in the cell membrane and others - in the cytoplasm. The membrane receptors perceive signals from the regulators which, in turn, perceive signals from the regulators that cannot enter the cell, whereas those of extracellular regulators which pass through the cell membrane, influence the cytoplasmic reticulum directly.

The intracellular regulators are divided into the following groups:

1) nutritive matters and metabolites-participate in the regulation of the activity of enzymes, but do not influence their number;

2) vitamins and cofactors containing vitamins-regulate activity of enzymes (entering the enzyme's active center) and as extracellular regulators (especially fat-soluble vitamins), take part in the regulation of their number;

3) intracellular "intermediaries" (calcium ions, oligopeptides, prostaglandines, cyclic nucleotides-adenosine monophosphate, guanozine monophosphate etc.) - do not function independently; they begin to act under the influence of the extracellular regulative mechanisms. These consist of nervous and humoral (including endocrine) mechanisms of regulation.

Lecture 22

Energy Metabolism. Nutrition. Temperature Regulation

The prevailing result of power processes in organism is thermogenesis, and therefore, all the energy, which is formed in the organism, can be expressed in the units of heat, i.e., in calories and joules. To determine the power formation in the organism the direct calorimetry and indirect calorimetry are used.

The direct calorimetry is based on immediate calculation of the amount of the heat given off by the organism. It is carried out in the biocalorimeter which is the hermetic chamber with heat isolation. In the chamber the water is circulating along the tubes. The heat given off by the man or animal that is in the chamber warms the circulating water. According to the amount of the circulating water (m) and change of its temperature (t_2 - t_1) the amount of the heat, given off by the organism (Q), is calculated by well - known in physics formula: $Q = cm (t_2 - t_1)$.

The indirect calorimetry is based on the calculation of heat production in the organism, taking into consideration the volume of the consumed oxygen and the volume of carbon dioxide which is given off. There are closed methods of indirect calorimetry when the special respiratory chambers are used and open methods which are used without them.

The oxygen, consumed by the organism, is used for oxidation of proteins, fats and carbohydrates. Oxydation of 1 g of each of these substances requires different amounts of oxygen and is followed by realizing of different amounts of the heat.

The amount of heat released when 1 g of nutritive matter is burnt in the organism, is called the calorific or thermal coefficient of nutritive matter. This coefficient is equal to 9.3 kcal for fats, 4.1 kcal for both proteins and carbohydrates.

The amount of heat released when 1 litre of oxygen is consumed by the organism is called the calorific equivalent of oxygen. This index is 5.05 kcal for carbohydrates, 4.69 kcal for fats and 4.60 kcal for proteins.

The ratio of the volume of the carbon dioxide given off by the organism to the volume of the oxygen consumed by the organism is called respiratory coefficient.

The respiratory coefficient is equal to 1 for carbohydrates:

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$$

$$\frac{6CO_2}{6O_2} = 1.$$
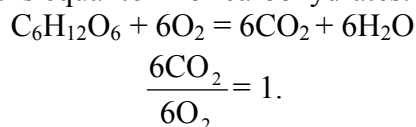
For fats this coefficient is 0.7 and for proteins - 0.8. When the mixed food is taken, the respiratory coefficient is equal to 0.85 - 0.9.

During the intensive muscular work the respiratory coefficient is increased up to 1, because the main source of energy during the strenuous activity are carbohydrates. Immediately after the intensive muscular work (the recovery period) the respiratory coefficient is increased and becomes more than 1, then it decreases sharply and only later it is normalized. These changes of respiratory coefficient are explained by accumulation of the lactic acid during the work.

Intensity of oxidation processes and transformation of energy in the organism depend on the individual peculiarities of the organism (sex, age, body mass, height, nutrition, muscular work, state of endocrine glands and nervous system) as well as conditions of the external environment (temperature, pressure, composition and humidity of the air, influence of radiant

energy). Power expenditures of the organism in resting state (lying with relaxed musculature), on an empty stomach (12 hours after the meal) and at the temperature of comfort (18-20°C) is called the basal metabolic rate. The power expenditures of the basal metabolism are connected with maintenance of the minimal level of the oxidation processes in the cells and activity of constantly working organs and systems (heart, liver, kidneys, respiratory system) as well as of the body temperature.

The basal metabolic rate in the body of the man of average age, body mass and height is equal to 1 kcal for 1 kg of body mass in 1 hour or 1700 kcal in day for the body. The basal metabolic rate in the woman organism is 10% lower than that of man. During the sleep it is decreased 10%.

The intensity of basal metabolism calculated for 1 kg of body mass in children is considerably higher than in adults and it is lower in elderly age. In the age from 20-40 (as long as 20 years) the basal metabolic rate remains in fairly constant level and does nor vary more than 5 to 10 per cent.

Intensity of basal metabolic rate calculated for 1 kg of body mass differs considerably in different species of warm-blooded animals and in men of different body mass and height. For example, it is 64.3 kcal for man, 128 kcal for pig and 0.018 kcal for mouse.

But when calculated for 1 sq.m. of body surface, the data do not differ so sharply: 1042 kcal for man, 1078 kcal for pig and 1188 kcal for mouse. So, the energy expenditure of warm-blooded animals is proportional to the area of body surface. This is called the law of body surface.

The law of body surface is not of absolute character. For instance, the basal metabolic rate of two individuals with equal body surface area, can be quite different.

The muscular work increases the energy expenditure, and therefore, the daily energy expenditure of the healthy organism exceeds the basal metabolic rate considerably. This is called the work increase.

During the muscular work the thermal and mechanical energies are released. The ratio of the mechanical energy to all the energy, expended on the work, is called the effective action coefficient. It is 16-25%.

Brainwork increases energy expenditures of organism insignificantly (2-3 %). But when it is followed by the emotional excitement and muscular activity, the work increase may be 11-19 % (in lecturers, actors).

According to the daily energy expenditure of the organism the following 4 groups of the representatives of different professions are distinguished:

I - brain-workers- 2200 - 3300 kcal;

II - workers of mechanized industries - 3300 - 3500 kcal;

III - workers of partly mechanized enterprises - 3500 - 4000 kcal;

IV - representatives of hard physical work - 4000 - 5000 kcal.

After the meal intensity of metabolism and energy expenditures of organism are increased. This is called the specific-dynamic effect of food. Albuminous food increases the metabolism 30%, fats and carbohydrates - 14-15 %.

The level of energy metabolism depends on the physical activity, emotional strain, character of food, intensity of thermoregulation and so forth.

Role of hypothalamus in the regulation of metabolism is significant. Its influences are realized by vegetative nerves or humoral ways. The metabolism is markedly increased under the influence of adrenal medulla hormone (adrenalin) and thyroid gland hormones (thyroxin and triiodothyronine).

The energy metabolism can be changed also by conditioned reflex way. If the person under hypnosis is suggested that he is fulfilling the hard muscular work, his metabolism may be increased considerably.

These facts show that the metabolism can be changed under the influence of brain cortex.

When the fats and carbohydrates are oxidized in the organism or burnt out of organism the same end products (carbon dioxide and water) are formed. It in known that the total thermal effect of chemical reactions depends on the initial and end products, and it is not dependent on the intermediate stages of reaction. Therefore, the physical and physiological thermal coefficients of fats and carbohydrates are equal.

But the physical thermal coefficient of proteins, is more than their physiological thermal coefficient. Because in the calorimeter the proteins are burnt to the CO_2, H_2O and NH_3, but in the organism they are oxidized only to the urea, uric acid and creatinine.

Not all of the food that is taken, is assimilated, i.e., absorbed from the gastrointestinal tract and used by the organism. Part of the food leaves the organism as residues. Therefore, to determine the assimilability, from the quantity of the proteins, fats and carbohydrates their content in the feces must be subtracted.

The assimilabilitty of the animal food is 95%, vegetable food - 80%, mixed food - 82-90%. Practically it is considered 90 %.

According to the rule of isodynamia the nutritive matters can substitute one another in conformity with their calorific coefficients: 1g of fat which gives to the organism 9.3 kcal may be replaced by 2.3g of carbohydrate or protein (each of them gives only 4.1kcal); 1g of protein or carbohydrate may be replaced by 0.44g of fat.

However, this rule takes into consideration only the energy needs of organism, whereas the nutritive matters fulfil also plastic functions. Therefore, the organism must take sufficient amounts of proteins, fats, carbohydrates, mineral salts and vitamins.

Decrease of daily norms of the nutritive matters for a long time causes the diseased state. Their quantity in the food, especially the amount of the proteins, must be somewhat higher than that of minimal wants of the organism. That is, the daily food rations must be based not on the minimal, but optimal norms of the nutritive matters which provide the good general condition, high capacity for work, sufficient resistibility to the harmful influences and for children - also the needs of growth.

Such optimal daily norms of the nutritive matters are : 80-100g of proteins, 70g of fats, 400-450g of carbohydrates.

No less than 30% of proteins and no less than 30-60% of fats must be of animal origin.

During the hard muscular work norms must be increased.

The daily food ration must contain also the sufficient amounts of mineral substances and vitamins.

Unlike the poikilothermal (cold-blooded) animals, the body temperature of the homoio-thermal (warm-blooded) animals as well as that of man is maintained on the relatively constant level (isothermia). This ability develops gradually. In newborn child the mechanism of thermoregulation is not perfect. Therefore, changes of the temperature of the external environment cause cooling (hypothermia) or overheating (hyperthermia) of the body.

The body temperature depends on the intensity of heat production and the size of heat loss.

In the muscles, liver and kidneys more heat is produced than in connective tissue, bones, cartilages,. The heat loss is more in the organs and tissues that are superficially situated (skin, skeletal muscles) than in the internal organs that are defended from the cooling.

Therefore, the temperature of different organs is not the same. For instance, the temperature of the liver is higher (37.8 - 38₀C) and more constant than that of the skin, the temperature of which depends on the external environment to considerable extent and is lower (29.5 - 33.9₀C).

Usually the temperature is measured in the axillary cavity where it is equal to 36.5-36.9₀C and in the rectum (especially in children) where it is 37.2 - 37.5₀C. The minimal temperature may be reserved only when the heat production and heat loss are equal. This equality is reached

by the chemical and physical mechanisms of thermoregulation.

The chemical thermoregulation is important mainly when the temperature of external environment is lower than optimal temperature (zone of comfort). This zone is within 18-20$_\circ$C when one is dressed and 28$_\circ$ for the naked body.

The chemical thermoregulation is realized by the way of increasing heat production, i.e., by strengthening of metabolism intensity in the cells.

The most intensive heat production in the organism occurs in the muscles. Even if the person is lying still, but with strained musculature, the heat production is increased 10%. The hard muscular work increases it 400-500%.

When the cold ceptors are excited, this causes reflex muscular contractions which are manifested as shivering. Even the imitation of shivering increases the heat production 200%.

Besides muscles liver and kidneys play a significant role in chemical thermoregulation. In the cold their activity is increased.

In organism the energy is released as a result of oxidation of the carbohydrates, fats and proteins. Therefore, all the mechanisms which regulate the oxidation processes, control also heat production.

The physical thermoregulation is important when the organism is in the condition of higher temperature of external environment. It is realized by the way of increasing heat loss.

The methods by which heat is lost from the skin to the surrounding include radiation, conduction, convection and evaporation.

About 60% of the total heat loss of a nude person at normal room temperature is realized by radiation, Loss of heat by radiation means loss in the form of infrared heat rays, a type of electromagnetic wave. The human body radiates heat rays in all directions. But these rays are also radiated from the walls and other objects toward the body. If the temperature of the body is greater than that of the surroundings, a greater quantity of heat is radiated from the body than it is radiated to the body.

Heat loss by convection is removal of heat from the body by convection air currents. Actually, the heat must first be conducted to the air and then carried away by the convection currents.

Only minute quantities of heat are normally lost from the body by direct conduction from the surface of the body to other objects, such as a chair or a bed. On the other hand, loss of heat by conduction to air does represent a sizable proportion of the body's heat loss even under normal conditions. A nude person seated in a comfortable room without gross air movement loses about 12% of heat by convection because of the tendency for the air adjacent to the skin to rise as it becomes heated.

Water has a specific heat several thousand times as great as that of air, so that each unit portion of water adjacent to the skin can absorb far greater quantities of heat than air does.

When water evaporates from the body surface, 0.58kcal of heat is lost for each gram of water that evaporates. Even when a person is not sweating, water still evaporates insensibly from the skin and lungs at a rate of about 600ml daily. This causes heat loss at a rate of 12-16kcal per hour.

As long as skin temperature is greater than that of the surroundings, heat can be lost by radiation and conduction. But when the temperature of the surroundings is greater than that of the skin, the body gains heat by radiation and conduction instead of losing it. Under these conditions the only means by which the body can rid itself of heat is evaporation.

During the hard muscular work in hot shops of factory 12 litres of sweat may be excreted in a day.

Clothing decreases the heat loss. Subcutaneous fat also prevents the heat loss. The temperature of skin and blood loss may change as a result of the redistribution of blood and change of circulating blood volume.

The higher temperature of the external environment causes reflex dilation of blood vessels of skin (mainly that of arterioles) and more blood is flowing into the body surface. The blood loss by radiation, conduction and convection is increased.

Goose-skin (the reaction of skin muscles-piloerection) and rolling oneself up into a ball (to decrease a body surface and limit the heat loss) in the cold are also manifestations of physical thermoregulation.

Constancy of body temperature is provided by complicated reflex acts which occur in response to the stimulation of thermoreceptors of skin and central nervous system.

From skin thermoreceptors to the central nervous system continuous rhythmical impulses come. The maximal frequency for cold receptors is within the $20-30_oC$, and for warmth recaptors-within $38-43_oC$.

Thermoreceptors of central nervous system are located in the anterior hypothalamus preoptic area, reticular formation of midbrain, spinal cord.

Existence of thermoreceptors in central nervous system was demonstrated in experiment. When the denervated hind legs of dog are dipped into the cold water, shivering of the muscles of head, forelegs and trunk is observed and the heat production is intensified. This effect is reached thanks to irritation of central cold receptors by the cooled blood.

Role of spinal cord in realization of temperature regulating reflexes is demonstrated on the animal, spinal cord of which is cut off from the higher parts of central nervous system. When the spinal cord of such animal is cooled. constriction of peripheral blood vessels and shivering are observed. But the thermoregulation reflex centers of spinal cord are of limited significance.

The main centers of thermoregulation are situated in hypothalamus. This is proved by the fact that destruction of hypothalamus causes loss of ability to control the body temperature, and the animal becomes poikilothermal. Whereas the removal of cerebral cortex, striate body and optic thalamus is not reflected noticeably in the processes of heat production and heat loss.

The chemical thermoregulation is controlled by caudal hypothalamus. After destruction of this area the animal cannot bear the cold, and cooling of the animal do not cause the shivering and compensatory increase of heat production.

The physical termoregulation is controlled by anterior hypothalamus. Destruction of this area (heat loss center) deprives the animal the ability to bear the higher temperature of the external environment, and its body becomes overheated rapidly.

There are intricated relations between the centers of physical and chemical thermoregulation and they suppress each other.

In the realization of thermoregulation by hypothalamus endocrine glands take part (especially the thyroid gland and adrenal glands).

Participation of thyroid gland in temperature control is provided by the fact that administration into the blood of animal the blood serum of another animal which has been in the cold for a long time, causes increase of metabolism in the first animal. But when the thyroid gland of the second animal is removed, this effect does not occur. Consequently, it was caused by the hormone of thyroid gland.

Participation of adrenal gland in temperature control is connected with excretion of adrenalin which, intensifying the processes of oxidation, increases heat production and constricting the blood vessels of skin decreases heat loss. Therefore, adrenalin can cause rise of body temperature (the adrenalin hyperthermia).

Experiments on animals and observation on men show that the processes of heat production and heat loss may be changed by conditioned reflex way, and this is realized by the participation of brain cortex.

When man stays in the conditions of considerably higher or lower temperature of external environment for a long time, the physical and chemical mechanisms of thermoregulation may turn out to be insufficient, and then the overheating of the body (hyperthermia) or its supercoo-

ling (hypothermia) occur.

The hypothermia is the state when the body temperature is lower than 35_oC. This state develops more rapidly when the body is plunged into the cold water. At first the sympathetic part of the vegetative nervous system is excited, by the reflex way the heat production is intensified and heat loss is limited, the muscle contractions (shivering) are observed. But then the body temperature falls and the state similar to narcosis is developing: the sensibility disappears, the reflex reactions weaken, the excitability of nervous centers decreases. The intensity of metabolism is sharply decreased, the respiration rate and heart rate as well as strike volume and arterial pressure are also decreased.

It is possible to decrease the body temperature by first administering a strong sedative to depress the reactivity of the hypothalamic thermoregulation centers and then cooling the person with ice, cooling blankets or otherwise. The temperature can then be maintained below $30\text{-}32_oC$ for several days to a week or more by continual sprinkling of cool water or alcohol on the body. Such artificial cooling is often used during heart surgery so that the heart can be stopped artificially for many minutes. Cooling to this extent does not cause severe physiological results. It slows the heart andactivity greatly depresses body metabolism.

The hyperthermia is the state when the body temperature is higher than 37_oC. This state develops in conditions of higher temperature of external environment especially when the humidity of the air is also high and effectiveness of sweating is low.

The hyperthermia can occur also under the continuous influence of endogenous factors which intensify heat production in the organism (thyroxin, fatty acids etc.).

The sharp hyperthermia when the body temperature reaches $40\text{-}41_oC$ is called heat stroke (heat apoplexy). It is followed by severe general state of the organism.

One must distinguish the hyperthermia from the fever when the external conditions are not changed but the process of thermoregulation itself is disturbed. Oftenly it is of infectious character. Because the hypothalamic thermoregulation centers are very sensible to some chemical compounds, including the bacterial toxins. Administration of minimal amount of bacterial toxin immediately into the anterior hypothalamus area is followed by rise of body temperature during many hours.

EXCRETORY PROCESSES

Lecture 23

Homeostatic Functions of Kidneys.
Glomerular Filtration and Tubular Roabsorption

The basic function of excretory organs is to maintain the constancy of composition and volume of fluids of internal environment of organism and first of all, that of blood. That is, the excretory processes are important for homeostasis. Kidneys, lungs, sweat glands gastrointestinal tract take part in secretion from the organism of unnecessary metabolic products, heterologous and toxic substances, surplus of water, salts and organic compounds. Among the excretory organs the special place belongs to the sebaceous and mammary glands. Because the cutaneous fatty secretion and milk are not the metabolic residues: they fulfil the important physiological functions.

Kidneys fulfil a number of homeostatic functions in the organism:

1. Excreting from the organism the surplus of water the kidneys take part in the regulation of the volume of blood and other fluids of internal environment. The kidneys can eliminate excess water by excreting a dilute urine or can conserve water by excreting a concentrated urine. In this process the volumoreceptors are significant. They react to the changes of the volume of intravascular and itracellular fluids. Regulation of excreted water volume is realized by the participation of antidiuretic hormone (vasopressin) of posterior pituitary gland, aldosterone (hormone of adrenal cortex), angiotensin etc.

The most important basis for blood volume control is a purely mechanical mechanism: the mechanical effect of increased arterial pressure to cause greatly increased fluid volume output by the kidneys. This is called pressure dieresis.

2. Kidneys are the main organs of osmoregulation. They provide constancy of osmotic pressure of blood and other fluids of organism. In this process central and peripheral osmoreceptors are important. The central osmoreceptors are situated in the supraoptic hypothalamus area and the peripheral ones - in liver, kidneys, spleen etc.

Since the regulation of body fluid volume and osmoregulation are closely intercomnected, above-mentioned hormones take part also in the regulation of osmotic pressure.

3. Kidneys are the most significant effector organs in the ionic homeostasis system. They take part in the regulation of the ionic composition of the internal environment and ionic balance of organism. The regulation systems exist for he balance of each ion, and for some ions the specific receptors are already discovered (for instance, sodium receptors).

Kidneys regulate not only the sodium content of blood but also the ratio between the sodium and potassium ions. During the sodium deficiency aldosterone increases reabsorption of sodium ions in tubules of kidney, but reabsorption of potassium ions is decreased.

Thanks to the secretory activity of kidneys the constancy of calcium, phosphorus, chlorine and other ions also is maintained.

4. Kidneys play an important role in the regulation of acid-base balance. They maintain constancy of the hydrogen ions concentration in the blood.

The active reaction of urine may be changed widely (from 4.5 to 8.0) and the concentration of hydrogen ions in it may differ 1000 times.

5. Kidneys excrete the end products of nitrogen metabolism and heterologus substances, as well as surplus of organic compounds which enter the organism with food or are formed in the process of metabolism.

6. Kidneys take part in the regulation of metabolism of proteins, lipides and carbohydrates.

7. Kidneys play an important role in the regulation of arterial pressure. When the blood supply of the kidneys is getting worse, in their juxtaglomerular cells renin is synthesized. Renin-angiotensin system causes the vasoconstriction. In the kidneys vasodilative substances (medullin, prostaglandins) are also synthesized.

8. Kidneys take part in the erythropoiesis. They secrete erythropoietin which stimulates the bone marrow to produce red blood cells.

9. Kidneys take part in regulation of the secretion of some enzymes and physiologically active substances (renin, bradykinin, prostaglandins, vitamin D3, urokinasa etc.).

The functions of kidneys are studied by the following experimental methods: urinary bladder chronic fistula, chronic fistula of ureters, micropuncture and microperfusion of tubules of kidney. To investigate the functional state of kidneys in clinic concentrations of substances in blood and urine are compared. To study the role of kidney in the synthesis of new compounds the blood composition of renal artery and renal vein are compared. The role of renal cells in different functions of kidney are studied by the help of the electronic microscopy, cytochemical, biochemical and electrophysiological methods of investtigation.

The basic functions of kidneys are the following:

1) glomerular filtration;

2) tubular reabsorption;

3) tubular secretion;

4) synthesis of physiologically active substances in the tubules.

The two kidneys together contain approximately 2000000 nephrons and each of them is capable of forming urine by itself. The nephron is composed basically of a glomerulus through which fluid is filtered from the blood and a long tubule in which the filtered fluid is converted into urine on its way to the pelvis of the kidney.

Blood enters the glomerulus through the afferent arteriole and leaves through the efferent arteriole. The diameter of afferent arteriole is twice wider than that of efferent arteriole. The glomerulus is a network of up to 50 parallel branching and anastomosing capillaries covered by epithelial cells and encased in Bowman's capsule. Pressure of the blood in the glomerulus causes fluid to filter into Bowman's capsule, and from here the fluid flows into the proximal tubule that lies in the cortex of the kidney along with the glomerulus.

From the proximal tubule the fluid passes into the loop of Henle that dips deeply into the kidney mass, some of the loops passing all the way to the bottom of the renal medulla. After passing through its descending and ascending limbs, the fluid enters the distal tubule, which like the proximal tubule, lies in the renal cortex. Then, still in the cortex, eight of the distal tubules coalesce to form the cortical collecting duct (collecting tubule), the end of which turns once again away from the cortex and passes downward into the medulla, where it becomes the medullary collecting duct (simply the collecting duct). Successive generations of collective ducts coalesce to form progressively larger collecting ducts the penetrate through the medulla, parallel to the loops of Henle. The largest collecting ducts empty into the renal pelvis through the tips of the renal papillae; these are conical projections of the medulla that protrude into the renal calyces, which are themselves recesses of the renal pelvis. In each kidney there are about 250 of these very large collecting ducts, each of which transmits the urine from about 400 nephrons.

As the glomerular filtrate flows through the tubules, over 99% of its water and varying amounts of its solutes are normally reabsorbed into the vascular system, and small amounts of some substances are also secreted into the tubules. The remaining tubular water and dissolved substances become the urine.

Characteristics of nephrons are somewhat different depending on how deep they lie within the kidney mass. Those nephrons of which the glomeruli lie close to the surface of the kidney are called cortical nephrons. Their loops of Henle penetrate only a very short distance into the outer portion of medulla.

1/5 - 1/3 of the nephrons have glomeruli that lie deep in the renal cortex near the medulla. These are called juxtamedullary nephrons. Their loops of Henle penetrate deeply into the inner zone of the medulla.

The juxtsmedullary nephrons differ from ordinary ones also by the equal diameter of afferent and efferent arterioles. then, efferent arterioles of juxtamedullary nephrons does not form a capillary network around tubules, but flows into venous system.

The juxtamedullary nephrons contain the juxtaglomerular complex where renin is secreted.

The basic function of the nephron is to clean (clear) the blood plasma of unwanted substances as it passes through the kidney. The substances that must be cleared include particulary the end products of metabolism, such as urea, creatinine, uric acid, urates. In addition, many other substances, such as sodium ions, potassium ions, chloride ions, hydrogen ions, tend to accumulate in the body in excess quantities; it is the function of the nephron also to clear the plasma of these excesses.

The principal mechanism by which the nephron clears the plasma of unwanted substances is the following. It filters a large proportion of the plasma in the flowing glomerular blood (1/5 of if) through the glomerular membrane into the tubular system of nephron. Then, as this filtered fluid flows through the tubules, the wanted substances, especially almost all of the water and many of the electrolytes, are reabsorbed back into the plasma of the peritubular capillaries, whereas the unwanted substances fail to be reabsorbed. In other words, the wanted portions of tubular fluid are returned to the blood and the unwanted portions pass into the urine.

A second mechanism by which the nephron clears the plasma of other unwanted substances is secretion. That is, substances are secreted from the plasma into the tubular fluid directly through the epithelial cells lining of the tubules. So, the urine that is eventually formed is composed mainly of filtered substances but also of small amounts of secreted substances. The fluid that filters through the glomerulus into Bowman's capsule is called glomerular filtrate and the membrane of the glomerular capillaries is called the glomerular membrane. In general, this membrane is similar to that of other capillaries of the body, but it has several differences. It has 3 major layers: the endothelial layer of the capillary itself, a basement membrane and a layer of epithelial cells. Despite the number of layers the permeability of the glomerular membrane is 100-500 times greater than that of the usual capillary.

Permeability of the glomerular memrane to substances of different molecular weights, expressed as the ratio of concentration of the dissolved substances on the filtrate side of the membrane to its concentration on the plasma side, is approximately as follows: for inulin (molecular weight - 5200) - 1; for very small proteins (molecular weight - 30000) - 0.5; for albumin (molecular weight - 69000)- 0.005.

Taking into account that the molecular weight of the smallest plasma protein (albumin) is 69000, the glomerular membrane is almost completely impermeable to all plasma proteins but is highly permeable to essentially all other dissolved substances in normal plasma. There are two basic reasons for the molecular selectivity by the glomerular membrane:

1. Pores of the glomerular membrane are large enough to allow molecules with diameter up to 8 nanometers (80 angstroms) to pass through.

2. The basement membrane of the glomerular pores have strong negative electrical charges. The plasma proteins also have strong negative charges.

The glomerular filtrate or primary urine has almost exactly the same composition as the fluid that filters from the arterial ends of the capillaries into the interstitial fluids. It contains no erythrocytes and about 0.03% protein. Because of the paucity of negative charged protein ions in

the filtrate the concentration of the nonprotein negative ions (chloride, bicarbonate ions etc.) is about 5% higher than in plasma; the concentration of positive ions is about 5% lower.

So, the primary urine is the same as blood plasma except it has no significant amount of proteins.

The total surface of the glomerular capillary walls is 1.5 - 2sqm, i.e., it is equal to the body surface. The quantity of glomerular filtrate that is formed each day averages about 180 litres. The daily blood flow through both kidneys is 1700- 1800 litres. So, approximately from each 10 litres of blood passing through glomerular capillaries, 1 litre of filtrate is formed. Over 99% of filtrate is reabsorbed in the tubules and the remaining small portion passes into the urine.

The same forces that cause fluid to filter from any high pressure capillary apply also to filtration from the glomerulus into Bowman's capsule:

1. The hydrostatic pressure inside the glomerular capillaries (70 mm Hg) promotes filtration through the glomerular membrane.

2. The pressure in Bowman's capsule outside the capillaries (20 mm Hg) opposes filtration.

3. The oncotic pressure of blood plasma (30 mm Hg) also opposes filtration.

4. The oncotic pressure in Bowman's capsule promotes filtration, but so little protein filters into the glomerular filtrate that this factor has nor significant effect and is considered to be zero.

So, the filtration pressure, i.e., the net pressure forcing fluid through the glomerular membrane, is equal to: 70mm Hg - (20mm Hg + 30mm Hg) = 20mm Hg. Consequently, if the pressure inside the glomerular capillaries is as low as 50mm Hg or the sum of capsular pressure and glomerular oncotic pressure is as high as 70mm Hg, the filtration pressure is equal to zero and filtration is stopped.

Constriction of the afferent arteriole decreases the rate of blood flow into the glomerulus and the glomerular pressure. Both of these effects decrease the filtration rate. Conversely, dilatation of the afferent arteriole increases the glomerular filtration rate.

Constriction of the efferent arteriole increases the resistance to the outflow from glomeruli. This increases the glomerular pressure and causes increase in glomerular filtration rate. But the blood flow decreases at the same time, and if the increase in efferent arteriolar constriction is moderate or severe, the plasma will remain for a longer period of time in the glomerulus, and extra large portions of plasma will filter out. This will increase the oncotic pressure of plasma to excessive levels, which will cause a paradoxal decrease in the glomerular filtration rate despite the elevated glomerular pressure.

The glomerular filtration rate remains nearly constant hour after hour, varying very little either above or below the normal value of about 125ml/min for the two kidneys. Even a change in arterial pressure from as little as 75mm Hg to as high as 160mm Hg hardly changes the glomerular filtration rate. This effect is called autoregulation of glomerular filtration rate.

Renal blood flow and glomerular filtration rate are controlled together by local feedback control mechanisms within the kidneys.

Maintaining a constant glomerular filtration rate in important. Because at a very slight glomerular filtration rate the tubular fluid would pass through the tubules so slowly that essentially all of it would be reabsorbed and the kidneys would fail to eliminate the necessary waste products. With a much too high glomerular filtration rate the fluid would pass so rapidly through tubules that they would be unable to reabsorb those substances that need to be conserved in the body.

Each nephron is provided with two special feedback mechanisms which provide the degree of glomerular filtration autoregulation that is required: 1) afferent arteriolar vasodilator feedback mechanism; 2) efferent arteriolar vasoconstrictor feedback mechanism. Their combination is called tubuloglomerular feedback. The feedback process occurs almost entirely at the juxtaglomerular complex. The initial portion of the distal tubule of the juxtamedullary nephron

passes in the angle between the afferent and efferent arterioles, actually abutting each of these two arterioles. Those epithelial cells of the distal tubule that come in contact with the arterioles are more dense than the other tubular cells and a collectively called the macula densa. The macula densa cells appear to secrete some substance toward the arterioles.

The smooth muscle cells of both the afferent and efferent arterioles are swollen and contain dark granules where they come in contact with the macula densa. These cells are called juxtaglomerular cells and the granules are composed mainly of inactive renin. The whole comlex of macula densa and juxtaglomerular cells is called the juxtaglomerular complex.

So, the anatomical structure of the juxtaglomerular apparatus suggest strongly that the fluid in the distal tubule in some way plays an important role in helping to control nephron function by providing feedback signals to both the afferent and efferent arterioles.

A low rate of glomerular filtration causes overreabsorption of sodium and chloride ions in the ascending limb of the loop of Henle and therefore decreases the ionic concentration at the macula densa. This initiates a signal from macula densa to dilate the afferent arteriole. This is the afferent arteriolar vasodilator feedback mechanism.

Too few sodium and chloride ions at the macula densa cause the juxtaglomerular cells to release active renin and this in turn causes formation of angiotensin. The angiotensin contracts mainly the efferent arteriole because it is highly sensitive to angiotensin II, much more than the afferent arteriole. This is the efferent arteriolar vasoconstrictor feedback mechanism.

When both these mechanisms function together the glomerular filtration rate increases only a few per cent though the arterial pressure changes between the limits of 75 and 160mm Hg.

The afferent vasodilator and efferent vasoconstrictor arteriolar feedback mechanisms are most important also for autoregulation of the renal blood flow.

Decrease in the mean arterial pressure from its normal value of about 100mm Hg down to about 50mm Hg causes complete cessation of urine output whereas an increase in arterial pressure to double normal (to 200mm Hg) increases the urine output as much as sevenfold to eightfold. Tubular reabsorption does not necessarily increase when the arterial pressure rises. Therefore, all or most of the increase in glomerular filtration becomes also an increase in urinary output. This effect of arterial pressure on urinary output is called pressure diuresis.

The glomerular filtrate entering the tubules of the nephron flows through the proximal tubule, the loop of Henle, the distal tubule, the cortical collecting duct and collecting duct into the pelvis of the kidney. Along this course substances are selectively reabsorbed or selected by the tubular epithelium and the resultant fluid after this processing enters the renal pelvis as urine. Reabsorption plays a much greater role than does secretion in formation of urine.

Daily 150-180 litres of glomerular filtrate, that is, primary urine is formed and only 1-1.5 litres of definitive urine is removed from the organism. The rest of the glomerular filtrate is reabsorbed in tubules. Such a large volume of reabsorption is provided by the great total surface of tubules.

The total length of tubules is 70-100km. On the tubular border of the epithelial cell is an extensive brush border that multiplies the surface of area of luminal exposure about 20-fold. So, the total surface tubules is 40-50sq m.

So, more than 99% of the water in the glomerular filtrate is reabsorbed as it is processed in the tubules. Consequently, if some dissolved constituent of the glomerular filtrate is not reabsorbed at all along the entire course of the tubules, this reabsorption of water obviously concentrates the substance more than 99-fold. But some constituents, such as glucose and amino acids, are reabsorbed almost entirely so that their concentrations decrease almost to zero before the fluid becomes urine. In this way the tubules separate substances that are to be conserved in the body from those that are to be eliminated in the urine, and they do this without losing much water in the urine.

The basic mechanisms for transport through the tubular membrane are essentially the same

as those for transport through other membranes of the body. These are divided into active and passive transport. According to the source of the energy used to cause the transport, active transport is divided into primary and secondary active transport.

In primary active transport the energy is derived directly from the breakdown of adenosine triphosphate (ATP) or some other high-energy phosphate compound. In secondary active transport the energy is derived secondarily from ionic concentration gradients that have been created in the first place by primary active transport. In both cases transport depends on carrier proteins that penetrate through the membrane.

The primary active tranmsport of sodium ions through tubular membrane always occurs in the direction from the tubular lumen to the interstitium. The tubular epithelial cell membrane contains Na+, K+ - ATP ase system that is capable of cleaving ATP and using the released energy to transport sodium ions out of the cell into the interstitium, while at the same time transporting potassium ions from the interstitium to the interior of the cell. This ATP ase system pumps 3 sodium ions for every 2 potassium ions.

There are sodium carrier proteins in the membrane of the epithelial cell brush border that bind with the sodium ions on the luminal surface of the membrane and provide facilitated diffusion of the sodium to the interior of the cell.

So, the sodium pumped from the tubule is eventually absorbed into the peritubular capillary and carried away by the blood.

Movement of sodium ions from the tubular lumen to the interior of the cell energizes most f the secondary transport of other substances. The carrier protein combines with both substance to be transported (glucose, amino acid etc.) and a sodium ion at the same time. As the sodium moves down its electrochemical gradient to the interior of the cell, it pulls glucose or amino acid ion along with it (co-transport).

Glucose, amino acids and several other organic compounds are especially strongly co-transported in the proximal tubules. Chloride ions are co-transported mainly in the thick segment of the ascending limb of the loop of Henle. Other substances also co-transported at some point in the tubular system include phosphate, calcium, magnesium and hydrogen ions.

Primary or secondary active transport of different solutes out of the tubule decreases their concentration inside the tubular lumen and increases it in the interstitium. A concentration difference created such way, causes osmosis of water in the same direction. So, the passive absorption of water is realized.

When sodium ions are transported through the tubular epithelial cell, a negative ion, such as chloride ion, is transported along with each sodium ion to maintain electrical neutrality. In some segments of the tubules chloride ions can be transported by secondary active transport. But in most tubular segments they are transported mainly by passive diffusion.

Urea also is passively reabsorbed but to much less degree than chloride ions. One of the principal functional purposes of the kidneys is not to reabsorb urea but to allow as much as possible of this waste product of metabolism to pass into the urine. Unfortunately its molecules are very small and the tubules are partially permeable to it.

But the molecules of another waste product - creatinine, are larger and none of them are reabsorbed. Therefore, all creatinine that is filtered passes on through the tubular system and is excreted in the urine.

There are basic differences between the absorptive and secretary capabilities of the different tubular segments.

The proximal tubular epithelium cells provide extremely rapid active transport processes. About 65% of the glomerular filtrate is reabsorbed before reaching the loops of Henle.

The most important substances that are specifically absorbed by secondary active transport in the proximal tubules are glucose and amino acids.

The descending (proximal) and ascending (distal) limbs of loop of Henle function as a

single mechanism. The descending limb is permeable to water. The ascending limb actively reabsorbs sodium ions, but it is impermeable to water. So, the transport of water in the descending limb causes reabsorption of sodium ions in ascending limb, and active reabsorption of sodium ions in ascending limb causes the transport of water in the descending limb.

The distal tubule is divided into two functional segments: the diluting segment and the late distal tubule. The diluting segment absorbs most of the ions avidly but is almost entirely impermeable to both water and urea.

The late distal tubule, as well as cortical collecting duct, is entirely impermeable to urea, reabsorbs sodium ions avidly and simultaneously potassium ions are actively transported in the opposite direction. Both transports are controlled by aldosterone. These two segments contain a special type of epithelial cell (intercalated cells or "brown cells") that secretes hydrogen ions by primary active secretion. Both are permeable to water in the presence of antidiuretic hormone but impermeable when this hormone is absent.

The collecting duct epithelium too is capable of secreting hydrogen ions against a very high gradient. Therefore, the late distal tubule and the collecting duct system play an exceedingly important role in controlling the acid - base balance of the body fluids.

Five different substances in the glomerular filtrate of particular nutritional value to the body (glucose, proteins, amino acids, acetoacetate ions, vitamins) are completely or almost completely reabsorbed by active processes in the proximal tubules of the kidneys.

The total amount of the substance that filters through the glomerular membrane into the tubules each minute is called its tubular load. For example, if 125 milliliters of glomerular filtrate is formed each minute with a glucose concentration of 100 mg/dl, the tubular load of glucose is 100 mg x 1.25 =125 milligrams of glucose per minute.

Each substances that is actively reabsorbed (or secreted) requires a specific transport system in the tubular epithelial cells, and therefore, the maximum amount that can be reabsorbed often depends on the maximum rate at which the transport system itself can operate, and this in turn depends on the total amounts of carrier and specific enzymes available. Consequently, for most actively reabsorbed substances there is a maximum rate at which each of them can be reabsorbed. This is called the tubular transport maximum for the substance (Tm). For example, Tm for glucose averages 320 mg/ min, and if the tubular load of glucose becomes greater than 320 mg/min, the excess above this amount is not reabsorbed but instead passes on into the urine.

Every substance that has a reabsorptive transport maximum also has a threshold concentration in the plasma below which none of it appears in the urine and above which progerssively large quantities appear.

Thus, glucose begins to spill into the urine when its tubular load exceeds 220mg/min. The threshold concentration of glucose in plasma that gives this tubular load is 150-180mg/dl.

All of the substances that are reabsorbed by diffusion do not exhibit a transport maximum. Instead, their rates of transport are determined by two factors:

1) the concentration gradient of the substance across the membrane without any maximum;

2) the time that fluid containing the substance remains within the tubule.

Therefore, transport of this type is called gradient - time transport.

Sodium transport in the proximal tubules obeys mainly gradient - time transport principles rather than tubular maximum transport principles.

The ability of the kidneys to clean (clear) the plasma of various substances is called plasma clearance. If the plasma passing through the kidneys contains 0.1gram of a substance in each deciliter and 0.1gram of this substance also passes into the urine each minute, 1 deciliter of the plasma is cleaned or cleared of the substance per minute.

The normal concentration of urea in each milliliter of plasma and glomerular filtrate is 0.26 milligram, and the quantity of urea that passes into the urine each minute is about 18.2mg. The equivalent quantity of plasma that completely loses entire content of urea each minute can be

calculated by dividing the quantity of urea entering the urine each minute by the quantity of urea in each milliliter of plasma:

18.2:0.26 = 70. This is the plasma clearance of urea.

Plasma clearance for any substance can be calculated by the following formula:

$$\text{Plasma clearance (ml/min)} = \frac{\text{Urine flow (ml/min)} \cdot \text{Concentration in urine}}{\text{Concentration in plasma}}$$

Lecture 24

Tubular Secretion. Synthesizing Function of Kidneys. Renal Function Tests. Diuresis. Removal of Urine (micturition). Renal Activity Regulation. Artificial Hemodialysis. Perspiration (sweating)

When some colloidal dyes, which cannot pass through the glomerular wall, are administered into the blood, then they are found in the urine. The histological investigations show that these dyes are absent in the Bowman's capsule but are revealed in the lumen of the tubules and in the protoplasm of the tubular epithelium.

This fact proves that the tubular epithelium realizes not only reabsorption, but also secretion, that is, some substances (potassium ions, hydrogen ions etc.) are transported from the plasma directly through the epithelial cells lining of the tubules into the tubular fluid (in the direction just opposite the reabsorption).

The tubular secretion is directed opposite the concentration or electrochemical gradients. It is the result of active function of tubular epithelium cells. This is proved by several facts. First of all, the secretion is connected with intense processes of metabolism. Then, suppression of tissue respiration by cyanides decreases the secretion. Administration of substanses blocking up the formation of macroergic phosphoric compounds (adenosine triphosphoric acid and so on) ceases the secretion.

So, the secretion is the active process and its mechanisms are the same of primary and secondary active transport which were described for the reabsorption.

The organic acids (phenol red, para-aminohippuric acid), diodrast, penicillin and organic bases are secreted in the proximal portion of tubules, the ions (potasium ions, hydrogen ions etc.) - mainly in distal portions of tubular system.

Besides excreting the products of metabolism which are delivered by blood the kidneys synthesize some compounds which are excreted in urine (hippuric acid, ammonia etc.) or enter the blood (renin, prostaglandins, glucose etc).

Hippuric acid is synthesized in the tubular cells from benzoic acid and glycocoll. In the experiment on isolated kidney when the solution of benzoic acid and glycocoll were administered into renal artery, hippuric acid appeared in the urine.

As a result of deamination of amino acids (mainly-of glutamine) in tubular cells ammonia is formed.

To study the renal functions the volumes of glomerular filtration, tubular reabsorption, secretion, renal blood flow etc. are determined.

Determination of glomerular filtration volume is based on the study of inulin clearance coefficient. Because inulin is easily filtrated through the glomerular capillary walls and its concentration in the filtrate is equal to that of in blood plasma. All the amount of filtrated inulin passes into the urine.

If the concentration of inulin in blood plasma (P_{in}) and in urine (U_{in}) as well as volume of the urine excreted during the investigation (V) are known, the volume of the filtrate (F) may be calculaled. Since the amount of inulin in filtrate ($F \cdot P_{in}$) is equal to that of in urine ($V \cdot U_{in}$), we have the following equation from which the volume of the filtrate can be determined:

$$F \cdot P_{in} = V \cdot U_{in}$$

$$F=\frac{V \cdot U \text{ in}}{P \text{ in}}$$

To determine the volume of tubular reabsorption glucose is administered into the blood and its concentration in blood is raised higher than threshold level, so that the glucose appears in urine. If the concentration of glucose in blood is Pg, in urine - Ug and the volume of excreted urine - V, then the difference between the total amount of filtrated glucose ($F \cdot Pin$) and the part of it that was excreted in urine ($V \cdot U$ in) is equal to the volume of tubular reabsorption (R):

$$R = F \cdot Pg - V \cdot Ug$$

To determine the volume of tubular secretion a substance is administered into the blood which is excreted from the organism mainly by the way of tubular secretion (for instance, diodrast).

If the concentration of diodrast in blood plasma is Pd, in urine - Ud and the volume of excreted urine - V, then the volume of tubular secretion of diodrast (S) will be equal to the difference between the amounts of the diodrast in the urine ($V \cdot Ud$) and in the filtrate ($F \cdot Pd$):

$$S = V \cdot Ud - F \cdot Pd$$

To determine the volume of renal blood flow para-aminohippuric acid (PAH) is administered into the blood. (Because the blood is completely cleared of this substance when it passes through the kidneys the first time).

If the volume of plasma flow through the kidneys is C, the concentration of PAH in blood plasma - P_{pah}, in urine - U_{pah} and the volume of excreted urine - V, then the amount of PAH flowing into the kidneys is - $C \cdot P_{pah}$ and its amount in the urine - $V \cdot U_{pah}$. Since these are equal, we have an equation from which the flow of plasma through the kidneys may be determined:

$$C \cdot P_{pah} = V \cdot U_{pah}$$

$$C = \frac{V \cdot U_{pah}}{P_{pah}}$$

If the hematocrit is known, it is easy to calculate the volume of renal blood flow.

Besides above - mentioned, other renal function tests are used which can be divided into three categories:

1) determination of renal clearances;

2) measurement of substances in the blood that are normally excreted by the kidneys;

3) chemical and physical analysis of the urine.

The volume of daily excreted urine is called the diuresis. Normally it is equal to 1-1.5 litres. The specific gravity of urine is 1.012-1.020, but it can be changed widely (1.001 - 1.033). At night the diuresis in decreased.

Urine contains organic substances (urea, uric acid, ammonia, creatine etc.) and inorganic salts (sodium chloride, potassium chloride, sulfates, phosphates etc.).

The pigments of urine (urobilin and urochrome) colour it.

In the urine some biologically active substances, hormones, vitamins, enzymes may be excreted.

In the pathological states in the urine the substances are revealed which are absent in normal urine: proteins, glucose, bile acids, acetone and so forth.

The urine which is formed in tubules enter the renal pelvis. When it is filled and the threshold is reached, the baroreceptors are excited the pelvis musculature is contracted and the urine passes into the urinary bladder. Since the wall of urinary bladder consists of smooth muscle characterized by the plasticity, accumulation of urine in the bladder do not cause the contraction till the volume of urine in the bladder reaches 250-300 ml and the pressure in it -15-16 cm of water column. Then the micturition reflex occurs that either causes micturition or, if it fails in

this, at least causes a conscious desire to urinate.

The center of micturition is located in the II-IV sacral segments of spinal cord. Sensory signals are conducted to sacral segments of the spinal cord through the pelvic nerves and then back again to the bladder through the parasympathetic fibers in these same nerves. The parasympathetic nerves stimulate the contractions of the musculature of the bladder walls and relaxe its sphincter. Thus, the urinary bladder is emptied, that is, the urine is removed from the organism.

The sympathetic impulses exercise the opposite effect, i.e., they relaxe the walls of uinary bladder and contract its sphincter. The micturition reflex is a completely automatic spinal cord reflex, but ut can be inhibited or facilitated by centers in the brain. These include strong facilitatory and inhibitory centers in the brain stem (in the pons) and several centers located in the cerebral cortex that are mainly inhibitory but can at times become excitatory.

In the regulation of renal activity the hormonal mechanisms are most significant. This may be demonstrated by the following experiment. The isolated kidney is transplanted into the area of the neck, its artery and vein are connected accordingly with the carotid artery and jugular vein. Such a kidney deprived of nervous connections with the organism, may function many months excreting the urine. Such denervated kidney can even react to the irritations.

The renal activity is regulated by the hormones of posterior pituitary gland (antidiuretic hormone or vasopressin), adrenal medulla (adrenalin), adrenal cortex (mineralocorticoids and especially - aldosterone, then desoxycorticosterone), thyroid and parathyroid glands.

The antidiuretic hormone increases the permeability of the wall of collecting ducts. This causes increase of reabsorption of water, and the volume of excreted urine decreases.

Insufficiency of posterior pituitary gland function causes the disease called diabetes insipidus. the walls of distal portions of the nephron become completely impenetrable for the water and it is excreted in urine in a great amount (20-25 litres daily).

Sceretion of antidiuretic hormone is controlled by the nuclei of hypothalamus.

Effect of the adrenalin depends on its dose. The small dose of adrenalin constricts the efferent arterioles and increases the filtration. But its large dose constricts also afferent arterioles and the diuresis is decreased or even ceased.

Mineralocorticoids (the hormones of adrenal cortex) increase the reabsorption of sodium in the tubules. This effects is especially marked in aldosterone, in lesser degree - in desoxycorticosterone.

The thyroid hormone increases the diuresis, the parathyroid hormone increases the excretion of calcium and phosphorus in urine.

Effect of the sympathetic nerves is similar to that of adrenalin. The weak stimulation of sympathetic fibers innervating the kidneys causes increase of diuresis, whereas as a result of the strong stimulation the diuresis is decreased or stopped.

Painful stimulations cause the reflex decrease or stopping of diuresis (anuria). This effect is realized by the strengthening of the antidiuretic hormone secretion.

The reflex anuria is observed also when the other ureter is obstructed by the calculus.

Diuresis is controlled also by cerebral cortex. It can be changed by conditioned reflex way as well as by the way of hypnotic suggestion.

The conditioned reflex influences on the kidney are realized by changing the secretion of antidiuretic hormone.

After the removal of both kidneys in experiment or during severe renal failure in the man uremia is developing. The basic reason of this state is accumulation of protein metabolism products in the blood. For instance, the concenration of urea may reach 900 mg/dl, whereas its normal level is 30 mg/dl. The uremia causes increasing weaknes, respiratory disorders, loss of consciousness and the death after 6-7 days.

To realize the hemodialysis in the patients with severe renel failure the artificial kidney is applied. It has now been developed to the point that many persons with permanent renal faiure

are baing maintained in health for years, their lives depending entirely on the artificial kidney.

The basic principle of the artificial kidney is to pass blood through the thin membrane-semipermeable thin spiral cellophane tube both ends of which are connected with cannulas. One of cannulas is introduced into artery and another one into vein.

On the other side of the membrane is a dialyzing fluid warmed to the body temperature, into which unwanted substances pass by diffusion from the blood.

Most artificial kidneys can clear 100-225 ml of plasma per minute of urea, which shows that, at least in the excretion of this substances, the artificial kidney can function about twice as rapidly as the two normal kidneys together, whose urea clearance is only 70 ml/min. But the artificial kidney is used for only 4-6 hours three times a week and the overall plasma clearance is considerably limited when it replaces the normal kidneys. Jet during 1 hour 6-16 g and more urea can be removed from the blood.

The sweat glands (sudoriferous glands) fulfil some functions in the organism. They:

1) excrete from the organism the waste products of metabolism;

2) take part in temperature regulation;

3) exreting from the organism surplus of water and salts, they take part in the regulation of osmotic pressure.

The sweat consists of 98-99% water, it contains inorganic (sodium chloride, potassium chloride) and organic (urea, uric acid, creatinine, volatile fatty acids, aromatic oxyacids etc.) substances. In diabetes mellitus the sweat contains also glucose.

Reaction of sweat is acid (pH - 3.8- 6.2). Its specific gravity is lower than that of urine (1.001 - 1.006).

Usually 500 ml of sweat is excreted daily. In the condition of higher temperature of the external environmet this amount is considerably increased. For example, in the special chamber with the temperature of 50-60$_o$ during 1.5 hours 2.5 litre of sweat was excreted.

Drinking of large amounts of fluid, the muscular work, emotions also increase the sweating. Renal diseases, when excretion of the urine is decreased, may cause increase of sweat excretion. During dehydration of organism (for instance, as a result of diarrhea) sweating is decreased.

The sweating is studied by the iodine-starch method of Minor. the skin is smeared with alcoholic solution of iodine, and when it is dried, is sprinkled with starch. When the sweat is excreted, the starch is coloured into blue.

The method of determination of electrical resistance of the skin is based on the fact that the sweating decreases the elctrical resistance of the skin.

The secretory nerves of sweat glands are sympathetic nerves. When the sympathetic nerves are cut, in the denervated areas the sweating in answer to the high temperature is ceased (in the Minor's test the skin is not coloured into blue).

Though the secretory nerves of sweat glands are sympathetic nerves, but in the nerve endings acetylcholine is secreted (as if they were parasympathetic nerve endings). Therefore, atropine ceases the sweating as a response to the high temperature.

Evidently, the emotional sweating is caused by sympathetic nerve endings of adrenergic nature.

The sweating is controlled also by hypothalamus and cerebral cortex. It occurs by unconditioned and conditioned reflex way.

ENDOCRINE SECRETION

Lecture 25

General and Local Hormones. Pituitary Gland (Hypophysis)

The endocrine or hormonal system is one of two major control systems regulating the functions of the body. The hormonal system is concerned principally with control of the different metabolic functions of the body, such as the rate of the chemical reactions in the cells, the transport of substances through cell membranes or other aspects of cellular metabolism like growth and secretion.

Many interrelations exist between the hormonal and nervous systems. For example, adrenal medullae and pituitary gland secrete their hormones almost entirely in response to appropriate neural stimuli. In turn, different pituitary hormones control secretion by the majority of other endocrine glands.

The endocrine system's effects are slow and long. But the nervous system acts rapidly, for a short time and more exactly (having a concrete "addressee").

The endocrinology is the science about the activity (in normal state and in pathology) of the endicrine glands.

A hormonal (Gr. hormon - to excite) is a chemical substance that is secreted into the body fluids by one cell or group of cells and has a physiological control effect on other cells of the body. There are general hormones and local hormones.

The general hormones are secreted by specific endocrine glands. Unlike the exocrine glands, the endocrine glands are ductless glands and their hormones are excreted immediately into the blood.

Circulating in the blood, the hormones exert their influence on different organs and tissues situated in the distance from the gland where the hormone was formed.

Four types of effects of the hormones on the organism are distinguished:

1) metabolic effects;

2) morphogenetic effects (stimulation of morphologic structures formation, differentiation, growth, metamorphosis);

3) kinetic effects (starting certan activity of executive organs);

4) correcting effects (changing the intensity of function of organs and tissues).

The characetristic property of hormones is that their physiological activity is very high. For instance, 1 g of insulin is enough to decrease the blood suger of 125000 rabbits.

The hormones are comparatively rapidly destroyed in the tissues, specifically in the liver, and therefore, to maintain their proper concentration in the blood the hormones must be continuously produced by the corresponding glands.

A few of the general hormones affect almost all the cells of the body. For instance, growth hormone of the anterior pituitary gland causes growth in most parts of the body, thyroid hormone increases the rates of most chemical reactions in almost all of the body's cells.

Other hormones affect only specific tissues, called target tissues because only these tissues have the specific receptors that will bind the hormones to initiate their actions: adrenocorticotropin from the anterior pituitary gland specifically stimulates the adrenal cortex, causing it to scerete the adrenocortical hormones; the ovarian hormones have specific effects on the female

sex organs, as well as on the secondary sexual chracteristics of the fmale body.

Chemically the hormones are of three basic types:

1. Steroid hormones-have a chemical structure similar to that of cholesterol and in most instances are derived from cholesterol itself. Steroid hormones are secreted by the adrenal cortex (cortisol and aldosterone), the testes (testerone), the ovaries and the placenta (estrogen and progesterone).

2. Derivatives of the amino acid tyrosine - two hormones of the adrenal medullae (epinephrine and norepinephrine) are catecholamines and two metabolic thyroid horemones (thyroxine and triiodothyronine) are iodinated forms of tyrosine derivatives.

3. All the remaining important endocrine hormones are either proteins, peptides or their immediate derivatives (the anterior and psterior pituitary hormones, insulin, glucagon, parathormone). The steroid hormones and the hormones - derivatives of amino acids have no specific differences, but the protein and peptide hormones have them. Therefore, these hormones of animals not always may be administered into human body: they can cause the immune reactions and allergy.

Each of the different hormones has its own charcteristic onset and duration of action. The two adrenal medullary hormones (epinephrine and norepinephtine) begin to be secreted in response to sympathetic nerve stimuli within the first second of stimulation and usually reach maximum concentrations within a minute after the onset of stimulation. But they are also destroyed rapidly by local tissue enzymes or absorbed ino cells. Therefore, duration of their action is no more than 1-3 minutes at most after the stimulation is over.

At the other extreme, the thyroid hormones are stored in the form of thyroglobulin in the thyroid follicles, sometimes for several months, before finally being secreted. Then, after secretion, several hours to several days are required before even initial activity begins, but their effect on enhancement of tissue metabolism can last as long as 6 weeks.

Separate fragments of molecules of hormones perform different functions: search of the place of action, (addressee) of the hormone, the specific effect of hormone on the cell, regulation of the degree of activity of the hormone etc.

The hormones are transported not only in free form (water-soluble hormones), they may be also found with blood plasma proteins or blood cells. In this case the activity of hormone is determined not only by its concentration in the blood, but also by the rate of its chipping off the transporting proteins or blood cells. The rate of absorption and destruction of hormones by the cells, the rate of their destruction by liver and excretion by kidneys are also significant.

To determine the intensity of the metabolism of the hormones their half-life period (T1/2) is used. That is the time during which the concentration of the radioactive hormone, introduced into the blood, is decreased twice.

Concentrations of hormones in the blood range from as little as 1 picogram (one millionth of a millionth of a gram) up to at most a few micrograms (one millionth of a gram) per milliliter of blood. The rates of secretion of the various hormones are also extremely small (measured in micrograms or milligrams per day). Highly specialized mechanisms in the target tissues allow even these minute quantities of hormones to exert powerful control over the physiological systems.

The rate of secretion of every hormone is controlled very exactly by some internal control system. In most instances this control is exerted through a negative feedback mechanism as follows. The endocrine gland has a natural tendency to oversecrete its hormone which exerts more and more of its control effect on the target organ. But when too much function of the target organ occurs, some factor about the function then feeds back to the endocrine gland and causes a negative effect on the gland to decrease its secretory rate.

For instance, the high concentrations of calcium ions in blood, influencing the cells of the parathyroid glands, suppress secretion of parathormone, and the low concentrations of calcium

ions stimulate its secretion. Also, the increased blood sugar causes the intensification of secretion of insulin.

Hormones almost never act directly on the intracellular mechanisms- they first combine with hormone receptors on the surfaces of the cells or inside the cells. Obviously, the target tissues that are affected by a hormone are those that contain its specific receptors. The membrane receptors (in or on the surface of the cell membrane) are specific mostly to the protein, peptide and catecholamine (epinephrine and norepinephrine) hormones. The receptors for the different steroid hormones are found almost entirely in the cytoplasm. The receptors for the metabolic thyroid hormones (thyroxine and triiodothyronine) are found in the nucleus.

So, the catecholamines and peptide hormones are fixed on the outside of the cell membrane, and therefore, the intracellular mediators are needed which transmit the effect of the hormone to certain intracellular structures: cyclic adenosine monophosphate (c AMP), cyclic guanosine monophosphate (c GMP), prostaglandins, calcium ions and so forth.

The c AMP is called a second messenger, for it is not the hormone itself that directly institutes the intracellular changes, instead, it is the c AMP that serves as a "second messenger" to cause these effects.

Thus, the protein, peptide and catecholamine hormones do not diffuse into the cells. Therefore, they are called the hormones of distant effect.

The hormones which diffuse through the cell membranes easily (steroid hormones, and in certain degree, the thyroid hormones), exercise immediate specific influence on certain intracellular structures. Changing processes of synthesis of cellular proteins, they exert their influence during a long time.

The steroid hormones regulate participation of some hormones of distant effect in the metabolism. This is called the permissive effect of steroid hormones.

Activity of endocrine glands is regulated by the nervous, nervous-endocrinous (through the hypothalamus) and endocrinous ways.

The nervous system influences on the activity of the endocrine glands mainly by changing the vascular tension and consequently, the blood supply of their parenchymal elements. But the nervous system influences some endocrine glands (the adrenal medullae, the neurosecretory nuclei of pituitary gland, the pineal gland) directly - by the way of changing their functional elements activity.

The adrenal medullae and the sympathetic nervous system function in close contact, and they form the united regulative system of the organism - the sympathoadrenal system.

The close connections exist between the functional state of the nervous system and activity of the endocrine system. The emotional stress, psychic trauma are the causes of many endocrine disease, and many endocrine disturbances are followed by the changes in the nervous system (especialy in the higher nervous activity).

The nervous - endocrinous regulation of endocrine glands activity is realized through the hypothalamus and its neurohormones. In the neurosecretory nuclei of the hypothalamus two groups of hormones are produced which previously were called the releasing hormones or factors: the liberins and the statins. The liberins stimulate the synthesis of "tropic" hormones of the pituitary body and the statins inhibit it.

The endocrinous regulation of the endocrine glands functions is realized mainly by the pituitary body. The "tropic" hormones of the anterior pituitary gland stimulate the function of a number of peripheral endocrine glands. This way of the endocrine glands activity regulation is called the transhypophysial regulation.

The central nervous system regulates activity of the adrenal medulla, epiphysis, parathyroid glands, pancreatic islands passing by the pituitary body. This is called the parahypophysial regulation.

The biologically active substances having a specific effects are produced not only by the

endocrine glands, but also by the specialized cells located in different organs. They are called the local hormones, or tissue hormones (histohormones), or parahormones. These hormones have specific local effects, whence comes the name local homones.

A group of hormones of polypeptide structure is formed in the digestive tract: gastrin, secretin, cholecystokinin - pancreozymin, enkephalin, bombezin, motilin, villikinin, vasoactive intestinal polypeptide, somatostatin, substance P etc. They are important for regulation of motility, secretion and absorption in the digestive tract. A number of these substances is found also in the central nervous system, and some of them are mediators.

Kidneys secrete renin and erythropoietins. Thymus gland produces thymosine which increases number of lymphocytes and strengthens the reactions of immunity.

In many organs and tissues serotonin, histamine and prostaglandins are produced. Serotonin is one of the mediators of central nervous system; it causes contractions of smooth muscles, including that of blood vessels and increases the blood pressure. Histamine is the mediator of the sense of pain, it has a marked vasodilative effect, increases the permeability of the blood vessels. Prostaglandins have many different effects: they strengthen the contractile activity of the smooth muscles of the uterus, increase excretion of water and sodium in urine, influence function of some exocrine and endocrine glands. The prostaglandins inhibit releasing of the epinephrine and norepinephrine in the adrenal glands when the sympathetic nerves are stimulated.

In the brain neuropeptides are produced. They play an important role in regulation of the intensity of the pain reactions and normalization of the psychic processes.

Different methods are used to study the functions of the endocrine glands: the complete or partial removal of the gland, transplantation of the gland or adminisrtation of its extract or hormone into the organism, joining of the organisms (parabiosis) in one of which some endocrine gland is removed or damaged, comparision of the physiological activity of the blood flowing into the gland and out of it, determination of the content of hormones in the blood and urine, investigation of the patients with hyperfunction and hypofunction of certain gland. If the chemical structure of the hormone is unknown, its content is expressed in the biological units. One biological unit is the amount of the preparation which must be administered into the organism to obtain certain specific physiological effect. More biological units in 1 g or 1 ml of preparation- higher its activity.

The pituitary gland or pituitary body (hypophysis) is one of most important endocrine glands for its own functions, moreover, it takes part in the regulation of the functions of other endocrine glands.

Physiologically the pituitary gland is divisible into two distinct portions: the anterior pituitary (adenohypophisis) and the posterior pituitary (neurohypophysis). Between these is a small relatively avascular zone called the pars intermedia (this is almost absent in the human being, but much larger and more functional in some lower animals).

Six very important hormones and several less important ones are secreted by the anterior pituitary gland; two important hormones are secreted by the posterior pituitary gland.

The hormones of the anterior pituitary gland play major roles in the control of metabolic functions throughout the body:

1. Growth hormone (GH) or somatotropic hormone (STH) or somatotropin - promotes growth of the body by affecting protein formation, cell multiplication and cell differentiation.

2. Adrenocorticotropic hormone (ACTH) or corticotropin - controls secretion of some of the adrenocortical hormones, which in turn affect the metabolism of glucose, proteins and fats.

3. Thyroid - stimulating hormone (TSH) or thyrotropin - controls the rate of secretion of thyroxine by the thyroid gland.

4. Prolactin (PRL) or lactogenic hormone (LGH) - promotes the mammary gland development and milk production.

Two more gonadotropic hormones control growth of the gonads as well as their reproductive activities:

5. Follicle stimulating hormone (FSH).

6. Luteinizing hormone (LH).

The two hormones secreted by the posterior pituitary gland are:

1. Antidiuretic hormone (ADH) or vasopressin - controls the rate of water excretion into the urine and in this way helps to control concentration of water in the body fluids.

2. Oxytocin - helps in delivery of milk from the glands of the breast to the nipples during suckling and in delivery of the baby at the end of gestation.

There are many different types of secretory cells in the anterior pituitary gland, actually one cell type for each major hormone formed in this gland.

About 30-40% of the anterior pituitary cells are somatotropes that secrete growth hormone and about 20% are corticotropes that secrete ACTH. The other cell types (thyrotropes, gonadotropes, lactotropes) secrete the extremely powerful hormones for controlling thyroid function, sexual functions and milk secretion by breasts.

Somatotropes stain very strongly with acid dyes and therefore are called acidophils. So, pituitary tumors that secrete large quantities of human growth hormone are called acidophilic tumors.

The cell bodies that secrete the posterior pituitary hormones are not located in the posterior pituitary gland itself, but are large neurons located in the supraoptic and paraventricular nuclei of the hypothalamus. The hormones are then transported to the posterior pituitary glands in the axoplasm of the neuron's nerve fibers passing from the hypothalamus to the posterior pituitary gland.

Almost all secretion by the pituitary gland is controlled by either hormonal or nervous signals from the hypothalamus. When the pituitary gland is removed from its normal position (beneath the hypothalamus) and transplanted to some other part of the body its rates of secretion of the different hormones fall to low levels (in the case of some of the hormones - to zero).

Secretion from the posterior pituitary gland is controlled by nerve signals originating in the hypothalamus. Secretion by the anterior pituitary gland is controlled by releasing hormones (the liberins) and inhibitory hormones (the statins). These hormones or factors are secreted within the hypothalamus and then conducted to the anterior pituitary gland through minute blood vessels called hypothalamic - hypophyseal portal vessels. In the anterior pituitary gland these releasing and inhibitory hormones act on the glandular cells to control their secretion.

The liberins:

1) corticoliberin or corticotropin - releasing hormone (CRH);

2) thyroliberin or thyroid - stimulating hormone releasing hormone (TRH);

3) folliberin or follicle - stimulating hormone releasing hormone (FRH);

4) luliberin or luteinizing hormone releasing hormone (LRH);

5) somatoliberin or growth hormone releasing hormoe (GHRH);

6) prolactoliberin or prolactin releasing hormone (PRH);

7) melanoliberin or melanocyte - stimulating hormone releasing hormone (MRH);

The statins:

1) somatostatin or growth hormone inhibitory hormone (GHIH);

2) prolactostatin or prolactin inhibitory factor (PIF);

3) melanostatin or melanocyte stimulating hormone inhibitory factor (MIF).

All the major anterior pituitary hormones, besides growth hormone, exert their principal effects by stimulating target glands - the thyroid gland, the adrenal cortex, the ovaries, the testicles, the mammary glands. Growth hormone (somatotropin) exerts its effects almost on all tissues of the body. It causes growth of almost all tissues of the body that are capable of growing. It promotes increased sizes of the cells, increased mitosis with development of increased

numbers of cells and specific differentiation of certain types of cells such as bone growth cells and early muscle cells.

In experiment the growing rats received daily injections of somatotropic hormone, and the marked exacerbation of growth was observed in the early days of life and even after the rats had reached adulthood. In the early stages of development all organs of treated rats increased proportionately in size, but after adulthood was reached, most of the bones ceased lengthening while the soft tissues continued to grow. Because once the epiphysis of the long bone have united with the shafts, further growth of bone length cannot occur even though most other tissues of the body can continue to grow throughout life.

Aside from its general effects in causing growth, somatotropic hormone has many specific metabolic effects:

1) increased rate of protein synthesis in all cells of the body;

2) increased mobilization of fatty acids from adipose tissue and increased use for energy;

3) decreased rate of glucose utilization throughout the body.

Thus, growth hormone enhances the body protein, uses the fat stores and conserves carbohydrates.

When somatotropic hormone is administered, the cellular uptake of glucose is enhanced, and the blood glucose concentration falls slightly. But then (after 30-60 minutes) this is followed by exactly the opposite effect - decreased transport of glucose into the cells. Because the cells have already taken up an excess of glucose that they are having difficulty using. The blood concentration of glucose may increase to as high as 50-100% above normal. This condition is called pituitary diabetes. When this diabetes is treated by insulin, it is insulin insensitive, requiring excessive amounts of insulin for therapy.

Growth hormone has also a diabetogenic effect. Because the increase in blood glucose concentration caused by growth hormone stimulates the beta cells of the islets of Langerhans to secrete extra insulin. In addition, the growth hormone also has a direct stimulatory effect on the beta cells. Sometimes combination of these two effects over - stimulates insulin secretion by the beta cells so greatly that they literally "burn out", and diabetes mellitus develops.

Adequate insulin activity and adequate availability of carbohydrates are necessary for growth hormone to be effective. This hormone fails to cause growth in an animal lacking a pancreas and if carbohydrates are excluded from the diet.

The most obvious effect of the growth hormone is to increase growth of the skeletal frame. It stimulates all the processes of epiphyseal cartilage growth and growth of the long bones. But when the epiphyses have united with the shafts, growth hormone has no further ability to lengthen the bones.

Growth hormone strongly stimulates the osteoblasts. Therefore, the bones (especially the membranous bones) can continue to enlarge throughout life under the influence of growth hormone. The jaw bones can be stimulated to grow even after adolescence, causing forward protrusion of the chin and lower teeth; the bones of the skull grow in thickness and also give rise to bony protrusions over the eyes.

Growth hormone causes the liver (and in much less extent other tissues) to form several small proteins called somatomedins that in turn have the very potent effect of increasing all aspects of bone growth. The most important of these is somatomedin - C the concentration of which in the plasma normally follows closely the rate of secretion of growth hormone.

The pygmies of Africa as well as some other dwarfs (the Levi - Lorain dwarf) have a congenital inability to synthesize significant amounts of somatomedin - C. Therefore, even though their plasma concentration of growth hormone is either normal or high, there remain diminished amounts of somatomedin - C in the plasma, thus apparently accounting for the small stature.

Somatomedin -C has also insulin - like effects, promoting glucose transport through

membranes. Therefore, it has also been called insulin - like growth factor (IGF-G).

The rate of growth hormone secretion increases or decreases within minutes during starvation, hypoglycemia or low concentration of fatty acids in the blood, exercise, excitement, trauma. But growth hormone secretion is controlled almost entirely in response to growth hormone releasing hormone (somatoliberin) and growth hormone inhibitory hormone (somatostatin). Somatostatin is also secreted by the delta cells of the islets of Langerhans in the pancrease, and it can inhibit secretion of insulin and glucagon by the beta and alpha cells.

The major long-term cantroller of growth hormone secretion is the state of nutrition of the tissues themselves, especially their level of protein nutrition.

Decreased secretion of all the anterior pituitary hormones is called panhypopituitarism. The decrease of secretion may be congenital or it may occur at any time during the life of the individual (suddenly or slowly).

Generalized deficiency of anterior pituitary secretion during childhood in most instances results in dwarfism. In general, the features of the body develop in appropriate proportion to each other, but the rate of development is greatly decreased. A child who has reached the age of 10 years may have the bodily development of a child of 4-5 years, and on reaching the age of 20 years may have the bodily development of a child of 7-10 years.

The panhypopituitary dwarfs do not secrete a sufficient quantity of gonadotropic hormones to develop adult sexual functions. But in one third of the dwarfs the deficiency is of growth hormone alone; these individuals do mature sexually occacionally do reproduce.

The growth hormones of different species of animals are sufficiently different, and therefore growth hormone prepared from lower animals (except to some extent from primates) is not effective in human beings. To distinguish the growth hormone of the human being from the others, it is called human growth hormone (HGH).

Effects of adult panhypopituitarism are hypothyroidism, depressed production of glucocorticoids by the adrenal glands and suppressed secretion of the gonadotropic hormones to the point at which sexual functions are lost.

Occasionally, the acidophilic, growth hormone - producing cells of the anterior pituitary become excessively active and sometimes even acidophilic tumors occur in the gland. As a result, large quantities of growth hormone are produced. All body tissues grow rapidly, including the bones, and if the condition occurs before adolescence, that is, before the epiphyses of the long bones have not become fused with the shafts, height increases so that the person becomes a giant 240-270 cm tall and 150 kg or more body mass (gigantism).

The giant ordinally has hyperglycemia, and the beta cells of the islets of Langer-hans in the pancreas are prone to degenerate. In about 10% of giants finally full-blown diabetes mellitus develops.

In most giants panhypopituitarism eventually develops if they remain untreated, because the gigantism is usually caused by a tumor of the pituitary gland that grows until the gland itself is destroyed. This general deficiency of pituitary hormones usually causes death in early adulthood.

If an acidophilic tumor occurs after adolescence (after the epiphyses of the long bones have fused with the shafts), the person cannot grow taller; but the soft tissues can continue to grow, and the bones can grow in thickness. This condition is called acromegaly. Enlargement is especially marked in the bones of the hands and feet and in the membranous bones including cranium, nose, bosses on the forehead, supraorbital ridges, lower jawbone and portions of vertebrae. The jaw protrudes forward, the forehead slants forward, the nose increases to as much as twice normal size, the fingers become extremely thickened so that the hand develops a size almost twice normal. Changes in the vertebrae cause a hunched back (kyphosis). Many soft tissue organs (the tongue, liver, the kidneys) become greatly enlarged.

In persons who have lost their ability to secrete growth hormone, the aging process

accelerates (a person at age 50 will have the appearance of a person aged 65). This seems to result mainly from decreased protein deposition in most tissues of the body and in its place increased deposition of fat. The physical and physiological effects are: increased wrinkling of the skin, diminished rates of function of some of the organs, diminished muscular mass and muscle strength.

The gonadotropic hormones of the adenohypophysis (follicle-stimulating hormone, luteinizing hormone and lactogenic hormone or prolactin) take part in the regulation of the sexual glands activity.

Follicle-stimulating hormone (FSH) in females accelerates development of follicles in ovaries and their conversion into Graafian vesicles; in males it accelerates development of spermatozoons and prostate. Luteinizing hormone (LH) stimulates development of incretory elements in testes and ovaries and in this way intensifies formation of sex hormone (androgens and estrogens). It determines ovulation in ovaries and formation of yellow body (which produces progesterone) in place of burst Graafian vesicle. Lactogenic hormone (LGH) or prolactin (PRL) stimulates formation of progesteron in yellow body and lactation.

Gonadotropic hormones are very important for puberty. After removal of pituitary body (hypophysectomy) in preadolescent animals development of the sexual glands slows down and remains unfinished. If the hypophysectomy is performed in puberal animals, atrophy of interestitial tissue in testes and of follicles in ovaries is observed.

When the hypophysectomy is performed in suckling rats, the lactation stops. injection of prolatin can cause lactation even in males.

Secretion of gonadotropic hormones is regulated by hypothalamus by means of proper releasing and inhibitory hormones: folliberin, luliberin, prolactoliberin, prolactostatin. There are reciprocal relations between the secretion of FSH and LH on the one hand and of LGH on the other hand: intensification of secretion of FSH and LH inhibits secretion of LGH and vice versa.

Psychological experiences, emotions influence powerfully production of gonadotropic hormones. For example, during the war the fear of air attacks sharply disturbed the secretion of these hormones and caused cessation of menstrual cycle.

Thyroid - stimulating hormone (TSH) or thyrotropin stimulates function of thyroid gland. Hypophysectomy in young animals causes underdevelopment of the thyroid gland, in adult animals - decrease of its size and partial atrophy. Injection of TSH leads to expansion of the thyroid gland.

If the large amounts of thyrotropin are injected daily for a long time, symptoms of Basedow's disease appear.

Secretion of thyrotropin is stimulated by thyroliberin (thyroid - stimulating hormone) which is secreted in nerve cells of hypothalamus. It is regulated by the principle of negative feedback.

Brain cortex influences secretion of the thyroid - stimulating hormone.

Adrenocorticotropic hormone (ACTH) or corticotropin causes growth of zona fasciculata and zona reticularis of adrenal cortex, but does not influence zona glomerulosa.

Hypersecretion of ACTH is the main pathogenetic factor of Icenko-Cushing disease (pituitary dependent Cushing's syndrome). This disease is characterized by adiposis of the face ("moon face"), neck and trunk (but not the limbs), elevated blood pressure and increased erythrocyte count, hypogenitalism (phenomena of masculinization in women), hyperglycemia and glucosuria.

Hyposecretion of ACTH causes secondary weakness of the adrenal cortex function which is called Addison's syndrome. This must be distinguished from Addison's disease or bronze disease (primary insufficiency of the adrenal cortex).

Secretion of ACTH by anterior pituitary gland is intensified under the influence of all extreme stimulants causing the state of overexertion (stress). These stimulants effect on the

nuclei of hypothalamus by reflex way and by the way of increased production of adrenalin in adrenal medulla and intensify formation of corticoliberin (corticotropin - releasing hormone-CRH). Reaching adenohypophysis through blood vessels, CRH stimulates ACTH secretion. ACTH influences adrenal glands and intensifies production of glucocorticoids (which promote rise of organism's resistibility against the unfavourable factors) and in certain degree - that of mineralocorticoids.

So, the pituitary body regulates function of several other endocrine glands. The endocrine secretion of pituitary body in its turn, depends on the activity of these glands. For instance, deficiency of androgens and estrogens, glucocorticoids and thyroxine in the blood stimulates production of gonadotropic, adrenocorticotropic and thyrotropic hormones. On the contrary, surplus of above- mentioned hormones supresses production of corresponding tropic hormones of the pituitary gland.

In man as well as in most of animals the pars intermedia of pituitary body is isolated from adenohypophysis and joined with the neurohypophysis. Its hormone is called intermedin or melanocyte - stimulating hormone.

Intermedin is important for adaptation of the colour of the skin to the surroundings. It regulates pigmentation of the skin. In persons with the skin areas deprived of pigment, intracutaneous injection of intermedin gradually leads to normalization of their colour.

Secretion of intermedin by the pars intermedia of pituitary body is regulated in reflex way by the influence of light on the retina.

Posterior pituitary gland (neurohypophysis) is composed mainly of glial - like cells called pituicytes. But the pituicytes do not secrete hormones. They act simply as a supporting structure for large numbers of terminal nerve fibers and nerve endings from nerve tracts that originate in the supraoptic and paraventricular nuclei of hypothalamus. These tracts pass to the neurohypophysis through the pituitary stalk. The nerve endings are bulbous knobs containing many secretory granulas that lie on the surfaces of capillaries onto which they secrete two hormones of the posterior pituitary: antidiuretic hormone (vasopressin) and oxytocin.

Antidiuretic hormone (ADH) is initially synthesized in the supraoptic nuclei and oxytocin - in paraventricular nuclei of hypothalamus. They are then transported in combimation with " carrier" proteins called neurophysins down to the nerve endings in the posterior pituitary gland, requiring several days to reach the gland.

Extremely minute quantities of ADH (2 nanograms), when injected into a person, can cause antidiuresis (decreased excretion of water by kidneys). In the absence of ADH the collecting tubules and ducts are almost totally impermeable to water which prevents significant reabsorption of water and therefore allows extreme loss of water into the urine.

Hypofunction of posterior pituitary gland causes the disease called diabetes insipidus. The person feels a violent thirst, drinks a large amount of water, and the volume if excreted urine also increases greatly (some ten litres daily). Subcutaneous injections of the posterior pituitary preparation decreases the diuresis down to the norm.

In the presence of ADH the permeability of the collecting ducts and tubules to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts, thereby conserving water in the body.

Higher concentrations of ADH have very potent effect of constricting the arterioles everywhere in the body and therefore of increasing the arterial pressure. For this reason, ADH is called also vasopressin.

The hormone oxytocin powerfully stimulates the pregnant unterus, especially toward the end of gestation. Oxytocin plays an especially important role in the process of lactation, a role that is far more certain than its possible role in delivery of the baby. It causes milk to be expressed from the alveoli into the ducts (by reflex way) so that the baby can obtain it by suckling.

Lecture 26

Thyroid and Parathyroid Glands. Adrenal Glands

Thyroid gland is composed of large numbers of close follicles lined with cuboidal epithelioid cells that secrete into the interior of the follicles. The follicles are filled with a secretory substances (colloid) the major constituent of which is the large glycoprotein (thyroglobulin) containing the thyroid hormones within its molecules. Once the secretion has entered the follicles, to function in the body it must be absorbed back through the follicular epithelium into the blood. Therefore, the thyroid gland blood supply is very rich- its blood flow is about five times the weight of the gland each minute.

About 90% of the hormone secreted by the thyroid gland is thyroxine (T_4) and 10% is triiodothyronine (T_3). But most of the thyroxine is eventually converted to triiodothyronine in the tissues. The functions of both hormones are qualitatively the same, however, triiodothyronine is about four times as potent as thyroxine. But it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine.

Thyroxine and triiodothyronine have the profound effect of increasing the metabolic rate of the body. Extreme excesses of thryoid secretion can cause the basal metabolic rate to rise as high as 60-100% above normal, complete lack of secretion - to fall about 40% below normal.

Thyroxine and triiodothyronine are iodine containing hormones of the thyroid gland. To form normal amount of thyroxine about 1 mg of iodine (in the form of iodides) is required per week and 50 mg each year. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell (iodide trapping). In a normal gland the iodide pump concentrates the iodide to about 30 times its concentration in the blood. But when the gland becomes maximally active, the concentration ratio can rise to as high as 250 times.

The thyroid gland also secretes calcitonin (thyrocalcitonin), an important hormone for calcium metabolism.

There is a long latent period before thyroxine activity begins: after injection of a large amount of the thyroxine into a human being, no effect on the metabolic rate can be observed for 2-3 days. But when the activity begins, it increases progressively and reaches a maximum in 10-12 days. Then it decreases with a half-life of about 15 days. Some of the activity still persists as long as 6 weeks to 2 months later.

The latent period of triiodothyronine's action is shorter (6-12 hours) and maximum cellular activity occurs within 2-3 days.

Most of the latency and prolonged period of action of these hormones is caused by their binding with proteins followed by their slow release. But part of the latent period also results from the manner in which these hormones perform their functions in the cells.

The general effect of thyroid hormone is to cause wholesale nuclear transcription of large numbers of genes. Therefore, in all cells of the body great numbers of protein enzymes, structural proteins, transport proteins and other substances increase. The net result of all this is a generalized increase in functional activity throughout the body.

Under the influence of thyroid hormone the changes occur in functions of all systems of the organism.

When thyroxine or triiodothyronine is given to an animal, the mitochondria in most cells of the body increase in size and number. The total membrane surface area of the mitochondria

increases almost directly in proportion to the increased metabolic rate of the whole animal.

Under the influence of thyroid hormone the amount of heat produced in the body increases.

Thyroid hormone has both general and specific effects on growth. Thyroid hormone is essential for the metamorphic changes of the tadpole into the frog.

In hyperthyroid children excessive skeletal growth often occurs causing the child to become considerably taller at an earlier age. But the bones also mature more rapidly, and the epiphyses close at an early age so that the duration of growth and eventual height of the adult may actually be shortened. In hypothyroid children the rate of growth is greatly retarded.

Thyroid hormone promotes growth and development of the brain during fetal life and in the first few years of postnatal life. If the fetus does not secrete sufficient quantities of thyroid hormone, growth and maturation of the brain before and after are greatly retarded; the child remains mentally deficient throughout life.

Thyroid hormone stimulates almost all aspects of carbohydrate metabolism (rapid uptake of glucose by cells, enhanced glycolysis and gluconeogenesis etc.), fat metabolism (acceleration of the oxidation of free fatty acids by the cells, decrease of quantity of cholesterol, phospholipids etc.), vitamin metabolism and so forth.

Increased thyroid hormone production decreases the body weight and decreased production increases it. But thyroid hormone also increases the appetite and this may overbalance the change in the metabolic rate.

Blood flow, cardiac output, heart rate increase under the influence of thryod hormone. The mean arterial pressure usually is unchanged, but because of the increased stroke volume and blood flow, the pulse pressure is increased (the systolic pressure is slightly elevated and the diastolic pressure-correspondingly reduced).

Increased rate of metabolism under the influence of thryoid hormone causes increase of oxygen utilization and carbon dioxide formation. These changes lead to increase of the rate and depth of respiration.

Thyroid hormone increases secretory and motor functions of the gastrointestinal tract-diarrhea results. Lack of this hormone causes constipation.

Thyroid hormone hypersecretion increases rates of secretion of most other endocrine glands, but it also increases need of the tissues for the hormones. For example, increased thyroxine secretion increases the rate of glucose metabolism and causes a corresponding need for increased insulin secretion.

Thyroid hormone greatly effects also the sexual functions.

One of the most characteristic signs of hyperthyroidism is muscle tremor which is caused by increased reactivity of the neuronal synapses in the areas of the spinal cord controlling muscle tone. It is an important means for assessing the degree of thyroid hormone's effect on the central nervous system. The tremor can be observed easily by placing a sheet of paper on the extended fingers and noting the degree of vibration of the paper.

Because of the exhausting effect of thyroid hormone on the musculature and on the central nervous system, the hyperthyroid subject feels constant tiredness; but because of the excitable effects of the hormone on the synapses, it is difficult to sleep. On the contrary, extreme somnolence is characteristic for hypothyroidism.

In general, thyroid hormone increases the rapidity of cerebration, but also often dissociates this. Lack of thyroid hormone decreases this function. In hyperthyroid individuals extreme nervousness and many psychoneurotic tendencies, such as anxiety complexes, extreme worry or paranoia are observed.

In the structures of brain stem reticular formation iodine containing hormones of the thyroid gland accumulate in larger amounts than in other parts of the central nervous system. They raise the tonus of central nervous system and in this way exert activating influence on brain cortex.

Another hormone of thyroid gland-calcitonin (thyrocalcitonin) decreases the blood content of calcium. Because it inhibits the function of osteoclasts and activates the osteoclasts and activates the osteoblasts which promote formation of bone tissue and absorption of calcium ions from the blood. So, calcitonin saves up to calcium in the organism.

Calcitonin is formed in the parafollicular cells which are located outside the glandular follicles of the thyroid gland.

To control the rate of thyroid secretion specific feedback mechanism operates through the hypothalamus and anterior pituitary gland.

The anterior pituitary hormone thyrotropin or thyroid-stimulating hormone (TSH) increases secretion of thyroxine and triiodothyronine by the thyroid gland. Generally, the TSH increases all the known activities of the thyroid glandular cells. Most of varied effects of thyroid-stimulating hormone on the thyroid cells result from activation of the "second messenger" - cyclic adenosine monophosphate (c AMP) system of the cell.

Secretion of thyrotropin is controlled by thyrotropin - releasing hormone (TRH), which is secreted by nerve endings in the hypothalamus and then transported to the anterior pituitary in he hypothalamic - hypophyseal portal blood.

Rate of TRH secretion by the hypothalamus, and therefore TSH secretion by the adeno-hypophysis are greatly increased under the influence of the cold on the organism. This effect, results from excitation of the anterior hypothalamus and the preoptic area, where the center for body temperature control is located. People moving to arctic regions have been known to develop basal metabolic rates 15-20% above normal.

Various emotional reactions can also effect the output of TRH and TSH and indirectly - secretion of thyroid hormones.

Neither these emotional effects nor the effect of cold is observed after the hypophyseal stalk has been cut. This means that both effects are mediated by hypothalamus.

Increased thyroid hormone in the body fluids decreases secretion of TSH mainly by a direct effect on the anterior pituitary itself.

Some drugs, called antithyroid substances (thio-cyanate, propylthiouracil, high concentrations of inorganic iodides) suppress thyroid secretion.

Hyperfunction as well as hypofunction of thyroid gland lead to severe diseases. The hyperthyroidism causes Basedow's disease called also thyrotoxicosis, toxic goiter or Graves' disease. The hypothyroidism causes different diseases: cretinism, myxedema, endemic colloid goiter etc.

In most patients with hyperthyroidism the entire thryoid gland is increased to 2-3 times normal size with tremendous hyperplasia, and the number of cells is increased several more times than the seize of the gland. Radioactive iodine uptake studies indicate that some of these hyperplastic glands secrete thyroid hormone at rates as great as 5-15 times normal.

Changes in the thyroid gland are similar to those caused by excessive TSH. But the plasma TSH concentration is less than normal rather than enhanced and often essentially zero. However, other substances that have actions similar to that of TSH are found in the blood of almost all patients. These are immunoglobulin antibodies that bind with the same membrane receptors that bind TSH. They induce continual activation of the c AMP system of the cells with resultant development of hyperthyroidism. They are called thyroid-stimulating antibodies (TSAb). They have a prolonged stimulating effect on the thyroid gland (12 hours) in contrast to that of for TSH (a little over 1 hour).

The antibodies that cause hyperthyroidism develop as the result of autoimmunity that has developed against thyroid tissue. Presumably, at some time in the history of the person an excess of thyroid cell antigens has been released from the thyroid cells, and this has resulted in the formation of antibodies against the thyroid gland.

Hyperthyroidism rarely also results from a localized tumor (adenoma) that develops in the

thyroid tissue and secretes large quantities of thyroid hormone. As long as the adenoma continues to secrete large quantities of thyroid hormone, function in the remainder of the thyroid gland is almost totally inhibited because the thyroid hormone from the adenoma depresses the production of TSH by the pituitary gland.

Most effects and symptoms of hyperthyroidism are obvious from the preceding discussion of the physiological effects of thyroid hormone: intolerance to heat, increased sweating, weight loss, diarrhea, muscular weakness, extreme fatigue but inability to sleep, tremor of the hands, nervousness and other psychic disorders. The basal metabolic rate and body temperature are increased.

The main symptoms of Basedow's disease are: struma or goiter (greatly enlarged thyroid gland), exophthalmos (protrusion of eyeballs), tachycardia (fast heart rate), cachexia (severe inanition).

In major degree of exophthalmos the eyeball protrusion stretches the optic nerve enough to damage vision.

The cause of the protruding eyes is edematous swelling of the retro-orbital tissues and degenerative changes in the extraocular muscles. In most patients antibodies can be found in the blood that react with the eye muscles. Evidently, exophthalmos, like hyperthyroidism itself, is an autoimmune process.

The effects of hypothyroidism (deficient functioning of the thyroid gland) in general are opposite to those of hyperthyroidism, but some physiological mechanisms are involved which are characteristic only of hypothyroidism.

Hypothyroidism also results in most instances from autoimmunity against the thyroid gland, but immunity that destroys the gland rather than stimulating it. Most of these patients first have thyroiditis (thyroid inflammation). This causes progressive deterioration and finally fibrosis of the gland with resultant diminished or absent secretion of thyroid hormone. But several other types of hypothyroidism also occur, often associated with development of enlarged thyroid glands, called thyroid goiter.

Extreme hypothyroidism during fetal life, infancy and childhood causes the condition called cretinism. Its typical symptoms are retarded growth with disproportions of the body, delayed sexual maturity and mental development.

Cretinism results from congenital lack of thyroid gland (congenital cretinism), from its failure to produce thyroid hormone because of a genetic defect of the gland, or from iodine lack in the diet (endemic cretinism). The severity of endemic cretinism varies greatly, depending on the amount of iodine in the diet, and whole populaces of an endemic area have been known to have cretinoid tendencies.

Skeletal growth in the cretin is characteristically more inhibited than is soft tissue growth. As a result of this disproportionate rate of growth, the soft tissues are likely to enlarge excessively, giving the cretin the appearance of an obese and stocky, short child.

A gaping mouth with the tongue constantly hanging out is characteristic of the appearance; it is due to an extreme enlargement of the tongue which does not fit into the mouth. Occasionally the tongue becomes so large in relation to the skeletal growth that it obstructs swallowing and breathing, inducing a characteristic guttural breathing that sometimes chokes the baby.

Cretinism is also attended with symptoms of myxedema.

Whether hypothyroidism is due to thyroiditis, endemic colloid goiter, idiopathic colloid goiter, destruction of the thyroid gland by irradiation or surgical removal of the thyroid gland, the physiological effects are the same: fatigue and extreme somnolence (with slepping up to 14-16 hours a day) extreme muscular sluggishness, failure of many trophic functions in the body (evidenced by depressed growth of hair and scaliness of the skin), development of a froglike husky voice and edematous appearance throughout the body called myxedema (in Latin "myxedema" means mucuos edema).

In adult patient with almost total lack of thyroid function myxedema develops. Bagging under the eyes and swelling of the face is characteristic of them. Because greatly increased quantities of proteins mixed with hyaluronic acid and chondroitin sulfate form excessive quantities of tissue gel in the interstitial spaces, and this causes the total quantity of interstitial fluid also to increase. Because of the gel nature of the excess fluid, it is relatively immobile, and the edema is nonpitting in type.

Mucous edema of the tissues is attended with puffiness of the face and trunk, disturbances in sexual functions (cessation of menstruation in females), slowing of thinking and speech, apathy. Basal metabolism and body temperature fall. Body weight increases because of an increase in the volume of tissue fluid and partly owing to the deposit of fat in the adipose tissue.

In certain areas of the world, mainly in mountain regions (Swiss Alps, Ands, Pamirs, Urals, Tien Shan, Caucasus) unsufficient iodine is present in the soil and water for the foodstuffs to contain even its minute quantity, necessary for the formation of adequate quantities of thyroid hormone. Therefore, in many persons living in these areas extremely large thyroid gland develops, called endemic goiter.

The mechanism for development of the large endemic goiters is the following. Lack of iodine prevents production of both thyroxine and triiodothyronine but does not stop the formation of thyroglobulin. As a result no hormone is available to inhibit production of TSH by the anterior pituitary which secretes its excessively large quantities. The TSH causes the thyroid cells to secrete tremendous amounts of thyroglobulin (colloid) into the follicles, and the gland grows larger and larger. It may increase to as large as 300-500 grams or more (its normal weight is 35-40 grams).

Enlarged thyroid glands frequently occurs also in persons who do not have iodine deficiency. This is called idiopathic nontoxic colloid goiter. These goitrous glands may secrete normal quantities if thyroid hormones; but more frequently secretion of hormones is depressed, as in endemic colloid goiter.

Most of these patients show signs of mild thyroiditis. Therefore, their glands usually are very nodular, with some portions of the gland growing while other portions are being destroyed by thyroiditis.

In some persons with colloid goiter, the thyroid gland has an abnormality of the enzyme system required for formation of the thyroid hormone (deficient iodide- trapping mechanism or peroxidase system, deficient coupling of iodinated tyrosines in the thyroiglobulin molecule, deficiency of the deiodinase enzyme, etc.)

Finally, some foods (especially, some varieties of turnips and cabbages) contain goitrogenic substances that have a propylthiouracil - type of antithyroid activity, thus also leading to TSH - stimulated enlargement of the thyroid gland.

Normally there are four parathtyroid glands in the human being with total mass of 100 mg. They are located immediately behind the thyroid gland - one behind each of the upper and each of the lower poles of the thyroid gland. Parathyroid glands are very small (6 x 3 x 2mm), and microscopically they are like a dark brown fat. Therefore, they are difficult to locate during thyroid operations, and total or subtotal thyroidectomy frequently resulted in also total removal of the parathyroid glands.

Removal of half the parathyroid glands causes little physiological abnormality, three of four normal glands - transient hypoparathyroidism. But usually even a small remaining part of parathyroid tissue is capable of hypertrophying satisfactorily to perform the function of all of the glands.

The parathyroid gland of the adult human being contains mainly chief cells and oxyphil cells. The chief cells secrete most of the parathyroid hormone (parathormone).

When parathyroid hormone is infused into the organism, blood calcium ion concentration begins to rise, phosphate concentration falls. Rise of the calcium concentration is caused by two

effects: 1) absorption of calcium and phosphate from the bone, 2) decrease of the excretory of calcium by kidneys. The decrease in phosphate concentration is caused by excessive renal phosphate excretion. This effect of the parathyroid hormone is great enough to override increased phosphate absorption from the bone.

So, parathyroid hormone increases tubular reabsorption of calcium and diminishes phosphate reabsorption. It also increases the rate of reabsorption of magnesium ions and hydrogen ions whereas it decreases the reabsorption of sodium, potassium, amino acid ions.

Parathyroid hormone greatly enhances both calcium and phosphate absorption from the intestines by increasing formation of 1,25-dehydroxycholecalciferol from vitamin D. So, vitamin D in smaller quantities promotes bone calcification.

A large share of the effect of parathyroid hormone on its target organs is mediated by second messenger mechanism (cAMP).

Even the slightest decrease in calcium ion concentration in the extracellular fluid causes the parathyroid glands to increase their rate of secretion within minutes. If the decreased calcium concentration persists, the glands hypertrophy (up to five-fold or more). The parathyroid glands become greatly enlarged in rickets, pregnancy, during lactation (calcium is used for milk formation).

Any condition that increases the calcium ion concentration causes decreased activity and reduces size of the parathyroid gland (excess quantities of calcium and vitamin D in the diet, bone absorption caused by factors other than parathyroid hormone).

Thanks to the activity of two hormones having opposite effetcs-parathyroid hormone and calcitonin of thyroid gland - constancy of blood calcium level (9-11 mg/dl) is maintained. This is one of the most exaclty regulated parameters of the internal environment of the organism.

When all the parathyroid glands are removed in experiment, the attacks of cramp of skeletal muscles occur, which are called the parathyroprival tetany. Gradually these attacks become stronger and more frequent, and at last cause the death of animal from the cramp of the respiratory muscles.

The parathyroprival tetany develops as a result of the decrease of blood calcium level, which leads to disturbance in the central nervous system.

In hypoparathyrosis (the incretory function deficiency of parathyroid glands) in human beings also, as a result of decrease of calcium blood content, the central nervous system excitability is sharply increased, and the attacks of cramp occur.

In children with congenital deficient functioning of parathyroid glands the blood calcium content is decreased, the growth of bones, teeth and hairs is disturbed, the long contractions of muscle group (of forearm, chest, throat) are observed.

Hyperparathyrosis (the excess function of parathyroid gland) occurs rarely (for example, as a result of the tumor of the gland). In this condition the blood content of calcium is increased, but that of inorganic phosphate is decreased. Osteoporosis (destruction of the bone tissue), pain in back, arms and legs, are observed. The muscular debility forces the patient always to lie.

Each adrenal gland is composed of two distinct parts - the adrenal medulla and the adrenal cortex. The adrenal medulla (the central 20% of the gland) consists of chromaffin cells, which secrete the hormones epinephrine and norepinephrine called catecholamines or sympathomimetic amines. The adrenal medulla is functionally related to the sympathetic nervous system and secretes its hormones in response to sympathetic stimulation. In turn the effects of these hormones are similar to those of direct stimulation of the sympathetic nerves in all parts of the body. They form together sympathoadrenal system.

The adrenal cortex secretes an entirely different group of hormones called corticosteroids. All of these hormones are synthesized from the steroid cholesterol. Very slight differences in their molecular structures give them several different and very important functions.

Adrenaline (epinephrine) exercises influence on many functions of organism including

intracelular processes of metabolism. It causes the urgent reconstruction of function and increase of capacity for work in extreme conditions.

Adrenaline accelerates and strengthens heart contractions, constricts blood vessels (except those of heart and working muscles), increases excitability of receptors, raises blood sugar, increases blood coagulability.

But adrenaline inhibits the secretory and motor functions of gastrointestinal tract, dilates the bronchial tubes and pupils.

So, adrenaline maintains by the humoral way the changes caused by the sympathetic nervous system. Therefore, it is called figuratively " the liquid sympathetic nervous system"

Effects of norepinephrine are similar to those of epinephrine, but there are some differences. For example, norepinephrine causes contractions of rat uterus smooth muscles but adrenaline relaxes it. In human being norepinephrine increases the peripheral vascular resistance, systolic and diastolic pressures more considerably, than adrenaline, which increases only the systolic pressure. Adrenaline stimulates secretion of anterior pituitary hormones, but norepinephrine does not cause such effect.

Adrenaline and norepinephrine are destroyed by the enzymes monoamine oxidase and catecholomethyltransferase.

Secretion of adrenal medulla hormones is stimulated by the sympathetic nerve fibers (celiac nerve). The nervous centers regulating the secretory function of chromaffin tissue are located in hypothalamus.

All the conditions which arte followed by excessive activity of organism and intensification of the metabolism (emotional excitation, muscular work, cooling of the organism etc.), cause increase of the adrenal medulla secretion.

Among different endocrine diseases of human being there were not noted the diseases connected with the deficient functioning of chromaffin tissue of adrenal medulla. Because the chromaffin tissue exists also in other parts of the organism (on aorta, in carotid sinus, among the cells of the sympathetic ganglions of the small pelvis, in the separate ganglions of sympathetic chain). Besides, the substances produced as hormones by the adrenal medulla (adrenaline and norepinephrine) are secreted also by the nerve endings of the sympathetic fibers as mediators.

After removal of chromaffin tissue of both adrenal glands the endurance of the animals to the influence of different extremal factors is considerably decreased. Under the painful stimulation they perish more frequently than the animals with intact adrenal glands.

The adrenal cortex hormones are divided into three groups: mineralocorticoids (aldosterone, deoxycorticosterone, corticosterone, 9α-fluorocortisol, cortisol or hydrocortisone, cortisone), glucocorticoids (cortisol, corticosterone, cortisone, prednisone, methylprednisone, dexamethasone) and sex hormones (androgens, estrogens, progesterone).

The adrenal cortex is composed of three relatively distinct layers. The thin layer of cells on the surface - zona glomerulosa-secretes mineralocorticoids. Cortisol and several other glucocorticoids are secreted by both zona fasciculata (the middle layer) and zona reticularis (the deep layer), with more secretion of these hormones by zona fasciculata than by zona reticularis. The adrenal sex hormones are also secreted by both these layers, but mainly by zona reticularis.

All the adrenocortical hormones are ateroid compounds. Over 30 different steroids have been isolated from the adrenal cortex; two of them-aldosterone and cortisol (hydrocortisone) are of exceptional importance to the normal endocrine function of the human body.

The adrenal steroids are degraded mainly in the liver and conjugated especially to form glucuronides and to a lesser extent, sulfates. The conjugated forms of these hormones are inactive. The large amounts of these are excreted in the urine, the rest - in the bile and feces.

The mineralocorticoids effect especially electrolytes of the extracellular fluids - sodium and potassium in particular. The most active of mineralocorticoids is aldosterone. It activates the synthesis of enzymes increasing the efficiency of sodium-potassium pump in the epithelial cells

of tubules of the kidney. This causes increased absorption of sodium and chlorine and stimultaneous excretion of potassium by the tubular epithelial cells of kidney. So, aldosterone causes sodium to be conserved in the extracellular fluid while more potassium is excreted into the urine.

Aldosterone has almost the same effects on the stomach, intestines, salivary glands and sweat glands. Therefore, it can prevent loss of sodium during the considerable sweating as a result of overheating of the body.

When sodium is reabsorbed by the tubules, there is simultaneous osmotic absorption of almost equivalent amounts of water. A persistent increase in extracellular fluid volume leads to an increase in arterial pressure. This leads then to greatly increased kidney excretion of both water and salt, which is called pressure diuresis. This secondary increase in water and salt excretion by the kidneys is called aldosterone escape because the net gain of salt and water by the body thereafter is zero.

Conversely, when aldosterone secretion becomes zero, very large amounts of salt are lost in the urine, diminishing the amount of sodium chloride in the extracellular fluid and decreasing the extracellular fluid and blood volumes. Diminishing cardiac output leads to circulatory shock. This causes death within a few days after the adrenal glands suddenly stop secreting aldosterone.

This can be prevented by administration of mineralocorticoids, which are therefore said to be the acute "life-saving" portion of the adrenocortical hormones.

Excessive loss of potassium ions in the urine under the influence of aldosterone causes hypokalemia which leads to the severe muscle weakness (as a result of alteration of the electrical properties of the nerve and muscle fiber membranes, which prevents transmission of action potentials).

However, when aldosterone is deficient, the hyperkalemia develops, and this causes serious cardiac toxicity, including weakness of heart contractions and arrhythmia. A still higher concentration of potassium leads to cardiac death.

The following factors play essential roles in the regulation of aldosterone: potassium ion concentration of the extracellular fluid, renin-angiotensin system, sodium ion concentration in the extracellular fluid,adrenocorticotropic hormone (ACTH).

Even though mineralocorticods can save the life of an acutely adrenalectomized animal, its vital functions are far from normal: the animal's metabolic systems for utilization of proteins, carbohydrates, fats are considerably deranged; it cannot resist different types of physical or mental stress, and minor illnesses such as respiratory tract infections can lead to death.

So, the glucocorticoids have functions just as important to the long continued life of the animal as those of the mineralocorticoids. They are equally necessary allowing the organism to resist the destructive effects of different stresses.

The glucocorticoids exhibit an imoprtant effect in increasing blood glucose concentration. They also effect both protein and fat metabolism markedly.

At least 95% of the glucocorticoid activity of the adrenocortical secretions results from the secretion of cortisol (hydrocortisone), its small but significant amount is provided by corticosterone.

Cortisol and other glucocorticoids stimulate gluconeogenesis (formation of carbohydrate from proteins and some other substances). Cortisol also causes a moderate decrease in the rate of glucose utilization by the cells everywhere in the body. Both effects cause the blood glucose concentration to rise. Occasionally increase in concentration is great enough that the condition is called adrenal diabetes, and it has many similarities to pituitary diabetes.

Administration of insulin lowers the blood glucose concentration only a moderate amount in adrenal diabetes, not nearly so mush as it does in the pancreatic diabetes, but this decrease is greater than in pituitary diabetes. So, pituitary diabetes is weakly insulin sensitive, adrenal diabetes is moderately insulin sensitive and pancreatic diabetes is strongly insulin sensitive.

Cortisol causes reduction of the protein stores (decreased protein synthesis and increased catabolism of protein in the cells) in essentially all body cells except those of the liver. The liver proteins become enhanced, and the plasma proteins, which are produced by the liver, are also increased. This difference results from an effect of cortisol in enhancing amino acid transport into liver cells (but not into most other cells) and of enhancement of the liver enzymes required for protein synthesis.

In much the same manner that cortisol promotes amino acid mobilization from muscle, it also promotes mobilization of fatty acids from adipose tissue. This increases concentration of free fatty acids in the plasma, which also increases utilization for energy. Cortisol moderately enhances oxidation of fatty acids in the cells as well. These effects of cortisol help shift the metabolic systems of the cells in times of starvation or other stresses from utilization of glucose for energy to utilization of fatty acids. This is an important factor for long-term conservation of body glucose and glycogen.

Cortisol has a ketogenic effect-ketosis does not develop without fat mobilization caused by cortisol. But this effect occurs only under certain conditions (insulin deficiency).

Persons with excess cortisol secretion frequently develop a pecuilar type of obesity, with excess deposition of fat in the chest and head regions of the body, giving a buffalo-like torso and a rounded face, a "moon face". This obesity results from excess stimulation of food intake so that fat is generated in some tissues of the body at a rate even rapidly than it is mobilized and oxidized.

Almost any type of stress whether physical or neurogenic (trauma, infection, intense heat or cold, injection of catecholamines, restraining an animal so that it cannot move, debilitating disease etc.), will cause an immediate and marked increase in ACTH secretion by the anterior pituitary gland, followed within minutes by greatly increased adrenocortical secretion of cortisol. So, a wide variety of nonspecific stimuli can cause marked increase in the rate of cortisol secretion by the adrenal cortex.

When tissues are damaged, they almost always become inflamed. Administration of large amounts of cortisol can block this inflammation or even reverse many its effect once it has begun. It blocks also the inflammatory response to allergic reactions.

Almost no stimuli have direct effects on the adrenal cells to control cortisol secretion. It is controlled almost entirely by ACTH, which also enhances production of adrenal androgens. Its small amounts are also required for aldosterone secretion, providing a permissive role that allows the other, more important factors to exert their more powerful controls.

Almost any type of physical or mental stress can lead within minutes to greatly enhanced secretion of ACTH and consequently that of cortisol as well, often increasing cortisol secretion as much as 20-fold.

Cortisol has direct negative feedback effect on the hypothalamus to decrease formation of corticotropin-releasing factor (CRF) and the anterior pituitary gland to decrease formaion of ACTH. These feedbacks help regulate the plasma concentration of cortisol.

Secretory rates of CRH, ACTH and cortisol are high in the early morning and low in the late evening. When a person changes daily sleeping habits, this circadian rhythm changes correspondingly.

Failure of adrenal cortices to produce adrenocortical hormones results in Addison's disease. Basically, the disturbances in Addison's disease are the following.

Lack of aldosterone secretion decreases sodium reabsorption, and consequently sodium ions, chloride ions and water are lost in urine in great profusion. As a result, the extracellular fluid volume greatly decreases Hyperkalemia and mild acidosis develop. The plasma volume falls, the erythrocyes concentration rises markedly, the cardiac output decreases and the patient dies in shock during 4 days to 2 weeks after complete cessation of mineralocorticoid secretion.

Loss of cortisol secretion makes it impossible to maintain normal blood glucose concent-

ration between meals, reduces mobilization of proteins and fats from tissues. Lack of adequate glucocorticoids secretion makes the person with Addison's disease highly susceptible to deteriorating efects of different types of stress, and even a mild respiratory infection can cause death.

Characteristic of most persons with Addison's disease is melanin pigmentation of the mucous membranes and skin (hence the other name of the disease - the bronze disease). Because when cortisol secretion is depressed the normal negative feedback to the hypothalamus and anterior pituitary gland is also depressed, therefore allowing tremendous rates of ACTH secretion as well as simultaneous secretion of increased amounts of melanocyte-stimulating hormone (MSH).

An untreated person with total adrenal destruction dies within a few days to a few weeks because of consuming weakness and eventual circulatory shock.

Hypersecretion of cortisol by the adrenal cortex causes a complex of effects called Cushing's disease (syndrome). A special characteristic of Cushing's disease is mobilization of fat from the lower part of the body, with concomitant extra deposition of fat in the thoracic and upper abdominal regions, giving rise to "buffalo" torso.

Excess secretion of steroids also leads to an edematous appearance of the face, and the androgenic potency of some of the hormones sometimes causes acne and hirsutism (excess growth of facial hair). The total appearance of face is frequently described as a "moon face". About 80% of the patients have hypertension because of the slight mineralocorticoid effects of cortisol.

Abundance of cortisol secreted in Cushing's syndrome can cause increased blood glucose concentration (up to 200 mg/dl). If this "adrenal diabetes" lasts for many months, the beta cells in the islets of Langerhans in the pancreas occasionally "burn out" because the high blood glucose greatly overstimulates them to secrete insulin. The destruction of these cells causes evident pancreatic diabetes mellitus.

Cushing's syndrome causes greatly decreased tissue proteins almost everywhere in the body with the exceptions of the liver and the plasma proteins. Loss of protein from the muscles causes severe weakness. Loss of protein synthesis in the lymphoid tissue leads to a suppressed immune systeme, so that many of these patients die of infections. Even the collagen fibers in the subcutaneous tissue are diminished so that the subcutaneous tissues tear easily, resulting in development of large purplish striae. Lack of protein deposition in the bones causes very severe osteoporosis with consequent weakness of bones.

Occasionally a small tumor of the zona glomerulosa cells occurs and secretes large amounts of aldesterone. The most important effects of such primary aldosteronism are hypoklemia, slight increase in extracellular fluid volume and blood volume, very slight increase in plasma sodium concentration and hypertension. Hypokalemia causes muscular paralysis. One of the diagnistic criteria of primary aldosteronism is decreased plasma renin concentration as a result of feed-back suppression of renin secretion.

The sex hormones of adrenal cortex are important for the development of genital organs in childhood. In old age the adrenal cortex once again becomes the only source of secretion of androgens and estrogens.

An occasional adrenocortical tumor (hypernephroma) secretes excessive quantities of androgens that cause intense masculinizing effects throughout the body. If this occurs in a female, she develops virile characteristics, including growth of a beard, a much deeper voice, occasionally baldness, masculine distribution of hair on the body (especially on the pubis) growth of the clitoris to resemble a penis and deposition of proteins in the skin and muscles to give typical masculine characteristics.

In the prepubertal male a virilizing adrenal tumor causes the same charactheristics as in the female, plus rapid development of the male sexual organs and creation of male sexual desires. For example, typical development of the male sexual organs was observed in a 4 year old boy

with the adrenogenital syndrome.

So, certain community in the functions of the adrenal medulla and adrenal cortex may be noted: their hormones provide the strengthening of the protective reactions of the organism in emergency situations against the factors, threatening its normal state.

In extreme situations the adrenal medulla, secreting adrenaline, promotes intensification of active behavioural reactions of the organism. The adrenal cortex, whose activity is stimulated by the same adrenaline through hypothalamus, secretes hormones strengthening the internal factors of resistibility of the organism.

Laboratory Studies

Effect of Adrenaline and Acetylcholine on Frog Eye Pupil

The equipment: frog, 2 beakers, 2 watch glasses, 2 eye pipettes measuring glass (10-20 ml), small cork plank, pins, eye scissors, pincers, 1:20000 adrenaline solution, 1:100000 acetylcholine solution, 0.6% NaCl solution, cotton wool.

The upper jaw of the frog is cut out and fixed on the cork plank by the pins. Both eyes are cut out and put into the physiological salt solution on the watch glass. A drop of adrenaline solution is poured on one eye and a drop of acetylcholine solution - on the other eye. Then the eyes are washed by the physiological solution and this time a drop of adrenaline solution is poured on thr second eye and a drop of acetylcholine solution - on the first eye.

Under the influence of adrenaline the eye pupils dilate and under the influence of acetylcholine they are narrowed.

Lecture 27

Pancreas. Sexual Glands. Pineal Gland (epiphysis). Thymus Gland

Pancreas is the mixed gland. It is composed of two major types of tissues: 1) the acini - secrete digestive juices into the duodenum, that is, fulfil the exocrine function; 2) the epidermocytes in the islets of Langerhans - secrete hormones into the blood, that is, fulfil the endocrine function.

The islets contain three major types of cells: alpha, beta and delta cells. The beta cells (about 60% of all the cells) lie mainly in the middle of each islet and secrete insulin. The alpha cells secrete glucagon and the delta cells - somatostatin. The PP cells are present in small numbers in the islets which secrete pancreatic polypeptide (a hormone of uncertain function).

Among these different cell types the close interrelationships exist, which allow direct control of secretion of some of the hormones by others. For example, insulin inhibits glucagon secretion and somatostatin inhibits secretion of both insulin and glucagon.

Insulin was first isolated from the pancreas in 1922 by Banting and Best. This discovery changed the outlook for the severely diabetic patient from one of rapid decline and death to that of a nearly normal person.

Although insulin usually is associated with blood sugar, it affects fat and protein metabolism almost as much as it does carbohydrate metabolism.

Insulin plays an important role in storing the excess energy substances. When there is great abundance of energy-giving foods (especially carbohydrates, but also proteins and fats) in the diet, insulin is secreted in great quantity. It causes excess acrbohydrates to be stored as glycogen mainly in the liver and muscles, and fats - in the adipose tissue. Insulin has a direct effect in promoting aminoacid uptake by cells and conversing these into protein. Besides, it inhibits the breakdown of proteins in cells.

When insulin is secreted into the blood, it circulates almost entirely in an unbound form. Part of the insulin combines with receptors in target cells and the remainder is degraded by the enzyme insulinase in the liver and kidneys (to a lesser extent). Insulin has a plasma half-life averaging only about 6 minutes, so that it is mainly cleared from the circulation within 10-15 minutes.

One of the most important of all the effects of insulin is to cause most of the glucose absorbed after a meal to be immediately stored in the liver in the form of glycogen. Between meals, when the blood glucose consentration begins to fal, the liver glycogen is split back into glucose, which is released back into the blood to keep the blood glycose concentration from falling too low.

When the quantity of glucose entering the liver cells is more than can be stored as glycogen, insulin promotes the conversion of all of this excess glucose into fatty acids. These are packaged as triglycerides in very low density lipoproteins and transported to the adipose tissue and deposited as fat.

Insulin also inhibits gluconeogenesis - mainly by decreasing the quantities and activities of the liver enzymes required for gluconeogenesis but also by decreasing release of amino acids from muscle and other extrahepatic tissues.

When the muscles are not exercising during the period after a meal and yet glucose is transported into the muscle cells in abundance, then most of the glucose is stored in the form of

muscle glycogen.

The brain cells are quite different from most other cells of body in that they normally use only glucose for energy and are permeable to glucose without the intermediation of insulin. Therefore, it is important that the blood glucose content be maintained always above a critical level which is achieved by the blood glucose control system. When the blood glucose falls too low (down to 50-20 mg/dl), symptoms of hypoglycemic shock develop. This is characterized by progressive nervous irritability that leads to fainting, convulsions and coma.

Insulin lack causes excessive amounts of acetoacetic acid to be formed in the liver cells, this leads to formation of ketone bodies, presence of which in large quantities in the body fluids is called ketosis. In severe diabetes this can cause severe acidosis and coma, which often leads to death.

During few hours after meal when excess amounts of nutrients are available in the circulating blood, insulin causes protein storage as well as that of carbohydrates and fats. Insulin causes active transport of many of amino acids into cells, inhibits catabolism of proteins, depresses rate of gluconeogenesis in the liver.

When insulin is not available, the catabolism of proteins increases, protein synthesis stops, large amounts of amino acids are dumped into the plasma. Most of the excess amino acids are either used directly for energy or as substrates for gluconeogenesis. This degradation of amino acids also leads to enhanced urea excretion in the urine. Resulting protein wasting is one of the most serious of all of the effects of severe diabetes mellitus. This leads to extreme weakness and many deranged functions of organs.

Because insulin is required for the synthesis of proteins, it is equally as essential for growth of an animal as is growth hormone. The two hormones function synergistically to promote growth, each performing its own specific function.

Insulin secretion is controlled by the blood glucose concentration. But blood amino acids and other factors also play important roles in controlling insulin secretion.

Feedback relationship exists between blood glucose concentration and insulin secretion rate: any rise in blood glucose level increases insulin secretion, and the insulin in turn causes transport of glucose into liver, muscles and other cells, thereby reducing the blood glucose concentration back toward the normal value. Many of the amino acids have a similar effect, but in lesser degree, they potentiate the glucose stimulus for insulin secretion very strongly.

Any condition causing raise of blood glucose level (physical work, digestion, emotions and so forth) leads to increase of insulin production.

Several gastrointestinal hormones (gastrin, secretin, cholecystokinin, gastric inhibitory peptide) cause a moderate increase in insulin secretion.

Some other hormones (glucagon, growth hormone, cortisol, to a lesser extent - progesterone and estrogen) either directly increase insulin secretion or potentiate the glucose stimulus for insulin secretion. Prolonged secretion of any of these hormones in large amounts can occasionally lead to exhaustion of beta cells of the islets of Langerhans and cause diabetes mellitus. For instance, diabetes is particularly common in giants or acromegalic persons with growth hormone secreting tumors or in persons whose adrenal glands (or adrenal gland tumors) secrete excess glucocorticoids.

Blood concentration of insulin depends also on destruction rate of insulin by the enzyme insulinase. Insulin may be also inactivated by its antagonists, especially by synalbumin.

Glucagon has miltiple functions that are diametrically opposed to those of insulin. It is secreted by alpha cells of the islets of Langerhans when the blood glucose concentration falls, and increases it. On injection of purified glucagon into an animal, a profound hyperglycemic effect occurs. Therefore, it is also called the hyperglycemic hormone.

Two major effects of glucagon on glucose metabolism greatly enhance the availability of glucose to other organs of the body: breakdown of liver glucogen (glucogenolysis) and increased

gluconeogenesis in the liver.

Glucagon also activates adipose cell lipase, making increased quantities of fatty acids available to the energy systems of the body.

In very large concentrations glucagon enhances the strength of the heart, bile secretion and inhibits gastric acid secretion. But these effects are unimportant in the normal function of the body.

The most potent factor controlling glucagon secretion is the blood glucose concentration: decrease in the blood glucose concentration down to hypoglycemic levels increases the plasma concentration of glucagon and increasing of the glucose to hyperglycemic levels decreases plasma glucagon.

High blood concentrations of amino acids (usually after protein meal) stimulate secretion of glucagon. In this instant the glucagon and insulin responses are not opposites, because this is the same effect that amino acids have in stimulating insulin secretion. The glucagon then promotes rapid conversion of the amino acids to glucose, thus making even more glucose available to tissues.

In exhaustive exercise the blood concentration of glucagon increases (it prevents a decrease in blood glucose). One of the factors stimulating this process is increased circulating amino acids, but other factors (nervous stimulation of the islets of Langerhans) could also play a role.

Almost all factors related to the ingestion of food stimulate somatostatin secretion by delta cells of the islets of Landerhans. Somatostatin has multiple inhibitory effects. It depresses secretion of both insulin and glucagon, decreases secretion and absorption in the gastrointestinal tract as well as motility of the stomach, duodenum and gallbladder.

The principal role of somatostatin is to extend the period of time over which the food nutrients are assimilated into the blood. Its effect to depress insulin and glucagon secretion decreases utilization of absorbed nutrients by tissues, thus preventing rapid exhaustion of the food and making it available over a longer period of time.

Somatostatin is the same chemical substance as growth hormone inhibiting hormone, secreted in the hypothalamus.

Some other hormones, such as lipocaine, vagotonin and centropneuine, are also produced in pancreas.

Lipocaine stimulates formation of phosphatides (lecithin) and oxidation of fatty acids in the liver, that is, it promotes utilization of fats. Lipocaine prevents the adipose degeneration of the liver after removal of the pancreas.

Vagotonin increases the tonus of vagus nerves nuclei and raises activity of parasympathetic nervous system. Besides, it stimulates the hemopoiesis, especially formation of erythrocytes.

Centropneuine excites the respiratory center and dilates bronchi. Besides, it increases ability of hemoglobin to bind the oxygen and thus, improves transport of oxygen, also increases stability of the organism against the oxygen deficiency.

Diminished secretion of insulin by beta cells of the islets of Langerhans results in diabetes mellitus.

Decreased utilization of glucose by the body cells results in hyperglycemia (the blood glucose concentration increases up to 300-1200 mg / dl).

Whenever the blood glucose concentration rises above the threshold level (180 mg/dl), glucosuria occurs, that is, significant proportion of the excess glucose cannot be reabsorbed and spills into the urine. When the blood glucose level rises to 300-500 mg/dl (in untreated severe diabetes), 100 g or more of glucose is lost into urine each day.

Significant effect of the elevated blood glucose is dehydration of cells. Because glucose does not diffuse easily through the pores of the cell membrane, and the increased osmotic pressure in the extracellular fluids causes osmotic transfer of water out of the cells

One of the important features of diabetes is a tendency for both extracellular and intracellular dehydration, and these can contribute to development of circulatory shock.

As a result of the shift from carbohydrate to fat metabolism in diabetes, content of keto acids, acetoacetic acid and β-hydroxybutyric acid in the body fluids may rise from 1 to 10 mEq/liter. All of this extra acid result in acidosis. A second, even more important effect in causing acidosis is decrease in sodium concentration. Because keto acids are excreted combined with sodium derived from the extracellular fluid. Part of the sodium is replaced by hydrogen ions, thus adding greatly to the acidosis.

All the usual reactions that occur in metabolic acidosis ("Kussmaul respiration", marked decrease in bicarbonate content of the extracellular fluids) take place in severe diabetic acidosis and can lead to acidotic coma and death within hours when the pH of the blood falls below 7.

The earliest symptoms of diabetes are: polyuria (excessive elimination of urine), polydipsia (thirst and excessive drinking of water), polyphagia (excessive eating), asthenia (lack of energy), loss of weight.

The polyuria is due to the osmotic diuretic effect of glucose in the kidney tubules, the polydipsia - that of to dehydration resulting from polyuria. Loss of weight and tendency toward polyphagia are caused by the failure of glucose and protein utilization by the body; the asthenia results mainly from loss of body protein.

Small amounts of acetoacetic acid, which increases greatly in severe diabetes, can be converted to acetone. This is volatile and is voparized into the expired air. Therefore, frequently it is possible to make a diagnosis of diabetes mellitus simply by smelling acetone on the breath of a patient. Besides, keto acids can be detected by chemical means in the urine, and their quantition aids in determining the severity of the diabetes.

Hyperinsulinism (increased insulin production) occurs much rarer than diabetes. This results mainly from an islet of Langerhans adenoma. 10-15% of these adenomas are malignant and occasionally metastases from the islets of Langerhans, spread throughout the body, causing tremendous production of insulin by both the primary and the metastatic cancers. More than 100 grams of glucose have had to be administered every 24 hours to prevent hypoglycemia in such patients.

In patients with hyperinsulinism or in diabetic patients whom too much insulin was administered, the insulin shock syndrome may occur. As the blood sugar level falls into the range of 70-50 mg/dl, the central nervous system becomes quite excitable (this degree of hypoglycemia facilitates neuronal activity). The patient experiences extreme nervousness, trembles all over and breaks out in sweat. Sometimes various forms of hallucinations result. Fall of blood glucose to 50-20 mg/dl causes clonic convulsions and loss of consciousness. As the glucose level falls still lower, the convulsions cease and only a state of coma remains.

At times it is difficult to distinguish between diabetic coma as a result of insulin lack and coma due to hypoglycemia caused by excess insulin. But the acetone breath and the Kussmaul type breathing of diabetic coma are not present in hypoglycemic coma.

Proper treatment for a patient who has hypoglycemic shock or coma is immediate intravenous administration of large amounts of glucose. This brings the patient out of shock within a minute. Administration of glucagon (or, less effectively, epinephrine) can cause glycogenolysis in the liver and thereby increase the blood glucose level extremely rapidly.

Sexual glands are the place where the sex cells (spermatozoon and ovum) are formed. Besides, they perform the endocrine function and secrete the sex hormones into the blood.

The male sex hormones (androgens) as well as the female sex hormones (estrogens) are formed both in male and female sexual glands, but in different amounts.

The physiological role of sex hormones is to provide ability to perform the sexual functions. These hormones are necessary for the puberty, i.e., for maturation of the organism and its sexual apparatus to make the sexual act and child-bearing possible.

Owing to sex hormones the secondary sexual characteristics are developed. These are the peculiarities of the puberal organism, which are not connected immediately with the sexual activity, but are distinguishing features of the male and female organisms.

In female organism the sex hormones play a great role in the origin of the sex cycles, ensuring the normal course of the pregnancy and preparation to the feeding of new-born child.

Removal of sexual glands is called castration. Not only animals are castrated (or gelt), but castration is performed also in human beings because of some diseases or with religius end in view (eunuchs-guardians of harems or singers in church chorus of Roman Pope).

After castration the formation of the sexual hormones is not ceased completely, but the small amounts of androgens and estrogens continue to enter from adrenal cortex.

If the castration is performed long before the puberty, the sexual maturity stops; penis, prostate, vagina, uterus do not reach the maturity and even retrogress. The secondary sexual characterisitcs do not develop. But when the castration is performed after the puberty, the sexual apparatus is retrogressed in lesser degree and the secondary sexual characteristics are partly preserved. The secondary sexual characteristics which are preserved after the castration of the puberal organism, are called independent sexual characteristics, and those that are lost-are dependent sexual characteristics.

In normal male or female organism both sex hormones are produced. When function of testes or ovaries is disturbed, correlation between these hormones changes. This is called intersexuality. The intersexuality in men manifests itself by existence of some physical and mental features of the woman, and in women - by appearance of some features of the man.

The condition when on one side of the body there is testicle and on other side - ovary, is called true hermaphroditism.

Testicles secrete several male sex hormones, which are collectively called androgens, including testosterone, dihydrotestosterone and androstenedione. Testosterone is much more abundant than the others, but much of it is converted into more active hormone dihydrotestosterone in target tissues.

Testosterone is formed by interstitial cells of Leydig, which lie in interstices between seminiferous tubules and constitute about 20% of the mass of adult testicles. Tumors develop from the interstitial cells of Leydig and secrete great quantities of testosterone.

Ovaries also produce insignificant amounts of androgens. But rarely embryonic rest cells in the ovary can develop into a tumor (arrhenoblastoma) producing excessive amounts of androgens in women.

In general, testosterone is responsible for the distinguishing characteristics of the masculine body. Even during fetal life testes are stimulated by chorionic gonadotropin from placenta to produce moderate quantities of testosterone throughout the entire period of fetal development and for up to 10 or more weeks after birth. Then no testosterone is produced during childhood until approximately the age of 10-13 years. At the onset of puberty testosterone production increases rapidly under the stimulus of anterior pituitary gonadotropic hormones and lasts throughout most of the remainder of life, decreasing rapidly beyond the age of 50 to become 20-50% of the peak value by the age of 80.

Testosterone, secreted during fetal life, is responsible for development of the male body characteristics (formation of penis, scrotum, prostate gland, seminal vesicles, the male genital ducts), while at the same time suppressing formation of female genital organs.

Reinitiation of testosterone secretion after puberty causes development of adult primary and secondary sexual characteristics. Primary sexual characteristics include enlargement of penis, scrotum and testes all about eightfold before age of 20 years.

At the same time, beginning at puberty and ending at maturity, testosterone causes the secondary sexual characteristics of the male to develop:

1. Growth of hair over the pubis upward along the linea alba (sometimes to the umbilicus

and above), on the face, usually on the chest and less often on other regions of the body (the back). The hair on most other portions of the body becomes more prolific, but growth of hair on the top of the head decreases. A woman who has the appropriate genetic background and develops a long sustained androgenic tumor, becomes bald in the same manner as does a man.

2. Hypertrophy of the laryngeal mucosa and enlargement of the larynx. The effects cause at first a relatively discordant, "cracking" voice, but this gradually changes into the typical adult masculine bass voice.

3. Increase of the thickness of the skin over the entire body and of the ruggedness of the subcutaneous tissues; excessive secretion by the sebaceous glands (especially of the face) oversecretion of which can result in acne.

4. Increasing musculature following puberty (about 50 % increase in muscle mass over that in the female). This is associated with increased protein in other parts of the body as well.

5. Increase of the total quantity of bone matrix and calcium retention (the bones grow considerably in thickness and also deposit considerable additional calcium salt).

6. Specific effect on the pelvis to narrow the pelvic outlet, lengthen it, cause a funnellike shape instead of the broad ovoid shape of the female pelvis, greatly increase strength of the entire pelvis for load-bearing.

Large amounts of androgens (especially testosterone), secreted in the still - growing child, increase markedly the rate of the bone growth, causing a spurt in total body height as well. But they also cause the epiphyses of the long bones to unite with the shafts of the bones at an early age. Therefore, despite the rapidity of growth, this early uniting of the epiphyses prevents the person from growing as tall as he would have grown had testosterone not been secreted at all.

Considering the ability of testosterone to increase the size and strenght of bones, it is often used to treat osteoporosis.

The usual quantity of testosterone secreted by the testes during adolescence and early adult life, increases the rate of metabolism 5-10% above the value that it would be if the testicles were not active.

Injection of normal amounts of testosterone into a castrated adult causes increase of the number of erythrocytes 15-20%. The average man has approximately 700 000 more erythrocytes per cubic millimeter than the average woman. This difference is due partly to the increased metabolic rate following testosterone administration rather than to a direct effect of testosterone on the production of erythrocytes.

As many different steroid hormones, testosterone also can increase reabsorption of sodium in the distal tubules of the kidneys (to minor degree than mineralocorticoids). After puberty the blood and extracellular fluid volumes of the male in relation to his weight increase to some extent.

Almost all the effects of testosterone result from increased rate of protein formation in the target cells (especially the proteins which are responsible for development of the secondary sexual characteristics).

Control of sexual functions in both the male and female begins with secretion of gonadotropin - releasing hormone (GnRH) by the hypothalamus. GnRH in turn stimulates the anterior pituitary gland to secrete two gonadotropic hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In turn, LH is primary stimulus for secretion of testosterone by the testes and FSH stimulates spermatogenesis.

The testosterone secretion is controlled by negative feedback principle. The testosterone secreted by testes in response to LH has the effect of reciprocal inhibition of anterior pituitary secretion of LH anf FSH (by the way of direct effect mainly on the hypothalamus and weakly - on the anterior pituitary gland).

Sertoli cells in the seminiferous tubules secrete the hormone inhibin which has a strong direct effect on the anterior pituitary gland in inhibiting the secretion of FSH and a slight effect

on the hypothalamus in inhibiting secretion of GnRH.

During pregnancy the placenta secretes human chorionic gonadotropin (hCG)), which has almost the same effects on the sexual organs as LH.

Different psychic factors affect the rate of secretion of Gn RH by the hypothalamus and affect many aspects of sexual and reproductive functions in both the male and the female.

When a boy loses his testes prior to puberty, a state of eunuchism ensues in which he continues to have infantile sexual characteristics throughout life. The height of the adult eunuch is slightly greater, though the bones are quite thin, the muscles are considerably weaker than those of the normal man. The sexual organs and secondary sexual characteristics remain those of a child, the voice is childlike. The masculine hair distribution on the face and elsewhere does not occur.

When a man is castrated after puberty, some male secondary sexual characteristics revert to those of a child and others remain of masculine character. The sexual organs regress slightly in size and the voice regresses from the bass quality only slightly. But there is loss of masculine hair production, thick masculine bones, musculature of the virile male.

Some instances of hypogonadism are caused by the genetic inability of the hypothalamus to secrete normal amounts of GnRH. Often this is associated with a simultanous abnormality of the feeding center of the hypothalamus, causing the person to greatly overeat, and severe obesity occurs along with eunuchism. This is called hypothalamic eunuchism or adiposogenital (Frohlich's) syndrome.

Rarely interstitial Leydig cell tumors develop in the testes which sometimes produce as much as 100 times the normal quantities of testosterone. In young children such tumors cause rapid growth of the musculature and bones, but also early uniting of the epiphyses, so that adult height is less than that which would have been achieved otherwise. Excessive development of the sexual organs, muscles and other secondary sexual characteristics occurs.

Much more common are tumors of the germinal epithelium. Because germinal cells are capable of differentiating into almost any type of cell, many of these tumors contain multiple tissues (placental tissue, hair, teeth, bone, skin) all found together in the same tumorous mass called teratoma. Often these tumors secrete no hormones, but if a large amount of placental tissue develops in the tumor, it may secrete significant quantities of chorionic gonadotropin. Also, estrogenic hormones are frequently secreted by these tumors and cause growth of breasts (gynecomastia).

The female hormonal system also consists of three herarchies of hormones:

1) a hypothalamic hormone: gonadotropin-releasing hormone (GnRH) or luteinizing hormone - releasing hormone (LHRH);

2) the anterior pituitary hormones: follicle- stimualting hormone (FSH) and luteinizing hormone (LH), both of which are secreted in response to the releasing hormone of the hypothalamus;

3) the ovarian hormones: estrogen and progesterone, which are secreted in response to the two hormones of the anterior pituitary gland.

Placenta secretes estrogen, progesterone and chorionic gonadotropin. Effect of chorionic gonadotropin is close to that of pituitary gland luteinizing hormone. So, the hormones of placenta can replace the corresponding hormones of pituitary body and ovaries if they are removed during the second half of the pregnancy.

Above-mentioned hormones are secreted not in constant amounts, but at drastically differing rates during different parts of the female monthly sexual cycle (the menstrual cycle), causing in turn the cyclic ovarian changes.

During the fetal life the ovaries function because of stimulation by chorionic gonadotropin. But within a few weeks after birth this stimulus is lost, and the ovaries become almost totally dormant until the prepubertal period.

At the age of 9-10 years the anterior pituitary gland begins to secrete progressively more FSH and LH. This culminates in the initiation of monthly sexual cycles between the ages of 11 and 16 years. This period of change is called puberty, and the first menstrual cycle is called menarche.

Development of the primary follicle is not possibe without FSH and LH. LH is necessary for final follicular growth and ovulation. Ovulation in a woman who has a normal 28 day female sexual cycle, occurs 14 days after the onset of menstruation.

Following ovulation, the secretory cells of the follicle develop into corpus luteum. After another 2 weeks the corpus luteum degenerates, whereupon the ovarian hormones decrease greatly and menstruation begins. A new ovarian cycle then follows.

The change of granulosa cells into lutein cells is mainly dependent on the LH; in fact, this function gave LH its name "luteinizing".

The corpus luteum is highly secretory organ, secreting large amounts of progesterone and estrogen. These hormones have the strong feedback effect on the anterior pituitary gland of decreasing the secretion of both FSH and LH. The luteal cells also secrete small amounts of inhibin, which inhibits, especially FSH secretion by the anterior pituitary gland.

The two types of ovarian sex hormones are the estrogens and the progestins. All these are steroids.

Three estrogens are present in significant amounts in the plasma of the human female: beta-estradiol, estrone and estriol. The most important of them is beta-estradiol. Its potency is 12 times that of estrone and 80 times that of estriol.

The estrogens mainly promote proliferation and growth of pecific cells in the body and are responsible for development of most secondary sexual characteristics of the female.

The most important of the progestins is progesterone, though small amounts of another progestin, 17-α-hydroxyprogesterone, also are secreted along with progesterone and have essentially the same effects.

The progestins are concerned almost entirely with final preparation of the uterus for pregnancy and the breasts for lactation. Therefore, in the normal nonpregnant female progesterone is secreted in significant amounts only during the latter half of each ovarian cycle, when it is secreted by the corpus luteum. Only minute amounts of progesterone appear in the plasma during the first half of the ovarian cycle, secreted approximately equally by the ovaries and the adrenal cortices. Very large amounts of progesterone are also secreted by the placenta during pregnancy.

The liver conjugates the estrogens to form glucuronides and sulfates, about one fifth of which is excreted in the bile and most of the remainder - in the urine. Also, the liver converts the potent estrogens estradiol and estrone into the almost totally impotent estrogen estriol. Therefore, diminished liver function actually increases the activity of estrogens in the body, sometimes causing hyperestrinism. The liver is especially important also for the metabolic degradation of the progesterone, which is degraded to other steroids that have no progesteronic effect.

At puberty, when the quantity of estrogens secreted under the influence of the pituitary gonadotropic hormones increases some 20-fold or more, the female sex organs change from those of a child to those of an adult. The ovaries, fallopian tubes, uterus and vagina all increase several times in size. The external genitalia enlarge, with deposition of fat in the mons pubis and labia majora and with enlargement of the labia minora.

Estrogens change the vaginal epithelium from a cuboidal into a stratified type, which is considerably more resistant to trauma and infection.

During the few years following puberty, the size of the uterus increases two-to threefold. More important are the changes in the endometrium under the influence of estrogens. They cause marked proliferation of the endometrial stroma of the greatly increased endometrial glands that are later used to aid in nutrition of the implanting ovum.

The estrogens have an effect on the mucosal lining of the fallopian tubes similar to that on the uterine endometrium. Especially important, they cause the number of ciliated epithelial cells that line the fallopian tubes to increase. Activity of the cilia is considerably enhanced, these always beating toward the uterus (to propel the fertilized ovum toward the uterus).

The estrogens initiate growth of the breasts and the breast's milk-producing apparatus. They are also responsible for the characteristic external appearance of the mature female breast, but they do not complete the job of converting the breasts into milk-producing organs.

Estrogens cause increased osteoblastic activity. Therefore, at puberty, when the female enters her reproductive years, her growth rate becomes rapid for several years. But the effect of estrogens to cause early uniting of the epiphyses with the shafts of the long bones is much stronger than that of testosterone. Therefore, growth of the female usually ceases sevearl years earlier than that of male, and the female eunuch grows somewhat taller than the normal mature female.

After the menopause the estrogen deficiency leads to diminished osteoblastic activity in the bones, decreased bone matrix and decreased deposition of bone calcium and phosphate. This effect, if extremely severe, results in osteoporosis. This can greatly weaken the bones and lead to bone fracture (especially that of vertebrae).

Estrogens cause a slight increase in total body protein.. This results from the growth-promoting effect of estrogen on the sexual organs, the bones and a few other tissues of the body. But the enhanced protein deposition caused by testosterone is much more general and powerful as that caused by estrogens.

Estrogens increase the metabolic rate slightly (about a third as much as the testosterone). They also cause deposition of increased amounts of fat in the subcutaneous tissues. As a result, the overall specific gravity of the female body (as judged by flotation in water) is considerably less than that of the male body (containing more protein and less fat). Besides the breasts and subcutaneous tissues, estrogens cause deposition of fat in buttocks and thighs that is characteristic of the feminine figure.

Estrogens do not greatly affect hair distribution. But hair develops in the pubic region and in the axillae after puberty. Adrenal cortex androgens are mainly responsible for that.

Estrogens cause the skin to develop a texture that is soft and smooth but nevertheless thicker than that of the child or the female castrate. They cause the skin to become more vascular than normal. This effect is often associated with increased warmth of the skin and results in greater bleeding of cut surfaces than is observed in men.

Being chemically similar to adrenocortical hormones, estrogens, like aldosterone and some other adrenocortical hormones, cause sodium and water retention by the kidney tubules. But this effect of estrogens is slight and rarely of significance except in pregnancy.

The most important function of progesterone is to promote secretory changes in the uterine endometrium during the latter half of the female sexual cycle, thus preparing the uterus for implantation of the fertilized ovum. Besides, progesterone decreases the frequency of uterine contractions, thereby helping to prevent expulsion of the implanted ovum.

Progesterone also promotes secretory changes in the mucosal lining of the fallopian tubes, which are necessary for nutrition of the fertilized, dividing ovum as it traverses the fallopian tube prior to implantation.

Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, to enlarge and to become secretory in nature, but does not cause the alveoli actually to secrete milk. Because milk is secreted only after the prepared breast is further stimulated by prolactin from the anterior pituitary gland.

Progesterone in very large amount can enhance sodium, chloride and water reabsorption from the distal tubules of the kidney (like estrogens, testosterone, adrenocortical hormones).

The hypothalamus does not secrete GnRH continuously, but in pulses lasting several

minutes that occur every 1-3 hours. This causes also pulsatile output of LH. To a slight extent, secretion of FSH is also modulated by the hypothalamic pulses of GnRH, but there s more important prolonged effect on FSH secretion that persists for many hours rather than changing greatly from one pulse to the next.

Estrogen in small amounts and progesterone in large amounts imhibit production of FSH and LH. These feedback effects operate mainly directly on the anterior pituitary gland, but to a lesser extent on the hypothalamus to decrease secretion of Gn RH (especially by altering the frequency of the GRH pulses).

Inhibin has the same effect in the female as in the male of inhibiting the secretion of FSH and LH to a lesser extent.

At the age of 40-50 years the sex cycles become irregular and ovulation fails to occur during many of the cycles. After a few months to a few years the cycles cease altogether. This period, during which the cycles cease and the female sex hormones diminish rapidly to almost none at all, is called menopause.

Hypogonadism, that is, less than normal secretion by the ovaries can result from poorly formed ovaries, lack of ovaries or genetically abnormal ovaries that secrete the wrong hormones because of missing enzymes in the secretory cells. When the ovaries are absent from the birth or become nonfunctional before puberty, female eunuchism occurs: the usual secondary sexual characteristics do not appear and sexual organs remain infantile. Especially characteristic is prolonged growth of the long bones.

When the ovaries of a fully developed woman are removed, the sexual organs regress to some extent so that the uterus becomes almost infantile in size, the vagina becomes smaller and the vaginal epithelium becomes thin and easily damaged. The breasts atrophy and become pendulous. The pubic hair becomes thinner. These same changes occur in woman after menopause.

In hypogonadism the ovarian cycle will not occur normally, several months may elapse between menstrual periods or menstruation may cease altogether (amenorrhea).

Hypersecretion of ovarian hormones is a rare clinical entity, because excessive secretion of estrogens automatically decreases the production of gonadotropins by the pituitary gland, and this in turn limits production of the ovarian hormones. Hypersecretion of feminizing hormones is recognized clinically only when a feminizing tumor develops. These tumors secrete large amounts of estrogens, which exert the usual estrogenic effect, including hypertrophy of the uterine endometrium and irregular bleeding from the endometrium.

Two more glands concern the control of sexual activities, and this function is the common feature of quite different glands located far from one another - the pineal gland (epiphysis) and the thymus gland. Both epiphysis and thymus prevent the early puberty. When the child is 15-16 years old these glands regress and the puberty sets in. But in spite of age involution, these glands continue to function throughout the life. Each of them perform the most important vital functions in the organism.

The pineal gland hormone is melatonin. Melatonin causes delay of puberty in preadolescent mammals. In grown - up animals it causes decrease of the size of ovaries and inhibition of the estrous cycles.

The pineal gland function is controlled by the amount of light seen by the eyes each day. The light signals pass from the eyes to the suprachiasmal nucleus of the hypothalamus and from there - to the pineal gland to activate its secretion. Melatonin and several other similar substanes, secreted by pineal gland, pass to the anterior pituitary gland (either by way of the blood or through the fluid of the third ventricle) to control gonadotropic hormone secretion.

In some species of animals in the presence of pineal gland secretion, the gonaditropic hormone secretion is suppressed, and the gonads become inhibited and even involuted. This occurs during the early winter months when there is increasing darkness. After about 4 months of dysfunction, the gonadotropic hormone secretion breaks through the inhibitory effect of the

pineal gland and the gonads become once more ready for a full springtime of activity. So, the normal annual periods of seasonal fertility is secured, which is very important to lower animals because it allows birth of the offspring in the spring and summer months, when survival is most likely. In animals in which the pineal gland has been removed or the nervous circuits to the gland have been sectioned, the normal annual periods of seasonal fertility are lost.

When the pineal gland of children is damaged, early puberty occurs. Tumors often occur in the region of the pineal gland of man. Pineal tumors secrete excessive quantities of pineal hormones, whereas tumors of surrounding tissues press on the pineal gland to destroy it. Both types of tumors are often associated with serious hypo-or hypergonadal functions. This proves the role of the pineal gland in controlling sexual drive and reproduction in man.

Melatonin effects on the melanophores (the pigment cells of the skin). Its effect is opposite to that of intermedin (pituitary gland's pars intermedia hormone). Under the influence of the melatonin the skin gets lighter.

Pineal gland contains also a great amount of serotonin. The endocrine function of pineal gland is controlled by sympathetic nervous system.

Since the cycle of biochemical processes in the pineal gland reflects the alternation of night and day, its cyclic activity is regarded as a kind of biological rhythm ("clock") of organism.

The role of thymus gland in delay of puberty is confirmed by the fact that its mass increases up to the period of puberty and then begins to decrease. By the age the thymus is atrophied, but never disappears completely and performs important functions in the organism.

Thymus gland is the chief organ regulating the functions of lymphoid system. Its role in immunogenesis and immune reactions of the organism is exceptional. The lymphocytes which are responsible for cell-mediated immunity, are differentiated ("preprocessed") in the thymus gland (that is why they are called T lymphocytes).

Removal of the thymus several months before birth of the baby can completely prevent development of all cell-mediated immunity, and one can transplant organs with little likelihood of rejection. Because it is this cellular type of immunity that is mainly responsible for rejection of transplanted organs (heart, kidney etc.).

The thymus secrete stimulatory factors collectively called thymic hormone. It is supposed that this hormone spreads through the body fluids and increases activity of T lymphocytes that have already left the thymus gland and have migrated to the lymphoid tissue. This hormone causes further proliferation and increases activity of these lymphocytes.

In the thymus gland several biologically active substances with hormonal properties (thymosin, thymopoietin, thymarin, thymosterin, T-activin, hormonal thymus factor, ubiquitin) are revealed. They influence activity of the immunocompetent cells, provide the normal development of lymph nodes and spleen, take part in regulation of activity of other endocrine glands. When administered into the organism, thymosin increases the number of lymphocytes in the blood and strengthens immune reactions.

Absence or insufficient development of the thymus gland results in weakness of the protective function of the immune system and delay of development and growth of organism.

Removal of the thymus in new-born animals results in the severe atrophic disturbances and cessation of the immune system activity. Cachexia, delay of growth, fall of hair, dermatitis, diarrhea are observed. Lymphoid elements of spleen and lymph nodes are replaced by cells of the reticuloendothelial system and atrophy. In peripheral blood lymphopenia. and neutrophilia are revealed. Rate of immune reactions is decreased and at last the animal perishes.

Laboratory Studies

Influence of Insulin on the Blood Sugar of Mice

The equipment: 4 mice starving during 24 hours, syringe, glass cover, 20% solution of glucose, 0.9% NaCl solution.

Insulin is injected subcutaneously counting per 10 g of body mass: to the first mouse - 0.1 unit, to the second mouse - 0.5 unit, to the third mouse - 1 unit. To the control mouse subcutaneously 0.3 - 0.5 ml of physiological salt solution is injected. The mice are put under the glass cover and their behaviour is observed.

In 3 experimental mice hypoglycemic shock develops at different periods depending on the dose of injected insulin, whereas the behaviour of the control mouse does not change.

Into the peritoneal cavity of one of the experimental mice 0.25 - 0.5 ml of 20% glucose solution is administered. In this mouse the signs of the shock gradually disappear.

GENERAL PHYSIOLOGY OF EXCITABLE TISSUES

Lecture 28

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.

The modern investigations carried out by the help of the electronic equipment confirmed and sustained the theories of Galvani and Matteucci.

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 40-50 times higher than that of in the extracellular fluid. But the concentration of the sodium ions is 8-10 times higher and the concentration of chlorine ions 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. These are 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 - 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 conformatioal 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.

The original research that led to understanding of the sodium and potassium channels was so ingenious that it led to Nobel prizes for the scientists responsible (Hodgkin and Huxley).

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. 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) and descending (repolarization) phases. The duration of the spike of action potential in nerve and skeletal muscle fibers varies within 0.5-3 msec (the repolarization is longer than depolarization). The amplitude of afterpotentials is several millivolts, their duration varies from several to some ten or hundred milliseconds.

In some instances (for example, in heart muscle fibers) the excitable membrane does not repolarize immediately after depolarization, but the potential remains on a plateau near the peak of the spike for many milliseconds before repolarization begins.

Besides sodium and potassium ions at least three other types of ions must be considered in the generation of the action potential.

Inside the axon are many negatively charged ions that cannot go through the membrane channels (protein molecules, organic phosphate compounds, sulfate compounds etc.). Any deficit of positive ions inside the membrane leaves an excess of these impermeable negative ions, which are responsible for the negative charge inside the fiber.

The membranes of almost all cells of the body have calcium pump, which (like the sodium pump) pumps calcium ions from the interior to the exterior of the cell membrane, creating a calcium ion gradient. There are also voltage-gated calcium channels or calcium-sodium channels. When they open, both calcium and sodium ions flow to the interior of the fiber. The calcium chanels are also called slow channels in contrast to the sodium channels that are called fast channels. Calcium channels are very numerous in cardiac muscle and smooth muscle. In some types of smooth muscle the sodium channels are hardly present at all, and the action potentials are caused almost entirely by activation of the calcium channels.

Chloride ions leak through the resting membrane in the same way that small quantities of potassium and sodium ions. But they function passively in this process, and the permeability of the chloride leak channels does not change significantly during the action potential.

Initiation of the action potential is connected with any event that causes enough initial rise in the membrane potential from - 90 mV up toward the zero level. The rising voltage itself will cause many voltage-gated sodium channels to begin opening. This allows rapid inflow of sodium ions which causes still further rise of the membrane potential, thus opening still more voltage-gated sodium channels and more streaming of sodium ions to the interior of the fiber. This positive feedback vicious circle process will continue until all the voltage-gated sodium channels have become totally activated. Then, within another fraction of a millisecond, the rising membrane potential causes beginning inactivation of the sodium channels as well as opening of potassium channels, and the action potential soon terminates.

After action potentials sodium and potassium ionic gradients are re-established owing to the action of sodium-potassium pump: the sodium ions that have diffused to the interior of the cell during the action potentials and the potassium ions that have diffused to the exterior are returned to their original state. This process of recharging is an active metabolic process, using energy derived from the adenosine triphosphate energy system of the cell.

An action potential will not occur until the initial rise in membrane is great enough to create above-mentioned vicious circle. Usually a sudden rise in membrane potential of 15-30 mV is required. So, in a large nerve fiber a sudden increase in the membrane potential from -90 mV up to about -65 mV will cause the explosive development of the action potential. This level is the threshold for stimulation.

For continued propagation of an impulse to occur, the ratio of action potential to treshold for excitation must at all times be greater than 1. This is called the safety factor for propagation.

The all-or-nothing 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. When the excitability has been reduced so low that the safety factor is reduced below 1, a nerve impulse fails to pass through the anesthetized area.

Laboratory Studies

Observation of Membrane Potential and Action Potential
The equipment: frog, Galvani's arc, electrostimulator, scissors, pincers, conductors, the small cork plank, pins, 0.6% NaCl solution, cotton wool.

The frog is made motionless by the way of destruction of the central nervous system. Then it is cut by transverse section and the skin of the hind legs is taken off. This preparation of the hind legs of the frog connected with the low part of the spine is used to demonstrate Galvani's first experiment (the resting membrane potential).

Two ends of Galvani's arc are made of different metals (copper and zinc). Its one end is put under both sciatic nerves. At the moment other end touches the muscles of the thigh, the muscles contract.

To demonstrate Galvani's second experiment neuromuscular preparation of one hind leg of the frog is made. The sciatic nerve is thrown on the damaged muscles of the crus (so that to touch simultaneously their damaged and intact parts), and the muscles contract.

To demonstrate the first experiment of Matteucci two neuromuscular preparations are made. At the moment the nerve of one preparation is thrown on the dissected muscles of the second preparation, the muscles of the first preparation contract.

Matteucci's second experiment is demonstrated in the following way. Two neuromuscular preparations are made of hind legs of frog. The nerve of one preparation is thrown on the muscle of the second preparation, the nerve of which is stimulated. The muscles of both preparations contract.

This experiment of the "second contraction" proves that during the muscle contraction action potentials occur and they are strong enough to cause contractions of other muscles.

Lecture 29

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 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 (E_0) approaches to the critical level (E_c), that is, the partial depolarization occurs and the depolarization threshold (ΔV) decreases. Therefore, the excitability increases and the excitation is facilitated.

At the point where the anode is put to the tissue, the level of E_0 moves away from E_c, that is, hyperpolarization occurs and ΔV 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. These changes are connected with inactivation of the so-dium 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 trans-mitted. 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 and descending. The current is regarded as ascending when the anode is situated near the muscle. The reverse direction (cathode is near the muscle) is considered as descending.

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.

The power of	Ascending		Descending	
the current	closing	breaking	closing	breaking
Weak	+	-	+	-
Average	+	+	+	+
Powerful	-	+	+	-

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.

So, the neuromuscular synapses spare the muscles, letting pass to them even smaller amont of impulses than they are able to response.

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.

Laboratory Studies

1. Polar Rule of Excitation

The equipment: frog, electrostimulator, accumulator, Zn electrodes, scissors, pincers, the small cork plank, pins, ligatures, two glass tubes (4-5 cm long, diameter - 4-5 mm), the saturated Zn SO_4 solution, 0.6% NaCl solution, ammonia solution, kaolin (china-clay) powder, cotton wool.

Non-polarizing electrodes are prepared. They consist of two glass tubes one ends of which are covered with the paste of kaolin (on the physiological solution) in the form of the boot. The tubes are filled with the saturated solution of $ZnSO_4$ and zinc electrodes are put into the solution from the other ends of the tubes.

When stimulated with the help of these electrodes the tissues are not polarized.

The neuromuscular preparation is made from the hind leg of frog. It nerve is put on the non-polarizing electrodes. The average power of the current is determined which causes the contraction of the muscle both at the closing and breaking moments of the circuit. Then between the electrodes on the nerve the ammonia solution is dropped. After 1-3 minutes it is stimulated.

In the ascending direction of the current the closing of the circuit does not cause the contraction, but at the breaking of the circuit muscle contracts.

In the descending direction, on the contrary, at the closing of the circuit the muscle contracts, but the breaking does not cause the contractions.

2. Physiological Electrotonus

The equipment: frog, electrostimulator, accumulator, electrodes, non-polarizing electrodes, scissors, pincers, the small cork plank, pins, the physiological solution, NaCl crystals, cotton wool.

The neuromuscular preparation is made. The NaCl crystals moistened in the physiological solution are put on the nerve, and after 1-3 minutes the muscle begins to contract rhythmically.

Then between the crystals and the muscle the nerve is in addition stimulated by the powerful ascending direct current. The muscle does not contract any more. Because the anodic area with decreased excitability and conduction prevents the excitation caused by chemical stimulation to be transmitted to the muscle. If the electrodes are taken away, the muscle contracts again.

MUSCLE CONTACTION

Lecture 30

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 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. With that end in view at present the special sensing elements are applied which convert the mechanical changes into the oscillations of the electric current. These, after amplification, may be recorded as myogram (mechanogram).

Isotonic and isometric contractions of muscles are distinguished.

During the isotonic contraction the fibers of the muscle are shortened, 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 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 ($\Delta V \approx 40$ mV) than that of nerve fiber ($\Delta V \approx 20$ mV). Consequently, the threshold of stimulation is also higher for the muscle fiber than for the nerve fiber.

When measured by the help of intracellular electrodes, the amplitude of the action potential is 120 - 130 mv, its duration in the muscle fibers of extremities and trunk is 2 -3 msec, in the muscles, of the eyeball - about 1 msec. At the body temperature spreading velocity of action potential along the muscle fiber of the warm - blooded animals is 3 - 5 m/ses. 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).

After a fraction of a second 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/cm$_2$ 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 lamen 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.

Lecture 31

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:

$$W = L \cdot D$$

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.

Laboratory Studies

1. Making and Stimulation of the Neuromuscular Preparation

The equipment: frog, electrostimulator, electrodes, scissors, pincers, the small cork plank, pins, the subject glass, the metal stick, spirit - lamp, the crystals of NaCl, 0.6% NaCl solution, 10

% curare solution, thread, gause, cotton wool.

The frog is made motionless and cut by transverse section on the level of the lumbar part of the spine. The skin is taken off, and two hind legs are cut off by the longitudinal section. Each of these preparations is called the rheoscopic paw.

Moving aside the back group muscles of the thigh by the fingers, between them the sciatic nerve is found, the scissors are put under the nerve, the thigh-bone is cut nearer to the knee joint and removed together with the muscles. Under the knee joint the crus is cut and removed, reserving only the gastrocnemius muscle.

So, the neuromuscular preparation is ready which consists of gastrocnemius muscle with the Achilles tendon and sciatic nerve. On the nerve a small piece of the spine is preserved (to hold it and not to damage the nerve).

Using different stimuli the preparation is irritated: by the blunt end of the pincers the blows are stiken on the nerve (the mechanical stimulation), the end of the warmed up metal stick is touched to the nerve (the thermal irritation), the NaCl crystals moistened in the physiological solution are put on the nerve (chemical irritation). Putting the electrodes on the nerve or muscle the indirect or direct electrical stimulation is applied.

2. Recording of Solitary Muscular Contraction (myography)

The equipment: frog, myograph, kymograph, electrostimulator, electrodes, scissors, pincers, the small cork plank, pins, 0.6% NaCl solution, gauze, cotton wool.

The same neuromuscular preparation is made, but the lower one third of the thighbone is preserved on it. This bit of thighbone is seized by the clip of the myograph, Achilles tendon is put on the hook of the myograph's recording lever. The end of the lever touches the paper on the drum of the kymograph.

The nerve is put on the electrodes and irritated by single electric stimuli. Each time when the muscle contracts, the lever records the myogram on the revolving drum of the kymograph. In the myogram the latent period, periods of contraction and relaxation are distinguished.

3. Effect of the Temperature, Power and Frequency of Stimulation on Muscular Contractions

The equipment: frog, myograph, kymograph, electrostimulator, electrodes, scissors, pincers, the small cork plank, pins, spirit-lamp, hyposulphite crystals (or the cold physiological solution), 0.6% NaCl solution, cotton wool.

The myogram is recorded. After cooling the muscle and then after warming up the muscle the recording is repeated.

Under the infuence of cooling the amplitude of the solitary muscular contraction decreeses, its duration increases, especially the latent period gets longer. Warming causes shortening of the latent period and duration of the solitary muscle contraction and decrease of its amplitude.

To study the effect of the power of the stimulation on solitary muscle contraction, the minimum power of the stimulation (the lower threshold) is determined, and myogram is recorded. Then gradually the power of the stimulation is increased, and the myogram is recorded. Amplitude of the solitary muscular contraction is increased until the optimal power of the stimulation is reached. More powerful (pessimal) stimuli cause decrease of the amplitude. At last the upper threshold is reached when the most powerful stimulation does not cause contraction.

To observe influence of the stimulation frequency on the muscle contraction, at first the myogram of the solitary muscle contraction is recorded. Then gradually increasing the frequency of the stimuli, denticulated and smooth tetanus are observed.

4. Isolated Frog Muscle Fatigue

The equipment: frog, myograph, kymograph, electrostimulator, electrodes, scissors, pincers, the small cork plank, pins, 0.6% NaCl solution, coton wool.

The neuromuscular preparation is made and fixed to the myograph. The load is hanged on the lever of the myograph. The nerve of the preparation is stimulated and the myogram is recorded each time until the muscle fatigue occurs. During the process of fatigue decrease of the muscle contraction amplitude is observed.

5. *Ergography*

The equipment: ergograph, metronome, loads (1, 2, 3, 4 kg).

The person fixes his wrist on the ergograph, holds the handle by four fingers and by the middle finger or fore - finger lifts the load rhythmically 50-60 times in 1 minute (under the control of metronome). The pencil records the ergogram on the strip of paper. Gradually the amplitude of the ergogram decreases, that is, the muscles of ther finger are tired. When the complete fatigue occurs, the person cannot lift the load.

Lecture 32

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-or-nothing 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.

A type fibers are divided into 4 subgroups: A_α, A_β, A_γ, A_Δ. They are myelinated fibers. The thickest are $A\alpha$ 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_β, A_γ, A_Δ) 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.

B 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.

C 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 acetylcholine-gated 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 receptor 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.

Laboratory Studies

1.The Laws of Transmission of Excitation
The equipment: double- channel oscillograph, electrostimulator, stimulating and recording electrodes,scissors, pincers, the small cork plank, pins, the glass plate, 0.6%NaCl solution, ammonia solution, thread, cotton wool.

The three laws of transmission of excitation(the law of the physiological safety, the law of the isolated conduction, the law of the two- way conduction)are demonstrated by the aforesaid ways.

2. The Effect of Curare on Neuromuscular Junction
The equipment:_frog, myograph, kymograph, electrostimulator, electrodes, the glass

cover, scissors, pincers, syringe, the solution of curare or curare- like agent (0.1%solution of myorelaxin), 0. 6%NaCl solution, cotton wool.

The frog is placed under the glass cover and its behaviour (posture, quantity of movements, respiratory reactions)is observed. Then the frog's behaviour is observed when it is turned on its back.

0.1-0.3 ml of myorelaxin is injected into the lymphatic sac of frog and changes of its behaviour are observed. Its posture is changed. When the frog is turned on its back, it does not try to return to its normal position.

5 minutes later the frog's motor activity is ceased, the muscle tone falls, the posture is changed and it throws itself flat. The respiratory movements slow down, then disappear. But when the chest is opened, the heart beats.

The neuromuscular preparation is made from hind leg of the frog and at once the sciatic nerve is stimulated. To cause the muscle contraction more powerful stimulation is required than that in normal preparation (the excitation threshold is significantly increased). Later the muscle ceases to reply even to the powerful indirect stimulation. Then the muscle is stimulated directly and it contracts. During the direct stimulation the threshold is changed insignificantly.

PHYSIOLOGY OF THE CENTRAL NERVOUS SYSTEM

Lecture 33

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 10_{15}-10_{16}.

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 regions-with 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 axo-somatic, axondentric, axoaxonal, dendrodendritic, somatodentric 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 (γ-aminobutyric acid-GABA, glycine, glutamate, aspartate).

2. Neuropeptide, slowly acting transmitters:

A. Hypothalamic releasing hormones (thyrotropin-releasing hormone, luteinizing, hormone-releasing hormone, growth hormone-inhibitory factor-somatostatin).

B. Pituitary peptides (ACTH, β-endorphin, α-melanocyte-stimulating hormone, prolactin, luteinizing hormone, thyrotropin, growth hormone, vasopressin, oxytocin).

C. Peptides that act on gut and brain (leucine enkephalin, methionine enkephalin, substance P, gastrin, cholecystokinin, vasoactive intestinal polypeptide-VIP, neurotensin, insulin, glucagon).

D. 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 where-rever 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;
3) recurrent inhibition;
4) pessimal inhibition;
5) inhibition after excitation.

Laboratory studies

1. Inhibition of Spinal Cord Reflexes (Sechenov's inhibition, experiment of Holts)
The equipment : frog,support, scissors, eye scissors, pincers,scalpel, the small cork plank,pins,4 chemical glasses,metronome or second counter, sulphate acid solutions (0.1-0.5%), NaCl crystals,0.6% NaCl solution,a glass of water.

The frog is fixed on the cork plank by the pins in the position on the stomach.The skull cap is opened,the thalami are separated from the hemisperes by the transverse section,and the hemispheres are removed.

The frog is hanged from the support by lower jaw. 15 minutes later the fingers of the hind leg are put into the weak sulphate acid solution and the reflex time is determined.2-3 minutes later NaCl crystals are put on the thalami and once again the reflex time is determined.

To demonstrate the experiment of Holts the spinal frog (above the spinal cord the brain is removed) is hanged from the support, the fingers of the hind leg are put into the sulphate acid solution and reflex time is determined.

Then one of the hind legs is put into acid solution and simultaneously the other leg is pressed by the pincers.The reflex time is determined.

2.Effect of Strychnine and Chloroform on the Central Nervous System Excitability
The equipment: 2 frogs, glass cover, plate, syringe, scissors, pincers, the small cork plank, pins, 1% strychnine-nitrate solution, chloroform, cotton wool.

The frog is placed under the glass cap. One of limbs is irritated mechanically and its movement is observed. Then 2 ml of 0.1% strychine –nitrate is injected hypodermically or into the lymphatic sac.3-5 minutes later the mere touch to the skin or even knock on the plate by the pincers cause the strong motor reaction of the frog and even the trembling of all the body. Because strychnine blocks up the function of certain inhibitory synapses.

The other frog is put under the glass cap and the cotton wool moistened in the chloroform is put beside it. Several minutes later the reflex reaction of the frog are weakened or even temporarily disappeared. Because chloroform enters the blood through respiratory ways and decreases the excitability of the central nervous system.

Lecture 34

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 co-ordinates 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 reflecto-reflection) 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 significant 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;

2) bulbar (medulla oblongata) reflexes;

3) mesencephalic (midbrain) reflexes;

4) diencephalic reflexes;

5) 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 (to-and-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.

8. The micturition (urinary) reflex.

9. The defecation reflex.

Bulbar reflexes:

1. The sucking reflex - the touch to the lips of baby causes the rhythmical sucking movements.

2. The vomiting reflex - irritation of the back wall of gullet causes vomiting.

3. 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.

Laboratory Studies

1. Observation of Spinal Reflexes and Analysis of Reflex Arc

The equipment: frog, support, scissors, the filtering paper, the small cork plank, pins, two glasses full of water, two chemical glasses, tendon reflex hammer, 0,5% and 1% sulphate acid solutions, 0.5% novocain solution, chloroform, cotton wool.

To observe the flexor reflex the spinal frog is hanged from the support and its hind leg's fingers are irritated with the sulphate acid solution.

A filtering paper moistoned with sulphate acid solution is put on the skin of the frog's chest. By the movements of the upper limbs the spinal frog rubs the skin and removes the paper.

To observe the knee reflex the person sits on the chair and by the tendon reflex hammer a blow is striken on the tendon of the quadriceps muscle of thigh. The leg jerks forward.

The Achilles reflex is demonstrated in the follwoing way. The person is standing on knees on the chair and his feet are hanging freely. The blow on Achilles tendon causes flection of the foot.

For any reflex to be performed all parts of the reflex arc must be intact. To prove this the spinal frog leg's skin is put off or its sciatic nerve is cut or the spinal cord is destroyed. After this the irritation of the leg does not cause any of the reflexes.

2. Determination of Reflex Time

The equipment: frog, support, metronome or seconds counter, scissors, pincers, the small cork plank, 4 chemical glasses, the glass full of water, sulphate acid solutions (0.1%, 0.2%, 0.3% and 0.5%), cotton wool.

Sulphate acid solutions of different concentrations are poured into 4 glasses. The limb of spinal frog hanged from the support is stimulated by turns with each of solutions and in every case the reflex time is determined. This is the time from the moment of irritation to the moment of reflex contraction of muscles. Higher the concentration - shorter is the reflex time.

Lecture 35

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 depresses 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 exci-

tation 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.

Lecture 36

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.

Laboratory Studies

1. Irritation of Excitation in the Central Nervous System

The equipment: frog, support, scissors, pincers, the small cork plank, pins, the filtering paper, sulphate acid solutions (0.1, 0.2, 0.3, 0.4, 0.5 and 1%), the glass full of water, cotton wool.

The spinal frog is hanged from the support. Its hind leg is by turns irritated by sulphate acid solutions of different concentrations. After each irritation the leg is washed in the glass of water.

The weak solutions cause the flexor reflex only in the irritated limb. The stronger solutions cause the muscle contractions also in other limbs. Higher the concentration of the solution, more muscles of the body, are contracted. At last, the whole body of the spinal frog is moving.

This is the result of the irradiation of the powerful excitations in the broad areas of the central nervous system.

Lecture 37

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 Aγ 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.

Thetrigeminal 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.

Lecture 38

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:

a) reflexes of position or postural-tonic reflexes-ensure maintenance of a definite stance or posture of the body;

b) 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 self-stimulation 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).

Lecture 39

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 helps 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 stato-kinetic 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 aggre-

gation 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 non-specific 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.

Lecture 40

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 under-

developed, 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.

I- molecular (plexiform) layer contains few neurons and is mainly formed by interlacing nerve fibers;

II- external granular layer contains closely packed small neurons whose bodies have oval, triangular or polygonal shape;

III- external pyramidal layer contains pyramidal neurons of varying size;

IV- internal granular layer contains small neurons like the external granular layer ;

V- 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;

VI- 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 electroen-cephalograms 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.

Lecture 41

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 circuitry 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, self-preservation 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).

Laboratory Studies

1. Electroencephalography

The equipment: Cat or rabbit, electroencephalograph, electrostimulator, phonophotostimulator, electrodes, point electrodes, microelectrodes, stereotaxic apparatus, helmet with electrodes for human EEG recording, scissors, pincers, surgical knife, syringe, phosphate-cement, noracril, electrode paste, narcotic substance (urethane, nembutal, ether, chloroform), 2.5% solu-

tion of aminazine, 0.9% NaCl, gauze.

I. Head of the animal is fixed in the stereotaxic apparatus. Under the skin of the skull novocain is injected. The skin is dissected and removed, the bones are scraped by the surgical knife and cleared from the soft tissues. The bleeding is stopped. The sharp ends of the point electrodes are drived into the skull and they are connected with the electroencephalograph. The summary potentials of the cerebral cortex (electrocorticogram) is recorded.

To introduce the electrodes into the deep structures of the brain the stereotaxic atlas is used, where the coordinates of the wanted point are found. Then the electrodes are fixed on the head by the phosphate-cement.

To study the influence of the afferent system stimulation and different pharmacological substances on the electroencephalogram (EEG), the background EEG is recorded and after the influence the recording is repeated.

The pain stimulation causes desynchronization reaction in the EEG, that is, the slow waves with high amplitude are replaced by the rapid waves with small amplitude. But if aminazine (adrenolytic substance) is injected, after 5-6 minutes this reaction disappears.

II. To record human EEG the helmet is put on the head. The skin on the points of the head which will contact with the electrodes is wiped with ether, the paste is spread or the gauze moistened in physiological solution is put on these points. The electrodes are connected with the electroencephalograph.

The background EEG is recorded. Then the person closes his eyes 1-2 minutes and opens them. Accordingly alpha-waves and beta-waves are recorded. The sound stimulation at the time of recording alpha-waves causes their replacement by the desynchronization reaction.

2. Reaction of Self-stimulation in Rabbits

The equipment: The animal with the electrodes implanted into the reward center of the brain, technique for the self-stimulation.

The technique is switched on. The animal presses the lever and performs self-stimulation.

Lecture 42

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 (β_1 and β_2) 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 conditioned-reflex 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 (beta$_2$ 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 beta$_1$ 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 acetyl-choline liberated by the parasympathetic nerve endings. Atropine, homatropine and scopolamine block the action of acetylcholine on the muscarinic type of cholinergic effector organs (antimus-carinic 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, thermore-gulation, water-salt balance, carbohydrate, fat, protein metabolism, urination, endocrine func-tions. 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 43

Physiological Properties of Receptors. Nociceptors (pain receptors). Visceroceptors. Proprioceptive Sensation. Vestibular Apparatus

Since every living organism forms a single whole with its environment and cannot exist without the environment sustaining it, then the organism constantly requires information about the state and changes occurring in the environment. In the human organism this information is proceeded to elaborate on its basis plans and programs for the future activity. Input of information to the central nervous system about the outside world as well as inner state of the organism itself is provided by the receptors specialized to perceive stimuli.

From the receptors impulses are conducted along afferent nerve fibers to the central nervous system. From the first receptor neuron excitation is transmitted to a second and then to a third neuron (in the thalamus) and reaches the cerebral cortex. Although all links of this neuronal chain are important for analysis of the stimuli, the higher forms of analysis are performed by the cerebral cortex.

The entire aggregate of the nerve elements which ensures receiving stimuli, transmitting impulses to the brain and analysis of the information was considered by I. P. Pavlov to be a unified system and designated by the term "analyser". So, every analyser consists of three parts :
1) the peripheral end-receptors;
2) the conducting section –afferent neurons and conducting pathways;
3) the central end-the areas of the cerebral cortex stimulated by the receptors, that is, the representation of the receptive field in the cerebral cortex.

Various experimental and clinical methods are applied to study function of analysers: psychophysiological study of man's perception,investigation of sensory processes in animals by the conditioned-reflex method, electrophysiological, morphological and biochemical analysis, study of sensory processes according to the parameters of certain automatic functions, modelling and prosthetics of sensory functions, etc.

The most important functions of analysers are the following:
1) signal reception;
2) differentiation of signals;
3) transmission and transformation of neural signals;
4) coding of information;
5) detector processing of signals;
6) recognition or identification of images.

Reception and differentiation of signals are performed by receptors, and their detection and recognition-by highest cortical levels of analysers. Transmission, transformation and coding of signals are realized in all analyser layers.

All receptors are divided into two groups:
1) external receptors or exteroceptors signal the properties of objects and phenomena of the outside world and their influence on the organism: auditory, visual, olfactory, gustatory, tactile receptors;
2) internal receptors or interoceptors:

a) visceroceptors providing information about the state of visceral organs;

b) proprioceptors and vestibuloceptors emitting impulses that signal the position and movement of the body and its individual parts in space.

Receptors are also classified according to their adequate stimuli, that is, to the physical nature of the stimuli to which they are especially sensitive:

1) mechanoreceptors detecting mechanical deformation of the receptor (tactile receptors, baroreceptors, phonoreceptors, vestibular receptors, etc.);

2) chemoreceptors detecting taste in mouth, smell in the nose, oxygen level in the arte)rial blood, osmolality of the body fluids, carbon dioxide concentration, etc.;

3) thermoreceptors detecting changes in temperature (cold receptors and warmth recaptors);

4) nociceptors (pain receptors) detecting damage (physical or chemical) in the tissues (free nerve endings);

5) electromagnetic receptors detecting light on the eye retina (photoreceptors-rods and cones).

In addition, receptors are divided into two groups

1) contact receptors–are sensitive only to stimuli from objects directly applied to them (tactile, pain, taste receptors);

2) distance receptors –are sensative to stimuli arising from objects at a considerable distance from organism (visual, acousting, olfactory receptors).

Practically the most important is the psychophysiological classification of receptors based on the character of sensation arising on their stimulation. According to it organs of vision, hearing, smell, taste, touch, sensation of heat and cold, posture and pain are distinguished.

Each of the principal types of sensation that one can experience (sight, sound, touch, pain, etc.) is called a modality of sensation.

Receptors are extremely sensitive to adequate stimuli, that is, each type of receptor is very highly sensitive to one type of stimulus for which it is designed, and yet is almost nonresponsible to normal intensities of the other types of sensory stimuli. For example, the rods and cones are highly responsive to light, whereas they are almost completely nonresponsive to heat, cold or chemical changes in blood.

So, the threshold of stimulation of receptors by adequate stimuli is very low. For instance, photoreceptors can be excited by single quantum of light in the visible spectrum, olfactory receptors-by the action of single molecules of odoriferous substances.

Receptors can be excited also by the inadequate stimuli. For instance, a blow on the eye causes a sensation of light, on the ear –sensation of sound (hence the expressions: "he saw stars", "ringing in the ears"). But the threshold of stimulation of receptors by inadequate stimuli is very high, and their excitation is much less than normal: for mechanical stimulation of the eye to produce a sensation of light it has to be thousands of millions times stronger than an adequate stimulus.

Changes in the state of receptors as well as impulses from the central nervous system (especially from the reticular formation and cerebral cortex) may alter the excitability of receptors.

Whatever the type of stimulus that excites the receptor, its immediate effect is to change the membrane potential, and receptor potential or generator potential occurs. This has the properties of a local response.

Most receptors have background discharges (impulsation), that is, they spontaneously release neurotransmitter without any stimulation. As a result, information about a signal can be transmitted in the form of deceleration or acceleration of the flow of impulses.

The receptor potential results from release of acetylcholine which changes the membrane permeability and depolarizes it. In the photoreceptors the generation potential is originated by the breakdown reaction of visual purple.

When the receptor potential rises above the threshold the action potentials begin to appear

in the nerve fiber attached to the receptor. The more the receptor potential rises above the threshold level, the greater becomes the action potential frequency.

So, under the influence of stimulation receptors generate nerve impulses, that is, they transform the stimulation into excitation. They may be compared by transducers used in engineering in which the action of external forces produces an electric current.

Frequency of afferent impulses in the nerve fibers is directly proportional to the level of depolarization of the receptor membrane, that is, to the value of receptor potential. At the same time, the frequency of different discharges is proportional to the logarithm of the stimulus strength.

According to the law formulated by Weber (1834) the increase of stimulus in oder to be perceptible (differentational threshold) must exceed the stimulus already acting by a definite

proportion: $\underline{\Delta I} = \text{const}$

In this formula I is the stimulus and $\underline{\Delta I}$ is differential threshold. For example, when a weight of 100g (I) is applied on the skin of the hand, to produce the smallest perceptible increase in pressure an additional 3g (ΔI) must be added:

$$\text{const} = \frac{3}{100} = 0.03$$

Fechner established that gradations of stimulus strength are discriminated approximately in proportion to the logarithm of stimulus strength. This is known as the Weber-Fechner law:

$$S = a \log R + b$$

In this formula S is the intensity of the sensation, R-strength of stimulus, a and b – constants.

So, analysers have to respond to the minimal differences between stimuli, that is, the differential threshold.Spatial differentiation of signal is based on difference in distribution of excitation in space (in the receptor and neural layers). For example, if two stimuli excite the two neighbouring receptors, to distinguish them is impossible, and they are perceived as a single stimulus. For the spatial discrimination between these two stimuli to be possible, even though one unexcited receptor must be present between the excited receptors.

For temporal discrimination between two stimulations to be possible, the nervous processes elicited by them must not fuse in time, and the neural signal caused by the next stimulus must not fall in the refractory period of the preceding stimulation.

The value of the stimulus, the probability of whose perception is 0.75, is a stimulus threshold. Lower values are subthreshold and higher ones – suprathreshold. But a dinstinct reaction to the superlow or supershot stimuli is possible also in the subthreshold level. For instance, if the intensity of light is decreased so that the person cannot determine whether he saw the flash of light, then the objectively recorded skin-galvanic reaction reveals the exact response of the organism to a given signal.This means that the perception of such superlow stimuli occurs at the subthreshold level.

Transformation of the energy of a physical or chemical stimulus in receptors into nervous excitation is followed by a chain of processes the aim of which is to supply the highest levels of the brain with the most the essential information about a stimulus in the form most convenient for its reliable and quick analysis. Transformation of signals can be divided into spatial and temporal.

A number of universal and simple means exist for limitation of redundancy of information (compression of the afferent channel-the presence of a narrowing sensory "funnel", suppression or elimination of the arriving information about less significant events). Less important are those events which either remain unchanged or undergo slow changes both in time and space.

The information received by a receptor is "coded" or "ciphered" and transmitted to the central nervous system by the afferent nerve fibers in the form of a flow of nerve impulses.

Whether the sense organ is stimulated by chemical or mechanical stimuli, heart or cold, light or sound,the information about them is conveyed to the central nervous system in the form of homogenous signals. The information about the acting stimuli is transmitted in the form of individual groups or "volleys" of impulses.

The amplitude and duration of the individual impulses passing along the same fiber are identical, but the frequency and number of impulses in a volley may differ. So, during any one brief interval of time the fiber may or may not conduct an impulse, that is, transmission of impulses is effected by a binary code. For instance, a fiber capable of transmitting 100 impulses per second can carry any binary unit (bit) of information in 0.01 second (one impulse and one pause before the next impulse).

The character of signals is already differentiated to a certain extent in the peripheral receptors. Some receptors are excited only at the very outset of stimulation (on-receptors), others-at the moment when stimulation ceases (off-receptors);still others are excited both at the beginning and at the end of stimulation (on-and off-receptors).The receptors that are sources of a constant ("background") flow of impulses (providing the tone of organs) can react to stimuli by increase, reduction or cessation of the frequency of impulses. The "on-off" code is related to temporal coding.

At the highest level of analysers transition from the predominantly temporal coding to the spatial coding occurs.

Special neurons-detectors perform detector processing of signals, that is, a special type of selective analysis of individual stimulus characteristics and their actual biological significance.They can respond only to strictly defined parameters of stimulus.

The general principle of distribution of detectors is hierarchical graduation, that is, detectors of more simple characteristics ensuring simple analysis are located at lower levels, and those of more complex characteristics are concentrated at the highest levels of analysers.

The ultimate and most intricate operation of analysers is recognition or identication of images. This is done on the basis of all the previous processing of the afferent signal, its decomposition into separate elements by neurons-detectors and their parallel analysis.

Interaction among the analyser neurons is accomplished with the help of excitatory and inhibitory mechanisms. The excitatory interaction occurs mainly between the elements of successively located neural layers. The axon of each neuron entering the above-lying layer is divided in some ramifications which establish synaptic contact with several neurouns.

Then, the "dendritic tree" (neuron inputs) have synaptic contacts with axons of several cells of the preceding layer. Therefore, all the neurons of analyser have the totality of neurons at the next and higher levels of the analyser with which they interact (projection field). The totality of receptors whose impulses arrive at a certain neuron is called its receptive field.

Receptive and projection fields exist simultaneously for all the neurons of the system and they partly overlap. This intricate interaction of cells leads to the formation of nervous network in the analysers and provides them with high adaptability to changing environmental conditions. The inhibitory interaction in analyser occurs mainly between the neurons of one and the same layer with the help of inhibitory interneurons. When a continuous sensory stimulus is applied at first the receptors respond at a very high impulse rate, then at a progressively lower rate until finally many of them no longer respond at all. Such adjustment of receptors to the strength of the stimulus is called adaptation.

For instance, when entering a smoking –room, a person immediately notices the smell of tobacco, but after a few minutes he is no longer aware of it. One does not notice habitual noise or feel the pressure of his clothes on his skin. A person leaving a dark room is blinded by bright sunlight but in a short time his eyes are adapted to this effect and normal vision is recovered.

Some receptors adapt to a far greater extent than others. The pacinian corpuscle adapts extremely rapidly and hair receptors adapt within seconds, but joint capsule and muscle spindle

receptors adapt very slowly. The longest measured time for complete adaptation is about two days for the carotid and aortic baroreceptors.

An ability of adaptation is possessed in some degree by almost all receptors except vestibuloreceptors and proprioreceptors. The slowly adapting receptors, which continue to transmit impulses to brain as long as stimulus is present, keep the brain constantly apprised of the status of the body and its relation to its surroundings. For example, impulses from the muscle spindles and Golgi tendon apparatus allow the central nervous system to know the status of muscle contraction and the load on muscle tendon at each instant.

The slowly adapting receptors are called tonic receptors. Thanks to our continually changing bodily state, these receptors almost never adapt completely.

Receptors that adapt rapidly react strongly while a change is actually taking place, and the number of transmitted impulses is directly related to the rate at which the change takes place. They are called rate receptors, movements receptors or phasic receptors. For instance, sudden pressure applied to skin excites the pacinian corpuscle for a few milliseconds and then its excitation is over even though the pressure continues. But later it transmits a signal again when the pressure is released.

Importance of rate receptors is connected with their predictive function. That is, if a person knows the rate at which some change in body is taking place, he can predict the state of the body a few seconds or minutes later.

The adaptation mechanisms of sense organs are connected not only with processes occurring in a receptor, but also with a changes in the state of the nerve center to which impulses are transmitted from it and other receptors.

The sympathetic nervous system (the adaptational-trophic influence of the sympathetic nervous system) and brain stem reticular formation play an important role in the processes of adaptation.

The sensitivity of a sense organ may vary depending on the number of functioning receptors (functional mobility of receptors).

Similar to the development of a receptor potential, adaptation of receptors is also individual property of each type of receptor. For example, in the eye the rods and cones adapt by changing the concentrations of their light-sensitive chemicals. In mechanorecaptors part of adaptation result from readjustments in the structure of the receptor itself, and part results from accommodation in the terminal nerve fibril.

Although the pain is agonizing feeling from which we try to get rid of,but it is of great biological significance for the organism's survival. Because sensation of pain signals danger during the action of any extremely powerful and harmful agents. Pain is one of the first (in some cases the sole) manifestation of a morbid condition and an important diagnostic sign.

Probably that is why, unlike all other receptors, pain receptors do not have an adequate stimulus. Painful or nociceptive sensations can be caused by any stimulus of excessive intensity. Because such stimuli damage tissues, and the painful sensations from them signal danger to the organism and arouse defensive reflexes.

Two major types of pain are distinguished:
1) Fast pain – occurs within 0.1 second when a pain stimulus is applied and is transmitted through type A_Δ pain fibers. It is felt when a needle is stuck into the skin, skin is cut with a knife or is subjected to electric shock. Therefore, it is called also sharp pain, pricking pain, acute pain, electric pain, etc. Fast, sharp pain is not felt in most of the deeper tissues of the body
2) Slow pain – begins only after a second or more and then increases slowly over many seconds or minutes. It is transmitted through more primitive type C fibers. Slow pain is associated with tissue destruction. It can become excruciating and lead to prolonged, unbearable suffering. This type of pain can occur both in the skin and in almost any deep tissue or organ.

It is called also burning pain, throbbing pain, nauseous pain, chronic pain, etc.

Two hypotheses have been formulated related to the organization of pain perception. Some investigators consider that there are no special receptors for feeling pain, since overstimulation of any receptors or nerve trunk can cause pain. Others believe that painful stimuli are sensed by the free endings of nociceptive fibers.

The following facts are the main evidence of the latter view:

1. In the state of analgesia pain is absent, though the sense of touch is retained.
2. In the middle of the cornea there are no tactile points but there are painful points.
3. Pricking different areas of the skin with a very thin needle, one may hit upon points (painful points)where pain is aroused immediately without a preliminary sensation of touch.
4. After a nerve is cut and sutured, sensation of pain is recovered first during regeneration, but other forms of sensibility-some time later. In the early stages of regeneration any irritation of the skin (touching, stroking, pressure) causes a feeling of unbearable pain.

All pain receptors are free nerve endings. They are widespread in the superficial layers of the skin and in certain internal tissues, such as the periosteum, the arterial walls, the joint surfaces, and the falx and tentorium of the cranial vault. But the most of the other deep tissues are weakly supplied with pain endings. Any widespread tissue damage can summate to cause the slow-chronic-aching type of pain in these areas.

Some fibers are more likely to respond to excessive mechanical stretch (mechanical pain receptors), others to extremes of heat or cold (thermal pain receptors)and still others to specific chemicals in the tissues (chemical pain receptors).

Fast pain is elicited by the mechanical and thermal types of receptors, whereas the chemical substances cause the slow,suffering type of pain that occurs following tissue injury.

Bradykinin, serotonim, histamine, potassium ions, acids, acetylcholine, proteolytic enzymes excite the chemical type of pain receptors. Prostaglandins enhance the sensitivity of pain endings, but do not directly excite them.

Extracts from damaged tissues, when injected beneath the normal skin, cause intense pain. All the chemicals exciting the chemical pain receptors are found in these extracts.

The pain receptors adapt very little or not at all. Under some conditions as the pain stimulus continues, the excitation of the pain fibers becomes even progressively greater (hyperalgesia). This nonadapting nature of pain receptors is of a great biological significance.

Intensity of pain does not always correspond to the gravity of a morbid process. Serious diseases of the internal organs frequently have no attendant painful sensation, while a most excruciating pain may be caused by a negligible, innocuous malady. Nevertheless, the intensity of pain has been closely correlated with the rate of tissue damage from causes, such as heat, bacterial infection, tissue ischemia, tissue contusion, etc. For instance, pain is first perceived when the skin is heated above 45_oC which is the temperature at which the tissues begin to be damaged by heat.

One of the causes of pain ischemia is accumulation of lactic acid, in muscle spasm-stimulation of mechanoreceptive pain receptors and compression of the blood vessels which causes ischemia.

Two separate pathways transmit pain signals into the central nervous system and they correspond to the two different types of pain: a fast-sharp pain pathways (Aᴅ fibers, at velocities 60-30 m/sec) and a slow – chronic pain pathway (C fibers, at velocities 0.5-2m/sec).Therefore, a sudden onset of painful stimulation gives a double pain sensation- a fast-sharp pain followed a second or so later by a slow, burning pain.

The fast-sharp type of pain can be localized much more exactly in the different parts of the body than can slow-chronic pain. But when only pain receptors are stimulated without simultaneously stimulating tactile receptors, even fast pain is poorly localized (within 10 centimeters of the stimulated area). When tactile receptors are also stimulated, the localization

can be very exact.

Where the type C fibers synapse in the dorsal horns of the spinal cord, they release substanse P as the transmitter. As all neuropeptides, this is also slow to build up at the synapse and slow to be destroyed. This may explain the progressive increase in intensity of slow-chronic pain with time and its persistence even after the painful stimulus has been removed.

Localization of pain transmitted in the slow-chronic pathway is very poor (frequently to one limb but not to a detailed point on the limb). This is in keeping with the multisynaptic diffuse connectivity to brain and explains why patient frequently have serious difficulty in localizing the cause of some chronic types of pain.

After the complete removal of the somatic sensory areas of the cerebral cortex one's ability to perceive pain is not destroyed. This means that pain impulses entering the reticular formation, thalamus and other lower centers can cause conscious perception of pain. Nevertheless, the cerebral cortex plays an important role in interpreting the quality of pain.

The areas, where the slow-suffering type of pain pathway terminates (brain stem reticular areas and intralaminar nuclei of thalamus) are parts of the brain's principal arousal system and their stimulation has a strong arousal effect on the nervous activity throughout the brain. That is why a person with severe pain is often strongly aroused and cannot sleep.

The degree to which each person reacts to pain depends partly on the ability of the brain itself to control the degree of input of pain signals to the nervous system called an analgesia system. This system consists of the following three major components:

1) the periaqueductal grey area of the mesencephalon and upper pons surrounding the aqueduct of Sylvius, whose neurons send their signals to the next component;
2) the raphe magnus nucleus- a thin midline nucleus located in the lower pons and upper medulla from which the signals are transmitted down to the dorso-lateral columns in the spinal cord to the next component;
3) a pain inhibitory complex located in the dorsal horns of the spinal cord where the analgesia signals can block the pain before it is relayed on to the brain.

Electric stimulation in the periaqueductal grey area or in the rapthe magnus nuclear can almost completely suppress many very strong pain signals entering by way of the dorsal spinal roots. Stimulation of areas at still higher levels of the brain which excite the periaqueductal grey area (especially periventricular nuclei and medial forebrain bundle in hypothalamus) also can suppress pain (not quite so much).

Some different transmitter substances (especially enkephalin and serotonin) are involved in the analgesia system. Serotonin acts on set of local spinal cord neurons which secrete enkephalin. Enkephalin causes presypnaptic inhibition of both incoming type C and type A$_\Delta$ pain fibers where they synapse in the dorsal horns.

Injection of extremely minute quantities of morphine into some areas of the central nervous system causes an extreme degree of analgesia. Multiple areas of the brain, especially the areas in the analgesia system, have opiate receptors. Among the more important of the opiate substances are endorphins and enkephalins.

Stimulation of large sensory fibers from the peripheral tactile receptors depresses the transmission of pain signals (local lateral inhibition). This explains why rubbing the skin painful areas, liniments, acupuncture are effective in relieving pain.

Frequently pain may be localized in the part of the body considerably removed from the tissues causing the pain. This is called referred pain. For instance, during an attack of angina pectoris (spasm of the coronary vessels of the heart) painful sensations arise not only in the region of the heart but frequently in the left arm and shoulder-blade, left half of the neck and heard. These pains may be even much more intense than those in the heart region. In diseases of the internal organs referred pains may also be felt in definite areas of the skin, known as Head's zones.

The mechanism of referred pains is the following. Branches of the visceral pain fibers synapse in the spinal cord with some of the neurons receiving pain fibers from the skin. When the visceral pain fibers are stimulated, pain signals from the viscera are conducted through some of the same neurons that conduct pain signals from the skin, and the person has the feeling that the sensation actually originate in the skin itself.

The viscera have sensory receptors for no other modalities of sensation besides pain. But highly localized damage to the viscera rarely causes severe pain. Surgeon can cut the gut entirely in two in a patient who is awake without causing significant pain. Also a few visceral areas (the parenchyma of the liver and the alveoli of the lungs) are almost entirely insensitive to pain of any type.

On the other hand, diffuse stimulation of pain nerve endings throughout a viscus causes severe pain. Ischemia caused by occluding the blood supply to a large area of gut can result extreme pain. Also, the liver capsule, bile ducts, the bronchi, the parietal pleura are extremely sensitive to pain.

Painful stimuli cause different reflex reactions in which many organs are involved. Most of changes in the organism during the reactions are connected with the excitation of sympathetic nervous system, increase in the secretion of catecholamines, corticosteroids, hormones of the neurohypophysis. All of these components play a role in the mobilization of the organism's forces that is necessary in stimulations threatening life, when there is tissue damage. In the pain reflexes the following changes are observed: increase of muscular tone, heart rate and respiration rate, constriction of vessels, rise of blood pressure, reduced secretion of urine, increased sweating, inhibition of the functions of the gastrointestinal tract, increase of blood sugar and intensified glycogen breakdown, dilation of the pupils and so on.

Adaptation of pain receptors is observed as follows. If a needle is inserted into the skin and kept there, the sensation of pain disappears. But any movement causes the pain.

However, a significant feature of pain receptors in many cases is the absence of essential adaptation.

Visceroceptors perceive various changes in the state of the internal organs and blood vessels and through the central nervous system (especially its vegetative part) ensure reflex regulation of all internal organs, the interrelation and coordination of their activity. The visceral analysers are important in the maintenance of homeostasis, formation of adaptive-defence reactions, in complex acts of behaviour.

Changes in the state of internal organs brought on by disease frequently cause changes in the patient's mood, general feeling and behaviour.

The receptors of the internal organs react specifically to numerous stimuli, that is, the adequate stimuli for separate receptors are changes in pressure, mechanical stimuli, chemical agents (circulating in blood or being formed as a result of metabolism) changes in temperature, etc. Consequently, there are pressoreceptors, mechanoreceptors, chemoreceptors, thermal receptors in the internal organs and vessels.

The physiological role of visceroceptors consists in regulating the functions of the internal organs: Hering-Breuer reflex (self-regulation of breath),the reflexes from the presso- and chemoreceptors in the carotid sinus and carotid body, the reflex secretion of gastric juice,the reflex acts of urination and defecation, reflex coughing and vomiting, etc.

Stimulation of certain visceroreceptors arouse a particular conscious sensation (urge to urinate or defecate produced by distension of the walls of the urinary bladder or rectum). Thanks to visceroceptive impulses the sensations reflecting the condition of organism as a whole (hunger, thirst) occur.

Impulses arriving from the visceroceptors of many internal organs (heart, liver, kidneys, spleen, uterus, etc.) and blood vessels usually do not produce conscious sensations,but in certain pathological processes they may irradiate widely in the central nervous system and cause

uncertain ("vague") sensations,often accompanied by severe pains. The serous membranes have a very pronounced sensitivity and their stimulation is extremely painful.

Research of cortico-visceral interrelations revealed that different conditioned reflexes can be elaborated upon stimulation of interoceptors. This indicates the possibility of cortical analysis of interoceptive signals.

The feedback of information from each muscle to the nervous system, which is necessary for proper control of muscle function, is provided by two special types of sensory receptors (proprioceptors):

1) muscle spindles, which are distributed throughout the belly of the muscle and are excited when the muscle is stretched or relaxed;

2) Golgi organs which are in the muscle tendons and are excited when the muscle is contracted.

Existence of receptors reacting both to elongation (extension and relaxation) and contraction of the muscle fibers is very important to maintain the muscular tone on normal level.

Each spindle is built of 3-12 small intrafusal muscle fibers that are pointed at their ends and are attached to the glycocalix of the surrounding extrafusal skeletal muscle fibers. Each intrafusal fiber is a very small skeletal muscle fiber, the central region of which has almost no actin and myosin filaments. So, this central portion (nuclear bag) does not contract when the ends do, and it functions as a sensory receptor. The end portions are excited by the small gamma motor nerve fibers originating from the gamma motor neurons of the spinal cord which are called gamma efferent fibers.

The nuclear bag contains receptors, which are spiral-shaped endings of thick afferent nerve fibers (the primary and the secondary endings). When a muscle is stretched or relaxed, the muscle spindles are also stretched, the receptors of the nuclear bag are excited and send signals to the central nervous system, finally causing the muscle to contract. When the muscle is contracted, the tension of spindles is reduced and the impulses cease. Gamma-efferent nerve fibers regulate the degree of contraction of spindle elements and maintain their tone.

The Golgi tendon organ is an encapsulated receptor through which a small bundle of muscle tendon fibers pass immediately beyond their point of fusion with the muscle fibers. 10-15 muscle fibers are connected with each Golgi tendon organ and it is stimulated by the tension produced by this small bundle of muscle fibers.

When the Golgi tendon organs are stimulated by increased muscle tension, signals transmitted into the spinal cord cause inhibitory reflex effects in the respective muscles. So, Golgi tendon organ provides a negative feedback mechanism that prevents the development of too much tension on the muscle.

Thus, the muscle spindle detects changes in muscle length, whereas the Golgi tendon organ detects those in muscle tension.

The vestibular apparatus which ensures transmitting and analyzing information about the acceleration and deceleration arising in the process of lenear or rotatory movements of the head, plays a leading role in the spatial orientation of the body. It detects sensations of equilibrium. The impulses conducted to the central nervous system from the receptors of the vestibular apparatus give rise to the reflexes required to ensure body equilibration. They cause complex of coordinated tonic contractions of the skeletal musculature (redistribution of their tone) that keep the body upright and maintain its balance. Under conditions of rest vistibular analyzer receptors remain unexcited.

The vestibular apparatus is composed of a system of bony tubes and chambers in the petrous parts of the temporal bone called the bonny labyrinth and within this a system of membranous labyrinth. The labyrinth is composed of three semicircular canals (ducts), vestibulum (consisting of utricle and saccule) and cochlea. The semicircular canals, saccule and utricle are parts of the equilibrium mechanism, whereas the cochlea is the major sensory area of hearing.

The small space between the bone and the membranous labyrinth is filled with perilymph,

inside the membranous labyrinth is endolymph. The vestibular sacs contain the otolith apparatus, that is, accumulation of the receptor cells, lying on the raised spots (macula sacculi and macula utriculi).

The macula of utricle lies in the horizontal plane and the macula of the saccule in a vertical plane. The first plays an important role in determining the normal orientation of the head with respect to the direction of gravitational or acceleratory forces when a person is upright and latter- in equilibrium when the person is lying down.

Each macula is covered by a gelatinous layer in which otoliths or statoconia (small calcium carbonate crystals) are imbedded. Also in the macula are thousands of hair cells projecting cilia up into the gelatinous layer. The bases and sides of the hair cells synapse with sensory endings of the vestibular nerve.

Each hair cell has one very large cilium (kinocilium) and 50-70 small cilia (stereocilia) which become progressively shorter toward the other side of the cell. Their tips are connected with very minute filamentous attachments. When the brush pile of stereocilia and kinocilium is bent in the direction of kinocilium, several hundred channels in each cilium membrane open for conducting positive sodium ions which pouring into the cell cause depolarization. Bending the pile of cilia away from the kinicilium reduces the tension on the attachment, and this closes the ion channels causing hyperpolarization.

So, as the orientation of the head in space changes and the weight of the otoliths bends the cilia, appropriate signals are transmitted to the brain to control equilibrium.

A different pattern of excitation occurs in the nerve fibers from the macula for each position of the head. Because the hair cells in each macula are oriented in different directions so that some of them are stimulated when the head bends forward, some-when it bends backward, others-when it bends to one side, etc. This pattern apprises the brain of the head's orientation.

The three (anterior, posterior and horizontal) semicircular ducts are arranged at right angles to each other so that they represent all three planes in space.

In the semicircular ducts the receptor cells are located only in the ampullae, and they form cristae ampullaris. Their cilia can be bent by movement of the endolymph in the canals, during rotation of the head.

So, adequate stimuli for the vestibular apparatus are accelerated or retarded direct and rotatory movements of the head, that is regular movement without change of speed does not stimulate the receptors of the vestibular apparatus.

The otolith apparatus is stimulated by accelerating and decelerating direct movements of the head, by its jolting, pitch and roll or tilting. It perceives acceleration in direct movement equal to 2-20cm/sec_2. This is difference threshold of acceleration. The differrence threshold of inclination of the head is about 1_o to the side and $1.5-2_o$ forward or back.

Concomitant stimulations considerably increase this threshold. For instance, vibration in an aircraft raises the threshold to 5 $_o$ in forward or backward inclination and to 10 $_o$ in lateral inclination.

The receptors of the semicircular canals are stimulated by accelerated and decelerated rotatory movements in any plane. The receptors of the canal lying in the same plane as the direction of rotation are stimulated more than the others. The difference threshold of rotation is equal to 2-3 $_o$ per sec_2 of angular acceleration.

Stimulation of the vestibular apparatus causes vestibulo-motor reflexes, vestibulo-sensory reactions and vestibulo-vegetative reflexes. Stimulation of the vestibular apparatus by rotation of the body causes nystagmus of the eyes and head. Stimulation of the vestibular apparatus by movements of the body or head brings about redistribution of the tone of the skeletal musculature and triggers off tonic reflexes. These reactions of the skeletal musculate are called vestibulo-motor reflexes. Vestibulo-sensory reactions are observed particularly during the stimulation of the vestibular receptors with a heightened excitability. These consist of

characteristic sensations of dizziness which is a peculiar disturbance of orientation in the surroundings attended with an illusion of rotation of the surrounding objects.

Vestibulo-vegetative reflexes manifest themselves in changes of cardiac rhythm, constriction or dilation of vessels, decline of the arterial pressure, intensified movements of the stomach and intensive vomiting, etc.

Since excitability of the vegetative reflex centers is lower than that of motor ones, in healthy people vestibulo-vegetative reflexes are aroused by stronger stimuli than vestibulo-motor reflexes. But in some diseases vestibulo-vegetative reflexes are excited by weak stimulation, and this render certain subjects unfit for service in the navy, air force or transport system.

Subjects with heightened excitability of the vestibular apparatus and of the nerve centers connected with it, easily develop a pathological state known as seasickness. Its characteristic symptoms are: pallor of the face, cold perspiration of the forehead, dizziness and nausea followed by disorders of body balance, increased salivation, quickened breathing, fall of arterial pressure, accelerated or decelerated heart beat, vomiting. Severe cases show a general depression of the central nervous system.

After unilateral extirpation of the labyrinth tilting of the head to the operated side is observed (due to the stimulation of the receptors of the opposite side). This causes redistribution of muscular tone resulted from the stimulation of the proprioceptors of the cervical muscles: the tone of the extensor muscles of the extremity on the side operated upon and that of the flexor muscles on the opposite side, is increased; forcible rotatory movements occur and the body falls to the operated side.

Unilaterial damage to the labyrinth causes more severe disorders than bilateral damage. By spinning guinea-pigs in a centrifuge at 1000 r.p.m. isolated destruction of the otolith apparatus has been achieved. Then reactions to acceleration of direct movement were absent, whereas reactions to angular acceleration depending on the receptors of the semicircular canals were retained. After destruction of the horizontal canals in an animal, it moves its head incessantly and helplessly from side to side. After destruction of other canals the head is moved in the corresponding plane. As a result of destruction of all canals the animal is completely unable to make any movements or maintain its balance in the early period after operation.

Lecture 44

Tactile and Thermal Sensation. Sense of Smell.
Sense of Taste. Sense of Hearing

Tactile receptors are located on the surface of the skin. Numerous nerve endings, which respond to touch, pressure, vibration, heat, cold and to painful stimulation, are concentrated on the enormous (1,4 -2,1 m₂) receptor surface of the sensory skin. The skin of fingers, palms, soles, lips, genitals possesses the greatest number of nerve endings.

Touch, pressure and vibration are detected by the same types of receptors. But touch sensation results from stimulation of tactile receptors in the skin or in tissues immediately beneath the skin, pressure sensation - from deformation of deeper tissues, vibration sensation – from rapidly repetitive sensory signals.

A different character of skin sensation is based on the differences in the spatial and temporal distribution of impulses in afferent fibers excited in various types of stimulation of skin.

Skin receptors get excited in the following way. As a result of deformation of the receptor membrane, caused by a mechanical stimulus, its permeability to sodium ions grows and this leads to the generation of receptor potential. When the receptor potential reaches a critical level of depolarization, impulses are generated which spread along a nerve fiber to the central nervous system.

At least six various types of tactile receptors are known, but many more similar to these also exist.

1. Some free nerve endings everywhere in skin and many other tissues can detect touch and pressure.

2. Meissner's corpuscles - are elongated encapsulated nerve endings. These receptors are present in the nonhairy parts of the skin and are abundant in the fingertips, lips and other areas of the skin where the ability to discern spatial characteristics of touch sensations is highly developed. They are particularly sensitive to movement of very light objects over the surface of the skin and to low frequency vibration.

3. The fingertips and other areas contain also large numbers of expanded tip tactile receptors, one type of which is Merkel's discs. The hairy parts of the skin contain moderate numbers of expanded tip receptors. Merkel's discs are often grouped together as a single receptor organ called Iggo dome receptor. Merkel's discs along with Meissner's corpuscles play important roles in localizing touch sensation to the specific surface areas of the body and determining the texture of what is felt.

4. Each hair and its basal nerve fiber (the hair end organ) is also a touch receptor detecting movement of objects on the surface of the body or initial contact with the body.

5. Ruffini's end - organs are multibranched, encapsulated endings located in the deeper tissues, also in joint capsules. Adapting very little, they provide heavy and continuous touch and pressure signals and help signal the degree of joint rotation.

6. Pacinian corpuscles lying immediately beneath the skin and deep in the fascial tissues of the body, are stimulated only by very rapid movement of the tissues. Because they adapt in a few hundredth of a second. Therefore, they are important for detecting tissue vibration or other extremely rapid changes in the mechanical state of the tissues.

The tactile receptors are capable of quick adaptation. The most rapidly adapting are the tactile receptors locating in hair follicles and lamellated Vater- Pacini corpuscles. The capsule of a corpuscle plays the major role in adaptation. Its removal causes decrease in the adaptation process as a result of prolonged receptor potential. Owing to adaptation of mechanoreceptors, people do not feel constant pressure of their clothes or can wear contact lenses on the cornea.

A sensation of touch and pressure can be localized rather accurately, that is, a subject can establish to what part of the skin they are applied. The ability to localize the tactile sensation is developed through experience under the guidance of other sense organs (vision, proprioception). For instance, in Aristotle's famous experiment touching a small ball with acrossed index and third fingers gives a sensation like touching two balls, since in ordinary experience only two balls can be touched simultaneously with the inner side of the index finger and the outer side of the third finger.

Tactile sensibility is measured by means of Frey's esthesiometer, by which the pressure required to stimulate receptors and induce a sensation is measured. The tactile sensibility threshold varies from 50 milligrammes (in the most sensitive areas such as lips, nose tongue) to 10 grammes (in the least sensitive areas, such as back, sole of the foot, abdomen).

Simultaneous touching of two points on the skin does not always produce two separate sensations. If the points are very close together they are felt as one. The least distance at which two stimulated points on the skin can be perceived distinctly apart, is called the double-point (two – point) threshold and is measured by means of dividers or Weber's esthesiometer (which is pair of dividers with a scale indicating the distance between the legs in millimetres). The double –point threshold of spatial differentiation varies from 0,5 –2,5 mm (on tongue, finger tips, lips) to 60 mm (on the skin of the back, thigh, shoulder).

Double –point thresholds depend on the size of skin receptive fields and degree of their overlapping.

The information about the environmental temperature receptors is necessary for the processes of regulating body temperature. The thermoreceptors are located in the skin, cornea, mucous membranes, as well as in the central nervous system (hypothalamus).

Thermal gradations (freezing cold, cold, cool, indifferent, warm, hot, burning hot) are discriminated by at least three different types of sensory receptors : the cold receptors (presumably Ruffini's end organs), the warmth receptors (presumably Krause's end - bulbs) and pain receptors. The pain receptors are stimulated only by extreme degrees of heat or cold and are responsible (along with the cold and warmth receptors) for "freezing cold'' and "burning hot" sensations.

In most areas of the body there are 3 –10 times more cold receptors than warmth receptors. The total number of cold points on the whole surface of the human body is about 250 thousands, but of warmth points only 30 thousands. Also, the warmth receptors lie deeper (0,3mm) than cold receptors (0,17 mm). Therefore, the reaction time to cold is shorter than to warmth. Besides, warmth may induce paradoxical sensation of cold. For instance, application of a thin heated silver plate to the skin causes a sensation of cold, or a person in the first moment of taking a hot bath feels acute cold.

The temperature contrast is observed in the following way. Right hand is kept in water heated to 30_0C and left hand in that of heated to 20_0 C. Then both hands are put into the water heated to 25_0 C. The right hand would feel cold and the left hand –warmth.

In addition to ability to respond to steady states of temperature, the thermal recaptors respond markedly to changes in temperature. That is, when the temperature of the skin is actively falling or rising, a person feels much colder or warmer than he would at the same temperature if it was constant.

Adaptation of thermal receptors is observed when a hand (or leg) is put into hot water. After a short time the person ceases to feel a burning hot, if he does not move his hand (leg). But

the slighest movement causes the same burning hot sensation.

Smell and taste are ''chemical senses'' which allow to separate undesirable or even lethal foods from those that are nutritious. The sense of smell allows animals to recognize the proximity of other animals (even individuals amond animals). Both smell and taste are strongly tied to primitive emotional and behavioural functions of nervous system.

The olfactory receptors are located in the upper part of the nasal cavity, under the lamina perforata of the ethmoid bone. In each nostril the olfactory membrane has a surface area of approximately 2.4 square centimeters.

Since this area lies at a distance from the main respiratory tract, inhaled air reaches it by diffusion (slowly) or by means of vertical movements (quickly) during sniffing or smelling (short, rapid inhalations through the nose when the nostrils are widened).

The organ of smell is exceedingly sensitive ; in animals (especially in dogs) the sense of smell is even more acute. Eight molecules of mercaptan are sufficient for the threshold stimulation of one olfactory cell in man; threshold air concenration for trinitrobutyltoluene is 5 x10-6mg/m₃. Methyl mercaptan is mixed with natural gas to give the gas an odour that can be detected when it leaks from a gas pipe.

The total number of olfactory receptors (or cells) in man is 10 millions (in dog – 125 millions). These are bipolar neurons. A large number of fine cilia (outgrowths) on the surface of each olfactory cell greatly increase the area of contact between an odoriferious substance and the receptor (the surface area of the cilia is 100-150 times larger than that of the olfactory zone). It is these cilia that react to odours in the air and then stimulate the olfactory cells.

Odorant binding proteins contained in the membranes of the cilia can bind with different odorant substances, and this binding is the necessary stimulus for exciting the olfactory cells. Two different theories have been proposed for the mechanism of excitation:
1.	The molecules of the odorant binding proteins themselves open up to become ion channels when the odorant binds, allowing mainly large numbers of positively charged sodium ions to flow to the interior of the olfactory cell and depolarize it.
2.	The odorant binding protein acts via c AMP which opens ion channels through other membrane proteins.

Several physical factors affect the degree of stimulation: only volatile substances that can be sniffed into the nostrils can be smelled; to pass through the mucus and reach the olfactory cells the stimulating substance must be at least slightly water soluble; it must be also at least slightly lipid soluble because the lipid constituents of the cell membrane repel odorants from the membrane receptor proteins.

The intensity of the olfactory sensation depends on the chemical structure, concentration of the odoriferous substance in the air, the rate of its passage through the nose, as well as the physiological condition of receptor.

At the beginning of the odoriferous substance's action the sensation of smell is the strongest. Thanks to rapid adaptation of the receptors, later the sensation weakens. That is why a person staying in a room with a high concentration of an odoriferous substance in the air ceases to smell it after a time.

The great number of smell sensations are subserved by a few rather discrete primary sensations. But only minor success has been achieved in classifying the primary sensations of smell. On the basis of psychological tests and action potential studies from various points in the olfactory nerve pathways, it has been postulated that about seven different primary classes of olfactory stimulants preferentially excite separate olfactory cells : camphoraceous, musky, floral, pepperminty, ethereal, pungent, putrid.

The whole variety of olfactory sensations is due to the fact that these primary olfactory stimulants stimulate different groups of receptors in different combinations.

But there may be as many as 50 or more primary sensations of smell. Because persons

have been found who have odour blindness for single substances; and such discrete odour blindness has been identified for more than 50 different substances.

Smell has the affective qualities of pleasantness or unpleasantness. Therefore, it is important in the selection of food. A person that has previously eaten unpleasant food, is frequently nauseated even by the smell of the same food. In some animals odours are also the primary excitants of sexual drive.

As for olfactory pathways, entering the brain (at the junction between the mesencephalon and cerebrum) the olfactory tract divides into two pathways, passing into the medial and lateral olfactory areas.

The medial olfactory area (the very old olfactory system) consists of group of nuclei located in the midbasal portions of the brain anterior and superior to the hypothalamus. The lateral olfactory area (the old olfactory system) is composed mainly of the prepyriform, pyriform cortex and cortical portion of the amygdaloid nuclei. This is the only area of the entire cerebral cortex where sensory signals pass directly to the cortex without passing through thalamus.

But still a newer olfactory pathway has been found which does indeed pass through the thalamus, passing to the dorso – medial thalamic nucleus and thence to the lateroposterior quadrant of the orbitofrontal cortex. This newer system probably helps especially in the conscious analysis of odour.

So, there are: 1) a very old olfactory system subserving the basic olfactory reflexes ; 2) an old system providing automatic but learned control of food intake and aversion to toxic and unhealthy foods; 3) a newer system that is comparable to most of the other cortical sensory systems and is used for conscious perception of olfaction.

The gustatory (taste) receptors or taste buds supply information about the character of substances entering the mouth, and sense of taste allows a person to select food in accord with his desires and needs of tissues of his organism for specific nutritive substances. Stimulation of taste receptors excites numerous unconditioned reflexes exciting activity of the digestive organs.

Although taste is a function of the taste buds in the mouth, but one's sense of smell also contributes strongly to taste perception. Also, the texture of food (detected by tactual senses of the mouth) and the presence in the food of substances stimulating pain endings (pepper), greatly condition the taste experience.

Psychophysiological and neurophysiological studies had identified at least 13 chemical receptors in the taste cells which were collected into 4 general categories of the primary sensations of taste: sour, salty, sweet and bitter. Hundreds of different tastes are various combinations of the elementary sensations. The sour taste is caused by acids, and its intensivity is approximately proportional to the logarithm of the hydrogen ion concentration. The salty taste is elicited by ionized salts. The cations of the salts are mainly responsible for the salty taste, but the anions contribute to a lesser extent. The sweet taste and the bitter taste are not caused by any single class of chemicals. The substances that give these tastes are almost entirely organic substances.

Some types of chemicals causing the sweet taste are: sugars, glycols, alcohols, aldehydes, ketones, amides, esters, amino acids, sulfonic acids, halogenated acids, inorganic salts of lead and beryllium. Very slight changes in the chemical structure (addition of a simple radical) can often change the substance from sweet to bitter.

The bitter taste is caused by two particular classes of substances: long chain organic substances containing nitrogen and alkaloids (quinine, caffeine, strychnine, nicotine). Some substances (saccharin) that at first taste sweet have a bitter aftertaste which makes them objectionable to some people.

An important purposive function of the bitter taste sensation is that it causes the individual to reject the food (many of the deadly toxins found in poisonous plants are alkaloids, which all cause intensely bitter taste).

The taste buds are located in the papillae of the tongue, posterior wall of the pharynx, the soft palate, the tonsils, the epiglottis. They are the numerous at the tip, sides and rear of the tongue, but are not present in the middle and on the lower surface of the tongue. The sweet and salty tastes are located mainly on the tip of the tongue, the bitter taste on the posterior tongue and soft palate, the sour taste on the two lateral sides of the tongue.

Adults have about 10000 taste buds, and children a few more. Beyond the age of 45 years taste buds rapidly degenerate, and the taste sensation becomes progressively less critical.

The taste bud is composed of about 40 modified epithelial cells, some of which are supporting cells and others are taste cells. From the tip of each taste cell several microvilli or taste hairs protrude outward to approach the cavity of the mouth. These microvilli provide the receptor surface for taste.

Most of taste buds can be excited by two, three four of the primary taste stimuli as well as by a few other taste stimuli that do not fit into the primary categories. But usually one or two of the taste categories predominate.

The absolute threshold of taste sensitivity to various substances in different subjects differ widely up to "taste blindness" to separate agents (for instance, creatin). They depend on the body's condition and are changed during starvation, pregnancy and other conditions.

Taste receptors reveal a clearly defined adaptation to a particular taste, for instance to stimuli causing only a bitter or a sweet taste. Adaptation to sweet and salty substances develops more quickly than to bitter and sour ones. Cross- adaptation has been revealed, that is, changes in sensitivity to one substance under the action of another one.

The phenomena of taste contrast and taste mixture have been established. Taste contrast is sharpened perception of any one taste under the influence of another gustatory stimulus (heightened perception of acid due to a stimulus causing a sweet taste). Taste mixture is perception of a new taste during the simultaneous action of two or three stimuli that is unlike any of its compounds.

During evolution taste underwent development as a mechanism for the choice or rejection of food. Taste sensations are combined with olfactory, tactile and thermal sensations also produced by food. Preference to any food is partly based on the congenital mechanisms but for the main part on the mechanisms that were elaborated in ontogenesis by the way of conditioned reflexes.

With the appearance of articulate speech in man hearing plays an exceptional role, and the auditory analyzer is the second (after visual analyzer) in importance distance analyzer.

The perceiving part of the auditory analyzer (Corti's organ)is situated in the internal ear. But sound vibrations are transmitted to the acoustic receptors through a whole system of formations in the external ear and middle ear.

The external auditory meatus transmits sound vibrations to the tympanic membrane (eardrum) which separates the external ear from the middle ear.

Any sound coming from the side reaches one ear a few fractions of a millisecond earlier than the other, and so binaural (with both ears) hearing enables man to detect the point where the source of sound is located with an accuracy of the order of one angular degree. Besides, the ear on the side opposite to the source of the sound perceives a sound of reduced intensity. A person deaf in one ear can determine the direction of sound only by turning his head. Under the action of sound waves passing through the external auditory meatus, the tympanic membrane begins to vibrate. As a consequence of its irregular shape (a funnel pressed inwards) and unequal tension (it is woven of fibers passing in various directions) in its different parts the membrane does not have its own vibration period but reacts to any sound according to the wave length of the latter.

The ossicular system conducts sound through the middle ear. Attached to the very center of the tympanic membrane is the handle of the malleus (hammer). At its other end the malleus is tightly bound to the incus, the opposite end of which articulates with the stem of the stapes. The

faceplate of the stapes lies against the membranous labyrinth in the opening of the oval window where sound waves are conducted into the inner ear, the cochlear.

So, the vibrations of the tympanic membrane are transmitted to the longer arm of the lever formed by the handle of malleus and the process of the incus so that the stapes receives them reduced in amplitude but increased in intensity.

The surface of stapes adjoining the membrane of the oval window is 3.2 mm^2, and the area of the tympanic membrane is 70 mm^2. Thus, the faceplate causes about 22 times as much pressure on the fluid of the cochlea as is exerted by the sound wave against the tympanic membrane.

This enables the relatively weak sound waves striking the tympanic membrane to overcome the resistance of the membrane of the oval window and set in motion the layer of fluid (perilymph and endolymph) in the cochlea.

Thus, sound vibrations propagated in the air are transmitted to the oval window through the ossicles and transformed into vibrations of a fluid - the endolymph.

In the wall separating the middle ear from the internal ear, there is also round window. Vibrations of the cochlear endolymph arising at the oval window pass through the channels of the cochlea and reach the round window undamped. Without this aperture vibrations would be impossible because of the incompressibility of liquid.

Two muscles in the middle ear (stapedius and tensor tympani muscles), whose degree of contraction varies with changes in the amplitude of sound vibrations, automatically regulate the amount of sound energy entering the internal ear through the ossicles so protecting it against excessive vibration and damage.

Since the inner ear (the cochlea) is embedded in a bony cavity in the temporal bone (bony labyrinth), vibrations of the entire skull can cause fluid vibrations in the cochlea itself. A tuning fork (or an electronic vibrator) placed on any bony protuberance of the skull (especially on the mastoid process) causes the person to hear the sound. However, the energy available even in very loud sound in the air is not sufficient to cause hearing through the bone (except when a special electromechanical sound – transmitting device is applied directly to the bone).

Besides the semicircular canals and vestibulum (parts of the vestibular apparatus), the labyrinth in the petrous portion of temporal bone contains the cochlea (internal ear), which is the perceiving part of the auditory analyzer.

The cochlea is a spiral, gradually expanding bony canal describing two and a half turns. Along its whole length it is divided by two membranes (vestibular or Reissner's membrane and basilar membrane) into upper (the scala vestibuli), middle (the scala media) and lower (the scala tympany) tubes coiled side by side. At the apex of the cochlea these membranes communicate and there is an opening,the helicotrema.

The upper and lower canals communicate through the helicotrema and form a kind of a common duct beginning at the oval window and ending at the round window, which is filled with perilymph. The perilymph has a composition resembling that of cerebrospinal fluid and is separated from the air –filled cavity of the middle ear by the membranes of the oval and round windows.

The cavity of membranous cochlear duct (scala media) does not communicate with those of other canals and is filled with endolymph. Endolymph differs from perilymph in having about 30 times as many potassium ions and only 5% as many sodium ions. This difference in composition causes the positive charge of the endolymph in relation to the perilymph.

Inside the cochlear duct, on the basilar membrane, the acoustic apparatus, Corti's organ is located, which transforms sound vibrations into nervous excitation.

Sound vibrations are transmitted by the stapes to the membrane of the oval window and cause vibrations of the perilymph in the lower canal through the helicotrema in the region of the cochlear apex and reach the round window. But vibrations may also be transmitted from the

perilymph in the upper canal to that in the lower canal across the vestibular membrane, endolymph of the cochlear duct and the basilar membrane.

The vestibular membrane is very thin, and the fluids in the upper and middle canals vibrate in such a way as if they were not divided by the membrane.

Low frequency vibrations are transmitted from upper canal to the lower throughout all the length of the basilar membrane and through the helicotrema. During the action of high frequency sound vibrations the vibratory process involves not the whole column of the fluid in the canals but only the part closest to the oval window (at the beginning of the cochlear ducts). Higher the frequency of the vibrations, shorter the column of fluid involved, and closer to the oval window is the part of the basilar membrane through which vibrations are transmitted from the scala vestibuli to the scala tympani.

The Corti's organ is the receptor organ that generates nerve impulses in response to vibration of the basilar membrane. The actual sensory receptors in the organ of Corti are two types of hair cells: a single row of internal hair cells, numbering about 3500 and 3-4 rows of external hair cells, numbering about 15000. The bases and sides of the hair cells synapse with a network of cochlear nerve endings.

Minute hairs or stereocilia project upward from the hair cells and are embedded in the surface gel coating of the tectorial membrane lying above them in the scala media. These hair cells are similar to those in the vestibular apparatus. Bending of the hairs in one direction depolarizes the hair cells and bending them in the opposite direction hyperpolarizes them. This in turn excites the nerve fibers synapsing with their bases.

Five different electrical phenomena are recorded from different parts of cochlea: the membrane potential of the acoustic receptor cell and the potential of the endolymph or the endocochlear potential are unconnected with the action of sound and are observed also in the absence of sound stimuli; the cochlear microphonic potential, the summating potential and the acoustic nerve potentials are caused by the influence of sound stimuli.

If electrodes are inserted into the cochlea and connected to an amplifier and loud-speaker, and then the sound stimulus is applied, the loud- speaker will accurately reproduce the sound. For instance, a phrase uttered by the experimenter into a cat's ear will be reproduced by a loud-speaker connected to electrodes inserted in the cochlea in another room.

The phenomenon is called the cochlear microphonic effect and recorded electrical potential- cochlear microphonic potential.

For a long time two theories were well-known explaining the mechanism of perceiving sounds of different pitch (various frequencies of vibration) :

1. Helmholtz's theory of resonance (1863)- the dence transverse fibers forming the basilar membrane vary in length (0,5mm at the base of the cochlea and 0,04mm at the apex). They are tensioned like the strings of a harp and have different proper frequency to which they are capable of resounding. Under the action of sound those fibers vibrate most that are "tuned" to that frequency.

2. Rutherford's telephonic theory (1880) - the wave frequency of potentials in the acoustic nerve during perception of sounds of various pitch corresponds to the frequencies of perceived sounds, as in a telephone line transmitting sounds from a telephone.

Certain concepts underlying both the resonance and the telephone theories have proved justified.

Resonance phenomena take place in the cochlea. However, the resonant substrate is not a definite fiber of the basilar membrane, but a fluid column of definite length. Higher the sound (greater the frequency of vibrations), shorter is the length of the vibrating column of fluid in the cochlear canals and the closer is the maximum amplitude of vibration to the base of the cochlear and the oval window. As a result, for each pitch there is a definite number of receptors in which excitation arises. So, a spatial coding of sound information takes place in the cochlea under the

action of tones of different pitch (sound vibrations of various frequencies).

At lower frequencies vibrations of the perilymph are transmitted through the helicotrema, and all acoustic cells are excited – spatial coding becomes impossible. But low – frequency vibrations are reproduced undistorted by the acoustic nerve fibers, and information about pitch can be transmitted at a corresponding frequency of impulses along the acoustic nerve,as occurs in the transmission of electrical waves of sound frequency over a telephone cable.

Thus, the major method used by the nervous system to detect different frequencies is the spatial principle, whereas low frequency sounds (20–4000c.p.s.) are discriminated by frequency principle.

The stimulus threshold of the internal and external layers of receptor cells in the organ of Corti are unequal. The internal receptor cells require a stimulus of greater strength to excite them. It may be that the correlation between the number of excited internal and external cells varies depending on the intensity of a sound stimulus, and in such a way information about the strength of sound stimuli is perceived.

Man perceives sounds within a frequency range of 16 – 20000 cycles per second corresponding to 10–11 octaves. Older people are often unable to hear high tones (chirping of a cricket). In many animals the upper limit of hearing is considerably higher. In dogs it is possible to develop conditioned reflexes to very high sounds (inaudible to man).

In the frequency range between 1000-3000c.p.s. the human ear has a maximum sensibility : a sound with an energy as low as $1 \times 10^{-9} erg/cm^2 x$ sec. is audible. Out of these limits the sensibility is much reduced. For example, to be audible at 20c.p.s. and at 20000c.p.s. the energy of a sound has to be 1erg/cm2xsec.

The intensity of a sound of constant pitch can be increased to the point where it produces a disagreeable sensation of pressure and even a pain in the ear (upper limit of hearing).

The loudness of sound is determined by the complex interaction of its parameters such as intensity and pitch of tone (frequency). The sensation of loudness is not strictly proportional to an increase in the sound intensity. The unit of sound intensity is the bel – the decimal logarithm of the ratio of the effective sound intensity (I) and the threshold intensity (Io). 0.1 bel is called 1decibel (dB). The maximum level of loudness when the sound causes pain is 130 – 140dB above the audibility threshold in man.

Acuity of hearing is accurately measured by means of sound generators, audiometers, which enable the pitch and intensity of sounds to be regulated. The hearing sense is judged from the patient's answers or his reactions, and even by observing the galvanic reflex of the skin.

The sense of hearing deteriorates under the prolonged effect of sounds of great intensity because of adaptation of the auditory apparatus. The degree of adaptation depends on the sound duration, intensity and frequency.

The mechanism of adaptation is connected with several factors. Contractions of stapedius and tensor tympani muscles can change the amount of sound energy transmitted to the cochlea. Besides the processes taking place in the central links of the auditory analyzer, the level of "tuning" of the receptor apparatus has a certain significance. It was found that stimulation of definite points in the reticular formation of the mesencephalon inhibits the electrical activity of the cochlear nucleus and the cerebral cortex caused by a sound stimulus of constant intensity (clicking).

Laboratory Studies

1. Determination of Tactile Sensitive Threshold

The equipment: Weber's esthesiometer. Bringing together the legs of the esthesiometer maximally (the distance between them –1mm) different areas of the skin (fingers, palms, nose,

neck, back) of the person sitting with closed eyes are touched by the instrument. The person perceives two stimulations as one. Then gradually the distance between legs is increased and in each area of the skin the distance between two points is determined when the person begins to perceive them as two.

2. Study of Gustatory Sense

The equipment : eye pipette, glass, 0.5% solution of citric acid or tartaric acid, sugar, leaves of Zizyphus Mill (jujuba ; unabi – from Rhamnaceae).

The solutions are by turns dropped on different parts of the tongue (tip, base, lateral surfaces) and the sensitivity to the sweetness, bitterness, sourness and saltness is determined. After the influence of every solution the mouth is gargled by water.

The person chews the leaves of unabi which temporarily decreases the gustatory sensation. Then the taste of the different solutions is determined again. The person does not feel the sweetness of the sugar.

3. Determination of Bone Conduction of Sound

The equipment: tuning fork, the rubber tube, cotton wool.

Sounding fork is put on the middle line of the head. The person hears the tune equally by both ears. Cotton wool is put in ear, after which this ear perceives the sound stronger.

Then another ear is connected to an ear of another person with the help of rubber tube. The second person also hears the tune.

Lecture 45

Vision

The visual analyzer is the most important sense organ which supplies the brain with 90% of the information passing from all receptors.

Optically the eye is equivalent to the usual photographic camera: it has a lens system, a variable aperture system (the pupil) and retina that corresponds to the film.

On the way to the retina light rays pass through several transparent refractive media: the anterior and posterior surfaces of the cornea, the aqueus humor, the crystalline lens, vitrous body. On the whole the refractive power of the human eye is 59D for viewing distant objects and 70.5D for near ones (one dioptre is the refractive power of a lens with a focal distance of 100cm).

If all the refractive surfaces of the eye are algebraically added together and then represented considered to be one single lens, the optics of the normal eye may be simplified and as a "reduced eye" model, which is useful in simple calculations.

Most of the refractive power of the eye is provided by the anterior surface of the cornea. Because the total refractive power of the crystalline lens of the eye (as it normally lies in the eye surrounded by fluid on each side) is about one-third the total refractive power of eye's lens system.

If the lens was removed from the eye and then surrounded by air its refractive power would be about six times as great. The importance of the crystalline lens is that its curvature can be increased markedly to provide accomodation.

For an object to be seen clearly the rays of light from each of its points must be focused on the retina.

The lens system of the eye focuses an image on the retina upside-down in exactly the same way that a glass lens can focus an image on a sheet of paper. But the brain is trained to consider an inverted image as the normal, and the mind perceives objects in the upright position.

Adjustment of the eye to clear vision of objects at different distances is called accomodation. Accomodotion is effected through a change in the convexity of the crystalline lens, and consequently in its refractive power. When near objects are viewed the lens becomes more convex.

In the mechanism of accomodation an essential role belongs to the ciliary muscles the contraction of which changes the convexity of the lens. Therefore, they are called the muscles of accomodation.

The lens is enclosed in a thin transparent capsule passing at its edges into the fibers of Zinn's ligament attached to the ciliary body. These fibers are always tensed and distend the capsule that compresses and flattens the lens. Contraction of ciliary muscles reduces the tension of Zinn's ligaments, that is, the pressure on the lens, which becomes more convex by its own elasticity.

The ciliary muscles are innervated by the parasympathetic fibers of the oculomotor nerve. That is why administration of atropine into the eye interferes with transmission of excitation to the ciliary muscles and limits accomodation of the eye to see near objects.

For a normal eye in a young subject the far point of distinct vision lies in infinity, and the near point- at a distance of 10cm from the eye. This means that he can see distant objects without

any strain of accomodation, and cannot see clearly objects nearer than 10cm even with maximum contraction of the ciliary muscle, that is, at the great effort of accomodation.

So, emmetropic (normal) eye can see all distant objects clearly, with its ciliary muscle relaxed, but to focus object at close range it must contract its ciliary muscle providing various degrees of accomodation. This is called emmetropia.

As a person grows older, the lens becomes larger, thicker and less elastic, its ability to change shape progressively decreases. The power of accomodation decreases from approximately 14 diopters in the young child to less than 2 diopters at the age of 45-50 and to about zero at age 70. The lens is almost totally nonaccomodating. This is called presbyopia, that is, senile long- sightedness.

This condition is corrected by means of biconvex glasses. Since the eyes can no longer accommodate for both near and far vision, an older person must wear bifocal glasses with the upper segment normally focused for far seeng and the lower segment focused for near seeng.

There are two principal anomalies of light refraction in the eye, which are due, as a rule, not to defects in the refractive media but to abnormal length of the eyeball: hypermetropia or hyperopia (far-sightedness) and myopia (near-sightedness).

Hypermetropia is due mainly to an eyeball that is too short and occasionally to a lens system that is too weak. Parallel light rays from distant objects are not bent sufficiently by the lens system to come to a focus by the time they reach retina and converge behind it. A circle of diffused light, that is, an indistinct, blurred image of the object is formed on the retina. Therefore, hypermetropic persons strain the muscles of accomodation both when looking at near and distant objects. For reading they must wear biconvex glasses increasing the light ray refraction.

Myopia is usually due to too long an eyeball and occasionally to too much refractive power of the lens system of the eye. The light rays coming from distant objects are focused in front of the retina. The myopic person has no mechanism to focus distant objects sharply on his retina. But as an object comes nearer to his eyes, it finally comes near enough that its image will focus.

So, in a myopic person the far point of distinct vision is displaced from infinity to a definite (fairly near) distance. To see distant object clearly he must use concave lenses that diminish the refractive power of the lens so that the image is shifted to the retina.

Astigmatism is also refraction anomaly, caused by an oblong shape of the cornea or (rarely) an oblong shape of the lens. This leads to unequal refraction of light in different directions. Since all people are astigmatic to some degree, the condition should be attributed to structural imperfection of the eye as an optical instrument. Astigmatism is corrected by special cylindrical glasses.

Optical abnormalities may be corrected by use of contact lenses (glass or plastic) which are fitted snugly against the anterior surface of the cornea and held in place by a thin layer of tears that fills the space between the contact lens and the anterior eye surface. The tears have a refractive index almost equal to that of the cornea. Therefore, the contact lens nullifies almost entirely the refraction that normally occurs at the anterior surface of the cornea. Instead, the anterior surface of the contact lens now plays the major role and its posterior surface minor role. The contact lens gives a broarder field of clear vision than do usual glasses and has little effect on the size of the object that the person sees through the lens.

The pupil helps produce distinct images of the objects on the retiona, letting in only the central rays and preventing what is known as spherical aberration. Otherwise, circles of diffused light would form on the retina.

When light is shone into the eyes, the pupils constrict. This reaction is called the pupillary light reflex. If the eye is shut off from light and then opened to it, the pupil dilated in darkness, will quickly narrow by reflex action.

Stimulation of the sympathetic nerves excite the radial fibers of the iris and causes

pupillary dilatation (mydriasis), whereas stimulation of the parasympathetic nerves excites the pupillary sphincter muscle, decreasing the pupillary aperture (myosis).

Adrenalin causes dilatation of the pupils, acetylcholine and eserine contract it.

The pupils are also dilated in asphyxia (their dilation in deep narcosis is a warning that the narcosis must be reduced).

The pupils of both eyes are dilated or contracted simultaneously-when one eye is illuminated, the pupil of the other also contracts. This is called the consensual light reflex.

Anisocoria, that is, unequal diameters of the pupils, may result from an affection of the sympathetic nerve on one side (causing myosis), paralysis of n. oculomotorius or stimulation of n. sympathicus on one side (both causing mydriasis).

To examine the inner surface of the eye ophthalmoscope (eye mirror) is used. The eye that is examined is illuminated by rays of light reflected from a mirror. On their way back from the eye rays are concentrated by a biconvex lens; some of them pass through a small opening in the mirror and enter the observer's eye. The observer can see an inverted image of the ocular fundus between the lens and the mirror (he must fix his gaze on that point accomodating his eyes correspondingly).

The retina is the light- sensitive portion of the eye, containing photoreceptors-the cones that are responsible for colour vision and the rods that are mainly responsible for vision in the dark. When the photoreceptors are excited, signals are transmitted through successive neurons in the retina and finally into the optic nerve fibers and carebral cortex.

A minute area in the center of the retina, called the macula, is especially capable of acute and detailed vision. The central portion of the macula (fovea) is composed entirely of cones, and the cones have a special structure that aids their detection of detail in the visual image.

The point of entry of the optic nerve (the optic disc) contains no photoreceptors and is insensitive to light, forming the blind spot. The size of the blind spot varies depending on a number of physiological conditions (functional mobility).

The retina has a complex multilayer structure and is involved in analysis and processing of visual information. It can be considered as part of the brain transferred to the perifery.

The functional components of the retina arranged in layers from the outside to the inside are the following: 1)pigment layer, 2)layer of rods and cones projecting into the pigment, 3)outer lining membrane, 4)outer nuclear layer containing the cell bodies of the rods and cones, 5)outer plexiform layer, 6)inner nuclear layer, 7)inner plexiform layer, 8)ganglionic layer, 9)layer of optic nerve fibers, 10)inner limiting membrane.

Passing through the lens system of the eye and the vitreous humor, light enters the retina from the inside.

The outermost layer of the retina is formed of pigmented epithelium containing a black pigment (fuscin or melanin). Like the black coating of the inner walls of a camera, this pigment absorbs light (preventing its reflection and dispersion) which is important for clear vision.

The importance of melanin in the pigment layer is well illustrated by its absence in albinos (persons hereditarily lacking in melanin pigment in all parts of their bodies). When an albino enters a bright area, light that impinges on the retina is reflected in all directions by the unpigmented surfaces so that a single discrete spot of light that would normally excite only a few rods or cones is reflected everywhere and excites many of the receptors. Therefore, the visual acuity of albinos even with the best of optical correction is very low.

Some nocturnal animals have a light-reflecting layer between the photoreceptors and the pigment cells, and their eyes shine in the dark under external illumination.

The pigment layer stores large quantities of vitamin A which is exchanged through the membranes of the outer segments of the rods and cones. The pigment cells take part in the metabolism of the photoreceptors and in the synthesis of visual pigments.

Each photoreceptor (rod or cone) consists of four major functional segments: 1) the outer

(photosensitive) segment, 2) the inner segment, 3) the nucleus, 4) the synaptic body.

So, the photosensitive segments of photoreceptors containing visual pigment, face the side opposite to light.

The outer segment of each rod or cone comprises about 1000 discs. The light-sensitive photochemicals are incorporated into the membranes of the discs in the form of transmembrane proteins. In rods this is rhodopsin, and in cones-one of several "colour" photochemicals that function almost exactly the same as rhodopsin except for differences in spectral sensitivity.

Light produces the greatest stimulating effects when the direction of ray coincides with the long axis of a rod or cone, and a ray of light passing across a rod or cone excites the receptor considerably less. Because when a light ray is directed along the axis of the outer segment it passes successively through all the discs of the receptor. This phenomenon is called the directional effect of light rays (effect of ray direction).

The inner segment contains the usual cytoplasm of the cell with the usual cytoplasmic organelles. The mitochondria in this segment play an important role in providing the energy for function of the photoreceptors.

The synaptic body connects the photoreceptor with the next stage in the vision chain (subsequent neuronal cells, the horizontal and bipolar cells).

The human eye contains about 6-7 million cones and 110-125 million rods that are distributed irregularly over the retina. The fovea contains only cones, but toward the periphery of the retina the number of cones diminishes and the number of rods increases so that there are only rods at the periphery.

The cones function in bright illumination and perceive colours; the rods perceive light rays in conditions of twilight vision. This concept of the different functions of rods and cones underlies the duplex theory for which there is much evidence.

In nocturnal animals (owl, bat) the retina contains mostly rods, whereas in diurnal animals (pigeons, poultry, lizards) cones predominate.

Perception of various colours is more adequate when light stumuli acton the fovea centralis (where the cones are mostly located), and far periphery of the retina (which contains predominantly rods) does not perceive colour light.

The action of light rays of different wavelenght on the peripheral parts of retina gives rise to a sensation of colourless light, and man is colour blind in twilight ("all cats are grey in the dark").

Photosensitivity of the elements connected with cones is many times less than those of connected with rods. That is why in a dim light central cone vision is sharply diminished and peripheral rod vision predominates.

Lesion of the cones gives rise to photophobia, that is a person can see only in weak light and is blinded by bright illumination; achromasia, that is, total colour blindness, also develops.

A disturbance in the function of the rods causes nyctalopia (night- blindness), that is, the person is quite blind in the dark, although his vision is normal in daylight.

Inwardly to the layer of photoreceptor cells a layer of bipolar neurons is located to which a layer of ganglion nerve cells adjoins on the inside. The axons of ganglion cells make up fibers of the optic nerve.

In the synapses between bipolar and ganglion cells cholinesterase has been revealed which indicates that transmission of impulses from one cell to another is effected by means of acetylcholine. Both the rods and cones release glutamate, an excitatory transmitter, at their synapses with the bipolar and horizontal cells. There are many different types of amacrine cells secreting at least five different types of transmitter substances: GABA,glycine, dopamine, acetylcholine, indolamine. All of these normally function as inhibitory transmitters.

One bipolar neuron is connected with many rods, a few cones and one ganglion cell. For 130 million photoreceptor cells there are only 1250 thousand optic nerve fibers which are

processes of ganglion cells. So, impulses from numerous photoreceptors converge on the ganglion cell, which receives summated excitation arising in many photoreceptors.

The photoreceptors connected with a single ganglion cell form the receptive field of this cell. The receptive field of various ganglion cells partly overlap.

Horizontal and amacrine cells, whose processes connect bipolar and ganglion cells in the horizontal plane, ensure the interaction of adjacent neurons of the retina. The amacrine cells ensure the process of horizontal or lateral inhibition between the neighbouring elements.

The retina contains also efferent nerve fibers carrying impulses from the central nervous system to the retina, which act on the synapses between the retinal bipolar and ganglion cells.

Both the rods and cones contain chemicals that decompose on exposure to light and, in the process, excite the nerve fibers leading from the eye.

The rods contain the pigment rhodopsin (visual purple), the cones- iodopsin as well as chlorolabe, erythrolabe (the former absorbs rays corresponding to the green portion of the spectrum and the latter to the red one)and other pigments.

The light-sensitive chemicals in the cones have compositions only slightly different from that of rhodopsin, and the principles of photochemistry of rhodopsin can be almost exactly applied to that of cones.

Rhodopsin is a combination of the protein scotopsin and the carotenoid pigment (aldehyde of vitamin A) retinal (retinene), exactly 11-cis retinal (only this cis form can bind with scotopsin to synthesize rhodopsin). When light energy is absorbed by rhodopsin, it begins to decompose (within trillionths of a second), as a result of change of the cis form of retinal into an all-trans form, which has a different physical structure (though the same chemical structure). In this process certain intermediate substances (bathororhodopsin, lumirhodopsin, metharhodopsin I and II) are produced, after which retinal pulls away from scotopsin. It is the metarhodopsin II (activated rhodopsin) that excites electrical changes in the rods that then transmit the visual image into the central nervous system.

When the eyes are darkened, visual purple undergoes regeneration, that is, resynthesis of rhodopsin occurs. The first stage in reformation of rhodopsin is reconvert of the all-trans retinal into 11-cis retinal. This process is catalyzed by the enzyme retinal isomerase. The 11-cis retinal automatically recombines with the scotopsin to reform rhodopsin, which then remains stable until its decomposition is triggered again by absorption of light energy.

There is a second chemical route for conversion of all-trans retinal into 11-cis retinal in which vitamin A is necessary.

Treatment of the retina with an alum solution (its fixation) protects rhodopsin against further breakdown, so that the retina retains the image of the object last seen (optogram).

The only difference between the photochemicals in the cones and rods is that the protein portions -photopsin in the cones are different from the scotopsin of the rods. The retinal portion is the same in both types of photoreceptors. So, the colour –sensitive pigments of the cones are combinations of retinal and photopsins. Three different types of photochemicals in different cones make them blue senseitive, green-sensitive and red-sensitive.

Recording (from the eye or directly from the retina) of summated electric responses of the retina to the action of a light stimulus is called the electroretinogram (ERG). In ERG a, b, c, and d waves are distinguished. The a-wave reflects excitation of the external segments of photoreceptors ; the b-wave arises in the external nuclear layer, and the c-wave –in the pigmented layer. The c-wave is associated with rod vision. The d-wave reflects reactions occurring in the retina after the switching-off the illumination.

The slow variations of electrical potential recorded as an electroretinogram are accompanied with the appearance of action potentials in the ganglion cells of the retina, where the fibers of the optic nerve take their origin.

Movements of the eyes are very significant in looking at stationary or moving, near or

distant objects. The most important movements of the eye are those that cause them to "fix' on a discrete portion of the field of vision.

Two different neuronal mechanisms control fixation movements of the eyes:

1) voluntary fixation mechanism-allows the person to move his eyes to find the object upon which he wishes to fix his vision;

2) involuntary fixation mechanism-holds the eyes firmly on the object once it has been found.

The human eye can turn about any axis passing through its center of rotation lying about 1.3mm behind the center of eye. From its initial position of looking straight ahead the eye can turn outward by $42°$, inward by $45°$, upward by $54°$ and downward by $57°$.

The movements of eyes are performed by means of its six muscles. The eyes are moved simultaneously and concomitantly, that is, the visual axes of both eyes are always directed to one and the same object. When nearer or more distant objects are viewed the visual axes converge or diverge respectively.

For the continuous perception of visual information movement of the retinal image is necessary. Impulses arise in the optic nerve only at the moment when the light image is switched on or off. During the continual action of light on a visual receptor impulses quickly cease in the appropriate fibers of the optic nerve. When the eye and objects are immobilized, visual sensation disappears.

In looking at any object the eyes make incessant imperceptible jumps. Therefore, the retinal image is continually displaced from one point to another, stimulating new photoreceptors and eliciting new impulses in the ganglion cells and nerve fibers. More complex the object looked at, more intricate is the trace of eye movements. As if the eyes feel the contours of the image stopping and returning to those points that for some reason attract attention. In this way more detailed information is obtained about the elements of an image.

When the visual scene is moving continually before the eyes (when a person is riding in a car), the eyes fix on one highlight after another in the visual fields, jumping from one to the next at a rate of two to three jumps per second. The jumps are called saccades, and the movements are called opticokinetic movements.

During the process of reading a person makes several saccadic movements of the eyes for each line. In this case the visual scene is not moving past the eyes, but the eyes are trained to scan across the visual scene to extract the important information. The eyes can also remain fixed on a moving object (pursuit movement).

In addition to jumps, the eye twitches and drifts (slowly displaces from the point of gaze fixation). These movements are also important in disadaptation of the visual neurons.

The minimum amount of energy required for a visual sensation to arise is the index of the absolute threshold of vision. The magnitude of the threshold energy under the most favourable conditions is extremely small (1.10^{-10}-1.10^{-11}erg/sec). Only one quantum of light is required to excite one rod.

The sensitivity of rods is approximately proportional to the antilogarithm of the rhodopsin concentration, and the same is true also in the cones. The slight changes in concentration of the photosensitive chemicals cause tremendous alterations in the sensitivity of the rods and cones.

A person entering a brightly lit room from the dark is at first blinded. But sensitivity of eye is gradually decreased. Because large proportions of photochemicals both in rods and cones are reduced to retinal and opsins. Also, much of the retinal is been converted into vitamin A. This is called light adaptation.

A person entering darkened premises from bright light also at first can see nothing. But in darkness the retinal and opsins are converted back into the light sensitive pigments. Also, vitamin A is reconverted back into retinal to give still additional light-sensitive pigments. Gradually the sensititvty of photoreceptors is increased and the person begins to discern the

outlines of objects and their details. This is called dark adaptation.

In addition, the eye has two other mechanisms for light and dark adaptation: change in pupillary size and neural adaptation (change of intensity of signals). The processes taking place in the nerve elements of the retina play a significant role in the adaptation phenomena.

The adaption processes are regulated by the reticular formation, sympathetic nervous system as well as cerebral cortex. Stimulation of the receptive field of one ganglion cell produces an inhibitory influence on another one. This phenomenon, called light contrast, resembles that of simultaneous negative induction and is caused by the reciprocal inhibition of cells in different receptive fields of the retina. For instance, a grey strip of paper seems paler on a black background than the same strip on a pale background.

Very intense illumination causes a disagreeable blinding sensation. Higher the previous dark adaptation of the eye, lower the intensity of light causing a blinding effect. That is why drivers are blinded by the headlights of an oncoming car at night. Fine work of surgeons, long-term reading, setting up fine details require despersing (non-blinding) light.

A number of physical and physiological processes in the retina, the nerve fibers and the subcortical optic nerve centers precede the excitation of the visual area of the cerebral cortex and appearance of visual sensations. The time of "visual inertia" required for the appearance of a visual sensation is 0.03-0.1 sec.

In exactly the same way a sensation does not disappear immediately upon the cessation of a stimulus, but persists for a certain period of time. The sensations that continue after cessation of stimulation are called after-images. This property of the eye is used in cinematography and television: the intervals between separate frames are not perceptible, and pictures presented to the eye in rapid succession produce an illusion of continuous image and its motion.

If after a long fixation upon a lighted object the gaze is transferred to a white screen, a negative image of that object is perceived for some time, that is, its light parts appear darker and its darker parts lighter. Because fixation of the gaze on a lighted object causes a change in the condition of definite areas of the retina, and when the eyes are turned to a uniformly illuminated screen, the light reflected from it produces a stronger stimulating effect on the unexcited parts of the retina. This phenomenon is called negative after-image.

Since a sensation required a certain time to form and fade, light stimuli following one another in rapid succession merge into one summated sensation. For example, a circle with black and white sectors rotated at a high speed appears to be uniformly grey in colour.

Visual acuity is determined by the minimal distance between two points that the eye can distinguish. This ability depends on the angle at which these points are visible. The normal visual acuity of the human eye for light is about 45 second of arc. This means that a person with normal acuity looking at two bright pin point spots of light 10 meters away can barely distinguish them as separate ones when they are 1.5-2mm apart. The area of maximum visual acuity is the yellow spot.

Visual acuity is measured by means of special tables consisting of several lines of letters or incomplete circles (with gaps) of various size. Against each line is a number indicating the distance in metres from which the normal eye is able to distinguish the figures in it. Visual acuity measured from this table is expressed in relative units, and normal acuity is taken as a unit.

When the eye is fixed upon a definite point its image falls upon the yellow spot, that is, the point is seen by central vision. Points whose images fall on other parts of the retina are seen by peripheral vision. Space seen by the eye when the gaze is steadily fixed on one point is called the field of vision. The extent of the visual field is measured by an instrument called perimeter.

The boundaries of the visual field for colourless object are 90° outward, 70° downward, 60° upward and inward.

In human subjects the visual fields of both eyes partly coincide. The visual fields are smaller for coloured objects (the smallest for green).

When a person looks at an object with both eyes (binocular vision), the images fuse with each other on corresponding point of the two retinas, and in the viewer's mind the two images merge into one. This can be easily seen by gently pressing the side of one eye: the image is immediately doubled.

If a near object is looked at with convergence of the eyes, the images of a more distant point fall on non-identical points, that is, disparate, and the image appears doubled.

Binocular vision is of major significance for estimating the distance and depth of relief. The disparate divergence of retinal images is the principal cause of the perception of distance, though sensation of the muscular efforts accompanying convergence is also significant for appreciating the depth of relief.

With monocular vision the phenomenon of accomodation has a certain significance. The viewing of near object is attended with tension of the ciliary muscle, and perception of this muscular tension (proprioception) helps to estimatre the distance to an object. Besides, the retinal image of an object is larger the closer it is to the eye.

The size of an object is estimated as a function of two variables: the size of the retinal image and distance from the object to the eye. Gross errors are possible in appreciating the size of an unfamiliar object when it is difficult to estimate the distance to it because of its inadequate relief.

Rays of different wave-length (between 400 and 800 millimicrons) are perceived by the human eye as light of different colours. Light rays with a wave length above 800 millimicrons (infrared) or below 400 millimicrons (ultraviolet) are invisible.

The white colour is a mixture of many colours. The sum of all the spectral colours gives a sensation of absence of colour. This sensation may be produced also if any two of the following colours are taken: 1) red and blue-green, 2) orange and blue, 3) yellow and dark-blue, 4) yellow-green and violet, 5) green and purple.

Each of these combinations, when mixed, produces a white or grey colour, and they are called complementary colours.

According to the trichromacy theory, formulated by Young and Helmholtz, the retina contains three types of colour –sensitive photoreceptors (cones), containing different photosensitive substances (sensitive to red, green and violet). Any colour acts on all the three types but in varying degree.

The theory of trichomacy was confirmed by electrophysiological research of Granit who revealed among retinal elements dominators and seven modulators. The trichromacy of colour vision is obtained as a result of averaging the curves of the spectral sensitivity of modulators, which can be grouped according to the principal parts of the spectrum: blue-violet, green and orange.

If a coloured object is looked at for a long time, and the gaze is then turned to a white surface, the object will seem to have an additional colour. Because prolonged gazing at an object of particular colour causes fatigue of some one of the components of colour vision with the result that the corresponding colour is deducted from the consequent white, and a sensation of an additional colour is produced.

Some people (8% of all men and 0.5% of women) are unable to distinguish certain colours. This anomaly is called daltonism.

Colour vision is tested by means of special tables. Its testing is important in occupational selection (colour-blind persons cannot be employed as transport drivers).

The most frequent disorders of colour vision are protanopia (red-blindness) and deuteranopia (green-blindness). There are rare cases of tritanopia (violet-blindness).

In total colour blindness objects are visible in different tones of grey (as in black-and-white photography).

The eyeball is protected by the upper and lower eyelids. Their closing is a defensive reflex

act caused by bright light, stimulation of the cornea, conjunctiva or eyelashes. Periodic closing and opening of the eyelids (blinking) has the additional function of moistening the anterior surface of the cornea.

Tear fluid is secreted by lacrimal glands in the upper part of the external orbital margin, spreads over the conjunctival surface and collects in the lacrimal lacunae in the inner corner of the eye from which it passes to the nasolacrimal duct.

Tear fluid moistens the cornea and conjunctiva and removes foreign particles. It contains water (99%), salts (1%) and lysozyme (bactericidal substance). The lacrimal center is in the medulla oblongata.

The transparent media of the eyeball has no vessels and receives nutrition from a special intra-ocular fluid (aqueous humor). Its origin and circulation resemble the cerebrospinal fluid. The aqueous humor is formed in the ciliary body, through the pupil passes into the anterior chamber of the eye and at the margins of the iris is drained into Schlemann's canal. It is produced and drained approximately the same rate, and intraocular tension varies within very narrow limits (18-26mm Hg).

Increased production of the aqueous humor or reduction of its drainage causes increase in intracellular tension. A temporary reduction of drainage is observed during dilation of the pupil.

Laboratory Studies

Determination of Visual Acuity

The equipment: the table for determining of visual acuity, stick.

The person sits at a distance of 5m from the table and reads the letters in the table which are shown him by the stick (beginning from larger ones on the upper line). If the person distinguishes the small letter in the tenth line, his acuity of vision is 1. The visual acuity of each eye (closing the other one) is determined.

HIGHER NERVOUS ACTIVITY

Lecture 46

Unconditioned and Conditioned Reflexes.
Memory and Learning.
External and Internal Inhibition of Conditioned Reflexes

The cerebral cortex and adjacent subcortical formations (the cerebral hemispheres) are the highest division of the central nervous system performing complex reflex reactions which make up the basis of the higher nervous activity, that is, behavior.

In contrast to the lower nervous activity directed to unifying and integrating the internal functioning of the organism, the higher nervous activity ensures the most precise and perfect adjustment of the organism to the external environment.

In his book "Reflexes of the Brain" (1863) I. M. Sechenov developed concept of the reflex character of the brain activity, including the most intricate processes of the human mentality.

Up to the date physiologists and neurologists had not dared even to propound the question of the possibility of an objective, purely physiological analysis of the psychic processes. It is nor strange, therefore, that the origin title of Sechenov's book, expressing its philosophical basis, was forbidden by the censor: "An attempt to Put Psychic Processes on a Physiological Basis."

I.P. Pavlov opened the way to objective experimental investigation of functions of the cerebral cortex, elaborated conditioned-reflex method, created well-balanced theory of the higher nervous activity. According to this theory, while reflex reactions in the lower divisions of the central nervous system (basal ganglia, brain stem, spinal cord) are realized by inborn inherited nervous pathways, in the cerebral cortex a new nervous connections are developing in the process of individual life as the result of innumerable stimuli acting on the organism and perceived by the cerebral cortex.

So, the whole totality of reflex reactions taking place in the organism were divided into two principal groups - unconditioned and conditioned reflexes.

There are a number of differences between unconditioned and conditioned reflexes:

1. Unconditioned reflexes are inborn inherited reactions of the organism formed in the course of phylogenesis, whereas conditioned reflexes are reactions acquired by the organism in the course of its individual development on the basis of life experience. It is true that not all unconditioned reflexes appear immediately at birth, and many of them (such as those connected with locomotion or with the sexual act) appear long after birth. Bur provided that the nervous system develops normally they inevitably come into being.

2. Unconditioned reflexes are specific, that is, they are found in all representatives of a given species, while conditioned reflexes are individual and may be present in some members of a species and absent in others.

3. Unlike unconditioned reflexes which are relatively stable, conditioned reflexes are unstable and may be developed, reinforced or extinguished, depending on definite conditions (hence their name).

4. Unconditioned reflexes arise in response to adequate stimuli applied to a definite receptive field, whereas conditioned reflexes can be developed under the action of any stimuli of

any receptive field.

5. Unlike unconditioned reflexes, which can be realized at the level of the brain stem and spinal cord, conditioned reflexes are primarily the function of the cerebral cortex (especially in man and in animals possessing a well developed cerebral cortex). When the cerebral cortex is extirpated, established conditioned reflexes disappear, and only unconditioned reflexes remain. Cortical lesions in primates cause pathological disturbances even in the unconditioned reflexes and some of them also disappear. Because many complex unconditioned reflexes in man and apes necessarily involve the cortex.

6. Conditioned reflexes are built on the basis of unconditioned reflexes.

Formation of conditioned reflexes requires that some change in the external environment or in the inner state of the organism perceived by the cerebral cortex coincides in time (coming somewhat earlier) with occurrence of an unconditioned reflex. As distinct from the unconditioned stimulus giving rise to an unconditioned reflex, a stimulus causing formation of a conditioned reflex is called conditioned stimulus.

Biological importance of conditioned reflexes depends on their great adaptational significance. Conditioned reflexes ensure adaptation of the organism to the external environment in the course of its life experience and are necessary for its better orientation in changing conditions of existence. Thanks to the existence of conditioned reflexes the organism not only reacts directly to unconditioned stimuli but also reacts to the possibility of their action on it in future and is prepared in advance for the actions it must perform in a given situation. So, conditioned reflexes help the individual to find food, to avoid danger in time, to eliminate harmful influences and so forth.

Conditioned stimulation preceding unconditioned one intensifies the unconditioned reflex and accelerates its development (summation of the effects of the two stimulations). For instance, a conditioned nutritional stimulus preceding the intake of food quickens the act of eating (intensifies its motor reactions and speeds up unconditioned salivation) or the conditioned defensive motor reflex elicited by weak electrical stimulation of the extremities is much increased by the influence of prior conditioned stimulation.

The classification of reflexes closely resembles that of the instincts which are complex unconditioned reflexes. The distinguishing features of instinctive reactions are their chain-like character, their dependence on hormonal and metabolic factors (the sexual and parental instincts are associated with cyclic functional changes in the sex glands, while the nutritional instinct depends on metabolic changes resulting from hunger) and their dominant properties.

The entire totality of unconditioned reflexes and of conditioned reflexes formed on their basis is divided into a number of groups according to their biological significance:

1) the nutritional reflexes - the reflex acts of swallowing, chewing, sucking, salivation, the secretion of gastric and pancreatic juices, etc.;

2) the defensive reflexes - reactions eliminating injurious and painful stimuli;

3) the sexual reflexes - all reflexes associated with performance of the sexual act. To this group also may be added the parental reflexes connected with the feeding and rearing of progeny;

4) the stato - kinetic and locomotor reflexes - are responsible of maintaining a definite posture and of moving the body in space;

5) the homeostatic reflexes - those of temperature regulation, respiration, cardiac activity, the vascular reflexes stabilizing arterial pressure, etc.;

6) the orientation reflex - a reflex to novelty ("What is it?" reflex as Pavlov called it figuratively) has a special place among conditioned reflexes. It is elicited in response to any sufficiently quick change in the external environment and is expressed outwardly in alertness, listening to new sounds, sniffing, turning the eyes and head (sometimes the whole body) toward the emerging new stimulus, etc. The orientation reflex ensures better perception of an acting agent and has great adaptive significance. This is inborn reaction

which is retained even after complete extirpation of the cerebral cortex in animals. It is also observed in children with maldeveloped cerebral hemispheres, unencephalics. Unlike other unconditioned reflex reactions the orienttation reflex is weakened rather quickly and damped in repeating application of the same stimulus (influence exerted by the cerebral cortex).

The majority of unconditioned reflexes are complex reactions consisting of several components. For instance, the nutritional reflex has motor (grasping of food, chewing, swallowing), secretory, respiratory, cardiovascular and other components. The unconditioned defensive reflex aroused in a dog by a strong electrical stimulus applied to the skin of the leg comprises not only the proper defensive movements but also deepened and quickened respiration, accelerated heart beat, vocal reactions (yelping or barking) and changes in the blood system (leukocytosis, thrombocytosis, etc.).

Since the conditioned stimulus finally excites the same nerve centers as the unconditioned one, the components of the conditioned reflex are similar to those of unconditioned ones.

In every reflex act there are primary components specific for the type of reflex and secondary unspecific components. For example, in the nutritional reflex the leading role is played by the motor and secretory components, in the defensive reflex - by the motor component.

Changes in respiration, cardiac activity, vascular tone accompanying the chief components are also important for an integrated reaction to a stimulus, but they play a purely auxiliary role. For instance, the deepened and quickened respiration, accelerated heart beat, increased vascular tone caused by the conditioned defensive stimulus help intensify metabolic processes in the skeletal muscles and in this way provide optimal conditions for implementing defensive motor reactions.

During the study of conditioned reflexes one of their main components is revealed, either somatic or vegetative. In this case motor, secretory and vasomotor reflexes are conventionally implied. But they are only separate links of the organism's integral reactions.

Conditioned reflexes can be built on the basis of any unconditioned reflex. There is no organ in organism whose activity could not be changed under the action of a conditioned reflex. Any function of the integral organism can be intensified or inhibited by the action of conditioned - reflex influences.

A conditioned reflex can also be formed in combination of a conditioned signal with direct electrical or chemical stimulation of the cerebral cortex or basal ganglia. Repeated injections of morphine under the same conditions and at the same time produce a conditioned reflex which is manifested (salivation, vomiting, staggering gait, respiratory changes) under the influence of experimental conditions (preparation for injection) or in subcutaneous administration of an isotonic sodium chloride solution.

When a neutral stimulus is several times combinated with subcutaneous administration of bulbocapnine it acquires the capacity for a conditioned - reflex reproduction of bulbocapnine poisoning. The test animal develops the state of catalepsy and can be put in the most bizarre postures.

The best and most minutely studied conditioned reflexes are the salivary reflexes. All the principal laws of conditioned reflexes have been established through experimental analysis of this reaction. There are some principal rules for building conditioned reflexes, and a conditioned reflex can be produced only when they are kept:

1. Beginning of the action of the neutral (future conditioned) signal must precede that of unconditioned stimulation. With all other combinations (simultaneous application of both stimuli or use of a conditioned signal when unconditioned stimulation has already begun) a conditioned reflex is not developed or it proves very weak and is quickly extinguished.

2. A certain minimum time by which the beginning of a conditioned signal should precede the unconditioned stimulation, must be kept (for instance, 0,1 second for conditioned defensive

motor reflexes). With a shorter interval a conditioned reflex does not develop.

3. A stimulus which would become conditioned, must not produce a significant unconditioned reaction, i.e., biological significance or physical strength of conditioned stimulation must not exceed that of unconditioned stimulation.

4. There must not be any extraneous stimuli arousing orientation or visceral reflexes (apart from the conditioned and unconditioned reflexes under examination).

5. The state of cerebral hemispheres must be normal and active, and the absence of pathological processes must be secured.

Pavlov worked out an original method for investigating conditioned reflexes. The object under examination is isolated in a special chamber from the experimenter and extraneous influences. All instruments for both conditioned and unconditioned stimulation are mounted inside the chamber. The experimenter, the switches for the instruments used for conditioned and unconditioned stimulation, the apparatus for recording and counting the conditioned motor, secretory and vascular reflexes are located outside of the chamber.

The conditioned stimuli are usually whistles, bells, various sounds, the ticking of a metronome, light signals, screen images of various figures, mechanical stimulation, cooling or heating of the skin, etc. As an unconditioned stimulus food is given from automatically opening feeders, various solutions are poured into the mouth from an irrigator fastened to the check, or shocks of direct or alternating current are given through electrodes applied to the skin.

To study the mechanisms of formation of conditioned reflexes, besides recording of response reactions (salivation, motor activity, etc.,) the electrical activity arising in various brain structures must be investigated during the action of conditioned and unconditioned stimuli. Therefore, electrodes are chronically implanted in different areas of the cerebral cortex as well as different structures of the brain. Also, microelectrode methods are used for recording the electrical activity of separate neurons which are involved in a conditioned - reflex reaction.

Any change in the external environment or in the inner state of the organism which has reached certain intensity and has been perceived by the cerebral cortex may become a conditioned stimulus, when combined with unconditioned stimuli: light, sounds, colours, odours, flavours, pressure, heat and cold, touching the skin, muscular tension (contraction or relaxation), body position in the space, the state of visceral organs, influences on their mucous membrane, metabolic and energy changes in the organism and many others.

Cessation of various external signals (cessation of sound, the darkening of a lighted room) also may become the signal for a conditioned reflex (trace conditioned reflexes). To establish a trace conditioned reflex the unconditioned stimuli must be used not during the action of the signal agent but only at a definite interval (1-3 minutes) after its termination. In this case the trace of the conditioned agent in the cerebral cortex acquires the signal significance. If a dog is fed repeatedly every ten minutes, it will develop a conditioned reflex expressed in salivation and motor reaction of movement toward the feeding bowl, which arises at the end of the tenth minute after the animal was last fed (conditioned reflex to time).

Conditioned reflex can be produced for much longer intervals. For instance, a dog fed daily at a definite hour begins to secrete gastric juice at the hour even before it is fed.

Various conditioned time reflexes develop in man when he has a regular routine of work and living (a strict work timetable, regular means and hours for going to bed and getting up).

With a short interval (lasting minutes only) conditioned reflexes are established to the state of the nerve centers themselves (change of their excitability, trace from preceding stimulation) whereas those to long intervals can be interpreted as reactions to the condition of the organism as a whole (state and rate of metabolism, activity of the digestive organs).

Not only neutral stimuli but also those usually causing reactions of any kind (including unconditioned reflexes) may become conditioned stimuli, when combined with other unconditioned stimulus. For instance, the test animal was fed at the moment when weak

electrical stimuli were applied at its paw. After a series of such experiments electrical stimulation of the paw elicited conditioned nutritional reflexes (including salivation). So, stimuli arousing a strong unconditioned defensive reflex were converted into conditioned stimuli of a nutritional reflex and unconditioned defensive reflex gradually diminished. In this case the nervous process was switched over to other nerve centers from that for the unconditioned reflex.

Intensity of a conditioned reflex (other conditions being equal) depends both on the intensity of the unconditioned reflex on which it is based and on the strength of the conditioned stimulus. If the effect of a sound is combined with very weak electrocutaneous stimulation of the dog's extremity, the conditioned reflex is weak and unstable. But if the strength of the unconditioned stimulus is increased, it gives rise to stronger and more stable defence reflex.

When an unconditioned stimulus has a constant strength, the intensity of the conditioned reflex depends on the physical strength of the signal stimulus. The greater it is, the stronger is the conditioned reflex (the law of correlation of intensities). But this "law of strength" is valid only within definite limits, beyond which further increase in stimulation results in weakening of the conditioned reaction.

A conditioned reflex can be built not only on the basis of an unconditioned reflex but also on other conditioned reflexes established earlier. Conditioned reflexes built by combining a conditioned signal with an unconditioned stimulus are called conditioned reflexes of the first order. Conditioned reflexes established by combining an external stimulus with a conditioned signal that elicits a stable constant conditioned reflex of the first order are called conditioned reflexes of the second order. For instance, an unconditioned stimulus (nutritional) is combined with some neutral external signal (light). After a conditioned reflex (of the first order) to light has been established and reinforced, another neutral stimulus (sound) is applied in combination with light. After several such combinations (sound then light) the sound, which had never before been accompanied with feeding, begins to induce the conditioned reflex (of the second order).

To build a conditioned reflex of the second order the stimulus to which it is established must precede the action of the conditioned stimulus of the first order at least by ten or fifteen seconds.

Conditioned reflexes of the third order can be built in a dog; reflexes of the sixth order have been described in children.

The establishing of conditioned reflexes requires formation of temporary connections between the cortical cells perceiving the conditioned stimulus and those involved in the unconditioned reflex arc. The temporary connection is the basis of a conditioned reflex.

Initially it was supposed that the temporary connection was of horizontal character, that is, excitation was transmitted from the center receiving the conditioned stimulation to the center receiving unconditioned stimulation by horizontal nerve fibers passing within the depth of the cortex and by the white matter of the hemispheres. But dissociation of different areas of the cortex by section of the gray matter in dogs does not prevent the formation of temporary connections between the cells in these areas. Separation of the posterior central gyrus (somatic sensory area I) from the anterior (motor area) by a deep section in man does not disturb motor habits, in spite of the complete severance of all horizontal connections between them. Section of the corpus callosium in man also does not cause serious disorders in motor habits.

So, it was established that an important role in the mechanisms of interaction of the different cortical regions was played by the cortico - subcortico - cortical pathways. Afferent impulses generated by a conditioned stimulus are conveyed to the sensory area of the cerebral cortex. After being processed there, they are returned by descending pathways to the specific and non - specific subcortical formations, from which they are again transmitted to the cortex (to the area of cortical projection of the unconditioned reflex).

Thus, in the mechanism of temporary connections, which are of vertical character, the significant role (besides cerebral cortex) is played by subcortical structures of the brain, and especially by the brain stem reticular formation.

An important role in the mechanism by which a conditioned reflex is established, belongs to the phenomenon of dominant. When neutral and unconditioned stimuli are combined, the excitation aroused by them is summated, and a summation reflex is brought into play.

It has been established that the cortex, reticular formation, the thalamic nuclei contain many cells on which afferent impulses converge from different receptors: visual, auditory, tactile, temperature, muscular, etc. Evidently, just these cells are active in the formation of temporary connections.

The neural temporary connection that underlies the development of a conditioned reflex is only a special case of the general biological property concerned with retention of perceived information. This property which ensure impression of the connections between the environmental events and accumulation and use of living experience, is memory.

Memory mechanisms in the nervous system have acquired high development and are of major importance in behavior. By its manifestations memory can be of following types;

1) discriptive memory - reproduces the image of a vital object;
2) emotional memory - a similar situation elicits emotions that attended the previously experienced events;
3) verbal - logical memory - is inherent only in man.

Physiologically, memories are caused by changes in the capability of synaptic transmission from one neuron to the next as a result of previous neutral activity. These changes in turn cause new pathways (memory traces) to develop for transmission of signals through the neutral circuits of the brain. Memory traces, once established, can be activated by the thinking mind to reproduce the memories.

Memory traces can occur at all levels of the central nervous system. Even spinal cord reflexes can change at least slightly in response to repetitive spinal cord activation, which is part of the memory process. But most of the memory that we associate with intellectual processes is based on memory traces mainly in the cerebral cortex.

The brain is inundated with sensory information from all of senses. Fortunately, it has a peculiar ability to ignore information that is of no consequence. This results from inhibition of the synaptic pathways for this type of information, and resulting effect is called habituation. This is, in a sense, a type of negative memory.

For those types of incoming information that cause important consequences (pain, pleasure) brain also has the memory traces. This is positive memory. It results from facilitation of the synaptic pathways, and the process is called memory sensitization. Special areas in the basal limbic regions of the brain determine whether information is important or unimportant and make the subconscious decision whether to store the thought as an enhanced memory trace or to suppress it.

A common classification of memories divides them into three types, which are based on different mechanisms:

1) immediate memories that last for seconds or at most minutes unless they are converted into short-term memories;
2) short-term (operative) memory which lasts for days to weeks but eventually is lost; it ensures the accomplishment of current operations of thinking;
3) long-term memory, which once stored, can be recalled up to years or even lifetime later.

The mechanism of the immediate memory is displayed by the circulation of impulse flows along the closed circles of neuron chains. Therefore, it is easily disrupted under the strong influence of extraneous stimulation (narcosis, electrostimulation of the brain, hypoxia, different neutropic poisons) that have no influence on the long-term memory at the same strength of action. The short-term memory can result from temporary chemical or physical changes (or both) in the presynaptic terminals or postsynaptic membrane.

The long-term memory results from actual structural changes at the synapses that enhance

or suppress signal conduction. It is based on complex processes associated with the activity of synthesis of protein molecules in the brain cells.

Memory, as a single process, consists of three interconnected stages with different mechanisms: remembering, storage of experience and recollection (reproduction of experience).

Some limbic structures, especially hippocampus and amygdala, as well as dorsal medial nuclei of the thalamus, are important in making decision about which of thoughts are important enough on a basis of reward or punishment to be worthy of memory.

Conditioned - reflex activity, that is, the formation of the temporary connections is the basis of learning process.

Rehersal of the same information again and again accelerates and potentiates the degree of transfer of immediate memory into longer-term memory and therefore also accelerates and potentiates the process of consolidation. The brain has a natural tendency to rehearse newfound information and especially those which catch the mind's attention. Thus, over a period of time the important features of sensory experiences become progressively more and more fixed in the secondary memory stores.

Hippocampus plays an important role in learning. After the bilateral surgical removal of the hippocampi the human beings can recall most previously learned memories satisfactorily. But they can learn essentially no new information that is based on verbal symbolism. They cannot even learn the names of persons with whom they come in contact every day. Without the hippocampi consolidation of long-term memories of verbal or symbolic type does not take place.

Motive learning is formation of the new movements in the life of individual. It includes formation of professional - work, sports, everyday life motive skills, development of abilities and knacks. The motive learning is frequently connected by the reorganization of the inborn or earlier acquired motor coordinations, especially when precise specialized manipulational movements are produced. Three stages of the motive learning are distinguished;

1) formation of association;
2) formation of new coordination;
3) formation of the motive skill (automation).

Neurophysiological mechanisms of the motive learning are connected with formation of the plan and program of the movement in association areas of the brain and their realization through the cerebellum, basal ganglia and sensomotor area of the cerebral cortex. The latter ensures (through pyramidal tract) inhibition of coordinations making difficult the realization of the new movement.

Conditioned reflexes are inhibited by different ways. Two principal mechanisms of the inhibition of the conditioned reflexes are distinguished:

1) unconditioned (external and protective) inhibition;
2) conditioned (internal) inhibition.

Various external stimuli can easily inhibit the conditioned reflexes. If the beginning of a conditioned feeding reflex in a dog is suddenly preceded by a strange sound or smell, odour or sharp change in illumination, the conditioned reflex vanishes or is completely extinguished. Because any new stimulus arouses an orientation reflex which inhibits the conditioned reaction. But if this stimulus is repeated many times, the orientation reaction is vanished and its inhibitory effect on the conditioned reflex is weakened. Such extraneous stimuli were called "extinguishing inhibitors".

The stimuli which elicit extraneous (relative to a given conditioned reflex) unconditioned or conditioned reflex reaction, produce more stable inhibitory effect on conditioned reflexes. For example, painful stimulation or stimuli issuing from the visceral organs (overfilling of the urinary bladder, vomiting, sexual excitement, inflammatory process in any organ) markedly inhibit feeding conditioned reflexes.

The common feature of all these cases of inhibition is that they are induced by stimuli

which are extraneous, foreign for a given conditioned reflex, that is, they are due to stimuli arousing a new reflex reaction. Therefore, this inhibition is called external inhibition. The mechanism of the development of the external inhibition in the cerebral cortex is explained by the phenomenon of simultaneous negative induction. Definite structures of the reticular formation are involved in external inhibition.

A conditioned reflex can also be inhibited by an excessive increase of the strength of the conditioned stimulus. This is called protective (transmarginal) inhibition. It has a protective significance and prevents the exhausting action of strong and prolonged stimuli on the nerve cells.

The external and protective inhibitions are associated with the inborn features of the nervous system and therefore, they are referred to the category of unconditioned inhibition.

Unlike the external (unconditioned) inhibition which is characteristic of all divisions of the central nervous system and is produced by the first application of a stimulus, internal (conditioned) inhibition is cortical inhibition and has to be developed. Conditioned inhibition is extremely important for adaptive activity of the organism. Because it saves the organism from many superfluous biologically useless reactions. Conditioned inhibition is quite unstable and vulnerable. Different morbid conditions, fatigue, overstrain weaken it.

Four kinds of conditioned inhibition are distinguished:
1) delayed (retarded) conditioned reflex;
2) extinction;
3) differentiation of conditioned stimulus;
4) conditioned inhibitor.

If the unconditioned stimulus is constantly delayed by 2-3 minutes after the beginning of the conditioned stimulus (in place of 1-5 seconds), the conditioned reflex reaction lags behind more and more. Finally, this delay is 90-150 sec so that the reflex manifests itself only by the end of action of the conditioned signal. Because if the action of the conditioned stimulus is not reinforced by unconditioned stimulus during the first minutes, it acquires an inhibitory significance within this time.

A conditioned reflex can exist as long as the conditioned signal is accompanied and reinforced by an unconditioned stimulus. But if the conditioned signal is used alone (is nor reinforced by an unconditioned stimulus), the conditioned reflex gradually weakens after several applications and is finally extinguished. This is called extinction. An extinguished conditioned reflex can recover spontaneously if the conditioned stimulus is not applied for some time. It can also be recovered by adding an external stimulus that elicits a weak orientation reflex to the conditioned stimulus. This phenomenon is known as disinhibition.

If a conditioned feeding reflex is established to some stimulus, for instance, to a tone of 1000 Hz, similar stimuli (tones of 900 or 1100 Hz) will also elicit a conditioned reaction. This is called generalization of the conditioned reflex. If one stimulus is constantly reinforced by an unconditioned stimulus and signals, close to it are used without reinforcement, then the reflexes to them are gradually extinguished, whereas the reflex to a reinforced signal is retained. This is called differentiation of stimuli.

If a stimulus (the tick of a metronome) is constantly reinforced by an unconditioned stimulus, while the combination of stimuli (the tick of a metronome + the sound of a bell) is never used with unconditioned stimulation, this combination initially elicits the same conditioned reflex as that produced by application of a metronome (generalization). Later this combination loses its positive signal significance, whereas the metronome used alone retains its capacity to evoke a conditioned reflex. So, additional stimulus (the sound of a bell) acquires the independent inhibitory significance; it begins to inhibit the conditioned reflexes not to metronome alone, but to other conditioned stimuli as well with which it was never combined previously. This stimulus is called a conditioned inhibitor.

Laboratory Studies

The Conditioned Protective Reflex in Mouse

The equipment: the white mouse, the reflex camera for mouse, electrostimulator, metronome or bell.

The camera is divided into two parts by the barrier in which there is a hole for mouse. The floor of the camera is laid by the metallic net each part of which may be connected with the electrical current source.

The mouse is placed in one part of the camera which is connected with the current source. It runs to another part. Then the conditioned stimulation (metronome, bell, light) is combined by the electrical stimulus. This combination is repeated several times, and then the conditioned stimulation (without the electrical stimulus) is enough for mouse to run to another part of the camera.

Lecture 47

Analysis and Synthesis of Stimulation in the Cerebral Cortex.
Types of the Higher Nervous Activity.
The First and the Second Signaling Systems.
Mechanisms of the Purposeful Activity of Man

Analysis and synthesis of stimulation are the major functions of the cerebral cortex. Analysis of stimuli consists in discrimination between different signals and differentiation of various influences on the organism. Synthesis of stimulations is expressed in the association, generalization and unification of excitations arising in different areas of the cerebral cortex thanks to the interaction between different neurons and their groups. Cortical activity concerned with synthesis is manifested by the formation of a temporary connection on which every conditioned reflex is built.

Although analysis of stimulation begins straight in the receptor apparatus (its different elements respond to stimuli of a different character) and the lower divisions of the nervous system are also involved in elementary analysis, but processes of analysis are most developed in the cerebral cortex.

Signals of each receptor type are conveyed to definite groups of cortical nerve cells. Since every peripheral stimulation has its spatial - temporal pattern of excitation (its own "dynamic structural complex"), stimuli with similar characteristics can be discriminated.

Simple (lower) forms of cortical analysis, that is, the ability to differentiate between separate stimuli, is better developed in animals than in man (the sense of smell, differentiation of odours and sound stimuli are incomparably better in dog than in man), but the higher forms of analysis and synthesis of stimuli are incomparably superior in man to those in animals.

The form of analysis specific to the cerebral cortex consists in differentiation of stimuli according to their signal significance by means of internal inhibition.

Analysis and synthesis are inseparably interconnected. During the action of two separate stimuli on the organism the most primitive forms of analysis and synthesis are observed. To gain an idea of the more complex forms several signals are used following one another in a definite sequence, in a second sequence the same signals are used but not reinforced. The phenomenon of differentiation indicates that the cerebral cortex not only perceives each signal seperately and summates them but also perceives the way they alternate and the sequence in which they are applied.

Complex forms of cortical synthesis are clearly expressed in phenomena designated as dynamic stereotype or systematism. If different conditioned stimuli eliciting conditioned reflexes of varying intensity are applied day after day in experiments on a dog in a strictly definite order, the animal develops a definite stereotype of cortical reactions to the system of stimulations, a chain of conditioned reflexes following one another in a definite sequence. If the action of only one conditioned stimulus is repeatedly tested in some experiment, its effect varies, depending on the site to which it was applied. So, the cerebral cortex reacts to a signal after a definite pattern, in accordance with the formed dynamic stereotype, that is, the conditioned signal is perceived not as an isolated stimulus, but as an element in a definite system of signals associated with both the preceding and subsequent stimuli.

Under natural conditions dynamic stereotype forms the basis for the development of various habits (skills), automatic actions, and a definite system of behaviour. The effect (signal significance) of the conditioned stimulus can be modified, depending on the situation in which it is applied. For instance, if a sound stimulus is accompanied by feeding of the test animal in the morning and by electric stimulation of its leg at noon, then this stimulus acquires a different signal significance after several combinations: in the morning it elicits a conditioned feeding reaction and at noon a defence reaction. The time of day appears to be a factor that determines the character of the conditioned reaction as though the cortex was switched from one kind of activity to another.

This phenomenon is called conditioned- reflex switching. It plays an important role in the process of cortical analysis and synthesis of stimulations. The same stimulus in different conditions may act a conditioned signal or an inhibitory one. So, the conditioned reflex switcing provides the organism with more accurate adaptation to constantly changing environment. It is especially important in human higher nervous activity, since everyday life offers an infinite variety of instances of different reactions to the same stimuli (to the same word or object), depending on whether a person is at home, at work, on a visit, in the theatre or a trip.

Both excitation and inhibition processes that arise in some part of the cortex, are not confined to one point and involve new areas. Spread of excitation, as well as that of inhibition, from the origination point is called irradiation and its subsequent concentration at the initial site is concentration. Irradiation and concentration of excitation proceed more quickly than that of inhibition.

An important role in the irradiation of excitation from one part of the cortex to another is played (in addition to horizontal partways) by the vertical pathways (cortex- subcortex-cortex), especially those passing through the reticular formation of the brain stem.

Spread of excitation in the cortex, which is rapidly followed by its concentration at the initial site, is called dynamic irradiation. During this time the cortical cells involved in the spreading flow of excitation may undergo stable changes (manifested by the appearance of temporary connections with a given uncondiationed reaction), which are called static irradiation.

The phenomena of conditioned reflex generalization and specialization are associated with these properties of the spread of cortical processes.

In addition to a slow spread and centering of basic processes (irradiation and concentration), there is a rapid influence of excitation and inhibition arising in any cortical region on other cortical areas. This phenomenon is called induction. Excitation developing around the focus of inhibition (or at the same site after its termination) is called positive induction. The process of inhibition around the focus of excitation (or at the same site after its action has ceased) is called negative induction.

Irradiation and concentration, positive and negative induction of nervous processes ensure the interconnection of excitatory and inhibitory processes, their transition from one to another and continuing interaction. This movable interaction creates in the cortex an intricate pattern (mosaic) of excitation and inhibition with its constantly changing contours.

The aggregate of the individual qualities of the nervous system on which conditioned-reflex activity depends and which largely determines the character of the higher nervous activity, is preconditioned by the hereditary characteristics of the individual and his previous life experience, and is called the type of the higher nervous activity.

Attempts to understand the essence of individual differences of temperament are dated back to antiquity. Hippocrates distinguished four types of temperaments: sanguine, phlegmatic, choleric, melancholic. This classification is based on the concept of the "bodily humours" (blood, phlegm, yellow bile and black bile).

I. P. Pavlov profoundly studied these temperaments and putting them on the scientific basis, established his principal types of the higher nervous activity. Guided by the findings of his

many years' study of conditioned reflexes in experiment, Pavlov attached the greatest importance to several attributes that he considered the most reliable indices of nervous activity:1)the intensity of conditioned excitation and inhibition processes; 2) their reciprocal equilibrium (the ratio of their intensities); 3) mobility of these nervous processes (the rate at which excitation is replaced by inhibition and vice versa).

In experimental practice the following four principal types of nervous system are observed which coincide with the four temperaments in man described by Hippocrates:

1) a strong, well-balanced type with highly mobile nervous processes- energetic, active ("lively")type (sanguine);

2) a strong, well- balanced type with a low mobility of nervous processes- inactive or inert ("quiet" or "calm") type (phlegmatic);

3) a strong, but unbalanced ("unrestrained" or " pugnacious") type characterized by predominance of excitation over inhibition (choleric);

4) a weak type characterized by extremely weak development of both excitation and inhibition, with quick fatigability leading to loss of work capacity(melancholic).

Intensity of excitation and inhibition	Strong			Weak
Equilibrium of excitation and inhibition.	Balanced		Unbalanced	
Mobility of nervous processes	Mobile	Inert		
Types of higher nervous activity (Pavlov)	Lively	Quiet	Pugnacious	Weak
Temperament (Hippocrates)	Sanguine	Phlegmatic	Choleric	Melancholic

People with the lively (sanguine) type of the higher nervous activity readily overcome difficulties, have good orientation in new surroundings and are self- possessed. People of the quiet (phlegmatic) type are persistent and steadfast toilers in life, self- contained and well-balanced, but slow in making decisions and confined to their habits. People belonging to pugnacious (choleric) type are easily carried away, passionate, easily and quickly irritated and pugnacious. People with weak (melancholic) type are weak-willed, afraid of difficulties and easily subjected to the influence of others; they are always anxious and gloomy.

Individuals having different types of nervous system differ in their adaptation to various environmental influences and their resistance to pathogenic agents. It is extremely difficult to induce a pathological disorder of the higher nervous activity (neurosis or breakdown) in animals with a strong, well- balanced type of nervous system. Animals with a weak or strong but unbalanced nervous system are more liable to develop various disturbances of conditioned-reflex activity. A prolonged disturbance of the higher nervous activity is produced very easily in representatives of the weak type of the nervous system by the effect of difficult circumstances, complex problems in differentiating signals, strong destructive stimuli, etc.

Many diseases of the nervous system are connected with functional derangement of the normal properties of basic nervous processes and the higher nervous activity. Study of experimental neuroses helped to explain the essence of this derangement. Experimental neuroses arise in overstrain of the excitatory and inhibitory processes overstrain of the mobility or their collision.

Overstrain of the excitatory process under the action of superstrong stimuli was demonstrated in dogs trapped in flood in Leningrad (1924). Even when the conditioned reflexes were recovered, the animals had no normal response to strong stimuli, especially to those associated with the experienced breakdown. There are numerous examples of neuroses caused by serious shock. When the nervous system is weakened by excessive fatigue or disease, even common stimuli may become "super-strong" and cause neurosis.

Overstrain of the inhibitory process occurs in persistent differentiation of stimuli closely

resembling each other, retardation of the action of inhibitory stimuli and in long- term delay of reinforcement. In this way in a human subject neurotic state sets in when he attempts to solve difficult tasks concerned with discrimination or is constantly prevented from doing what he likes to do, or when he experiences bitter disappointment and broken hopes.

Overstrain of mobility of nervous processes can arise as a result of rapid and frequent transformations of a signal significance of positive and negative conditioned stimuli or urgent disruption of their stereotypes. That is why neurotic states are often caused by the unexpected events leading to the reappraisal of one's outlook or the necessity in radical changes of one's way of life (which is especially difficult in old age).

The collision of excitation and inhibition takes place in a too rapid change or during simultaneous action of stimuli of an opposite signal significance. For instance, experimental neuroses were obtained during the elaboration of feeding conditioned reflex to a signal of painful stimulus (which causes defence reaction). Many neurotic patients became ill under the pressure of colliding everyday life circumstances.

In experimental neuroses the nervous processes are weakened or their mobility changes. Reduction of excitation leads to lowering of the intensity of conditioned reflexes, and reduction of inhibitory process causes disturbance of differentiation of stimuli, delay or extinction of conditioned reflexes. Excessive mobility and a tendency to considerable irradiation, or reduction of mobility and inertness or inactivity of nervous processes are observed. Relation between the strength of the conditioned stimuli and the intensity of the conditioned reflex often undergoes characteristic phasic changes. There is a similarity between the phases of the experimental neurosis and those of parabiosis described by Vvedensky:

1) equalizing phase- stimuli of different strength begin to induce approximately equal reflex responces;
2) paradoxical phase-strong stimuli elicit a weak effect, and weak stimuli - a strong effect, or rather the effect elicited by frequent (strong) stimuli is weaker than those elicited by rare (weak) ones;
3) ultraparadoxical phase- positive stimuli begin to produce an inhibitory effect, and inhibitory stimuli elicit a positive conditioned reaction (or reinforced stimuli do not cause an effect whereas accidental ones cause it), that is, the reaction of the cerebral cortex to the stimuli is perverted;
4) inhibitory phase- all conditioned reflex reactions are weakened or totally disappear. Two transition phases were revealed between the equalizing and paradoxical phases:

1) narcotic phase- cessation of responses to weak, average and at last, to strong stimuli;
2) phase of stimuli of average strength- neurons respond only to stimuli of the average strength.

Neurotic disturbances may affect the entire cerebral cortex or only those circumscribed areas that are overstrained and functionally weakened. In cases when individual cortical areas are functionally deranged, changes of the higher nervous activity can be revealed only by application of definite visual, auditory or cutaneous stimuli. Deep - rooted neurotic conditions may cause somatic disturbances (eczematous lesions of the skin, deterioration or exacerbation of certain systemic diseases).

A normal state of the higher nervous activity after the developing neuroses can sometimes be restored by a sufficiently prolonged rest in new conditions and normalization of sleep. Pharmacological agents with selective action on excitatory (caffeine) and inhibitory (bromine) processes are employed.

In his experimental research of the higher nervous activity Pavlov firmly discarded idealistic concepts of the supernatural psychic activity in man. He has established that all laws of conditioned- reflex activity are common to the higher animals and man.

Analysis and synthesis of direct concrete signals from objects and phenomena of the external environment (from the visual, acoustic and other receptors of the organism) that are

common both to animals and man Pavlov called the first signaling system.

In the course of his social development and labour activity man has developed an extraordinary addition to the mechanisms of brain function which has become a second signals, that is, speech. The second signaling system consists in the perception of words heard, uttered (either loud or to oneself) and seen (in reading).

The ability to understand and then to pronounce words develops in a child as a result of the association of definite sounds (words) with visual, tactile and other impressions about the external objects.

Formation of temporary connections of the first signaling system in the cerebral cortex of a full-term baby begins within a few days after birth. The first conditioned reflexes can be developed when it is seven or ten days old. A baby about to be breast- fed makes sucking movements with his lips before the nipple is put into its mouth. The baby may develop conditioned reflexes to sound signals by the end of the first month and to light signals in the second month. Conditioned inhibition is developed in the second to fourth months. The first signs of development of the second signaling system appear during the second half of the first year of infant's life. After a conditioned reflex has been developed in children to any sound (ringing of a bell) or light signal (flashing of a red lamp), the words "bell" or "red colour" elicited the given conditioned reflex immediately, without preliminary combination with an unconditioned stimulus.

The conditioned- reflex response arises even if the person pronounces the word aloud to himself or reads the word "bell". And vice versa. When a conditioned reflex had been developed to a verbal signal (words "bell" or "red lamp" being the conditioned stimulus), the conditioned reflex was elicited after the first sounding of a bell or flashing of a red lamp as a stimulus, which had not previously been combined with an unconditioned stimulus. In these experiments the phenomena of elective irradiation are observed, that is, excitation from the cortical regions receiving signals of the first signaling system is transmitted to the regions perceiving words (and back).

If a conditioned reflex to a definite word like "road" has been developed, then the word synonim ("path") elicits the same reaction. A similar phenomenon was observed when a word in one language used as a conditioned stimulus, was replaced by its synonim in a foreign language known to the person. These facts prove that a word is perceived by man not only as a sound stimulus, but also as a definite concept, that is, having meaning.

So, the first and the second signaling systems are inseparable.

If man's sensations and concepts connected with the external environment are first signals of reality, then speech, words are the second signals, that is, signals of signals. They are an abstraction of reality and allow the generalization, which is precisely man's special higher thinking. The main distinction between the human psyche and the primitive psyche of animals is man's ability to think in abstract notions expressed in words thought, pronounced or written (second signaling system). A temporary connection is the most important physiological and at the same time psychic phenomenon and is called association in psychology. Different manifestation of higher nervous functions associated with man's intellect have a definite localization in the brain.

Combination of the physiological and psychological (objective and subjective) methods is valuable in the study of the higher nervous activity of man. In this way it was possible to reveal dissimilar significance of functioning of the second signaling system in the right and left cerebral hemispheres. The right half of the body is projected into the left hemisphere and the left half into the right one.

The left hemisphere in most people (right - handed) dominates and damage to its definite areas entails a disorder in the functions of speech, recognition and purposeful action, that is, specifically human functions associated with the second signaling system.

In all right- handed and 70% of the left-handed persons the left hemisphere ensures the development of abstract logical thinking (perception, processing, analysis and synthesis of signals of the second signaling system).

The right hemisphere is responsible for perception, processing, analysis and synthesis of signals of the first signaling system, that is, the direct impressions of reality. Functional division of the hemispheres is not absolute.

Existence of people who are "thinkers" and "artists", that is, subjects with predominance of logical or image- bearing type of thinking, is associated with functional predominance of the corresponding hemisphere.

A close connection between the first and the second signaling systems ensure their continuous interaction and certain interchangeability only in conditions of normal interaction of both hemispheres (through fibers passing in the corpus callosum, optic chiasma, anterior and posterior commissures of the brain).

Development of speech and logical thinking requires the participation of many brain structures. This is clearly manifested in affection of separate parts of the brain, when certain speech and thinking disturbances are observed.

Agnosia (Gr. gnosis- knowledge) is failure of recognition: 1. Visual agnosia (lesions of the occipital lobes) - the patient sees objects and goes around them without stumbling over, but is unable to recognise them. To recognize an object he has to feel it with his hands or hear a sound emitted by it. 2. Auditory agnosia (lesion of the temporal lobe of the brain)-the patient hears sounds, but is unable to associate them with a definite sounding body; however, recognizes them at sight. 3. Tactile agnosia (affection of the upper part of the parietal lobe)- the patient failures to recognize objects by touch.

Apraxia (Gr. praxis- action)- inability to perform a definite purposeful act, for instance, a voluntary movement (to wave a hand in greeting, to strike a match, to slice bread), though the hand is not paralysed, and certain simple separate movements can be performed.

Aphasia (Gr. phasis – speech)- a speech disorder:
1. Motor (Broca's) aphasia – ability to understand speech may be retained though the patient is unable to articulate a single word normally (individual sound like "no", "ta-ta" may be uttered). Motor aphasia is usually concomitant with agraphia(inability to write) and loss of ability to read aloud. The focus of lesions in motor aphasia is localized in the inferior frontal gyrus of the left hemisphere, and in a minority of people (left-handed), it may be in the right hemisphere.
2. Sensory (Wernicke's or temporoparietal) aphasia- disturbance of speech perception. The patient does not understand speech, and selective word – deafness appears though his power of speech is retained, and he is even unduly talkative. Sensory aphasia is usually concomitant with alexia (loss of ability to read) and amusia (loss of the ability of musical perception).

A special form of aphasia is amnesia (amnestic or parietal aphasia), that is, loss of memory for individual words which is due to lesion of the left inferior parietal gyrus. The patient is unable to recall the necessary word (most commonly nouns) and has to use long descriptions for objects. This form of aphasia is frequently accompanied by other symptoms, especially acalculia (loss of ability to do simple arithmetic)

It is supposed that the posterior part of the parietal region and the frontal gyrus are of special importance in the processes of recognition, purposeful actions and speech.

Although a lesion in certain parts of the cerebral cortex is particularly destructive of functions of the second signaling system, but any complex function (identification, purposeful action, speech, writing, reading, calculation) is also impaired, as a rule, by affections of many other brain areas far removed from one another. At the same time a lesion in one area usually entails disruption not of one, but of a number of functions. Therefore, references to centers for definite functions of the second signaling system are merely conjectural. Psychic activity is the

function of the entire brain.

In every act of human behaviour the following three groups of interneuronal connections are found to be involved: 1) unconditioned reflexes; 2) temporary connections of the first signaling system; 3) temperary connections of the second signaling system.

The second signaling system as the highest regulation of human behaviour dominates over the first and inhibits it to some extent. At the same time, the first signaling system controls the activity of the second to a certain degree.

Activity of the two signaling systems is verified by practice. If conditioned- reflex reactions do not correspond to the organism's external environment, they undergo alteration, the temporary connections are changed and certain conditioned reflexes become inhibited. The activity of both signaling systems and of the cortex as a whole, is intricately interconnected with the subcortical centers. Man can voluntarily inhibit his unconditioned- reflex reactions and restrain many of his instincts and emotions. He can suppress his defensive reflexes aroused by painful stimuli and his nutritional and sexual reflexes. At the same time, the subcortical nuclei and the nuclei of the brain stem and the reticular formation are the sources of impulses maintaining normal cortical tone.

Man gains knowledge of the world through information from receptors, which is processed in the whole aggregations of analysers (mainly in the cerebral cortex) and verifies its authenticity by his activity and practical experience.

Comparison of the information arriving from the different analysers is of major importance for authenticating sensations and perceptions. For instance, the optical system of the eye gives an inverted image on the retina. The notions of "top" and "bottom" are the result of comparing information supplied by the eye with that provided by other receptors perceiving the action of the force of gravity, the position of the body in space, etc.

In the highest division of the central nervous system, in the cerebral cortex afferent signals interact not only with other afferent signals arriving there at the moment, but also with traces which were left in the central nervous system by previously acting stimuli. This interaction makes possible evaluation of phenomena occuring not only in space but also in time. Human activity is associated with distinct idea of task goal and expected result of action to be achieved.

Goals that govern the activity of a subject, are determined by his biological and social needs. The hierarchial gradation of needs (lower and higher needs) exists, and their satifaction in the basic condition that ensures man's life.

The neurophysiological structure of purposeful (goal-directed) activity is very intricate. Physiologists ever tried to have an idea on the structure underlying the behavioural reactions in the form of some model or scheme which was always conceived in accordance with the mechanisms known at that particular time.

The reflex principle (Descartes) was formulated on the basis of analogy between the nervous system and mechanical automatic devices; the principle of a temporary connection (Pavlov) was borrowed from the switchboard construction of telephone exchange, schemes of the "reflex circle" (Bernstein) of the mechanisms of self- regulation of physiological processes were developed with the main emphasis being laid on the feedback processes discovered in the second half of the XX century.

To explain the mechanisms of self- regulation of physiological processes and the structure of the organism's behavioural reactions P. K. Anokhin suggested the scheme of functional system which develops Ukhtomsky's concept of the dominant. In Ukhtomsky's view, the dominant is a temporary union of nerve centers for the achievement of a goal set before the organism. This union is disintegrated, and the dominant ceases to exist at the moment the goal has been achieved, that is, the task is solved.

In accordance with Anokhin's theory, any goal- directed activity is preceded by decision making with the help of "afferent synthesis", that is, the analysis and synthesis of afferent

information which has four sources and dissimilar significance:

1) dominant biological motivation (instinctive needs: nutritional, sexual, defence, etc,);
2) situational afferentation (conditions of the external environment);
3) triggering afferentation (a direct stimulus of the reaction);
4) memory (information accumulated during living experience).

Afferent synthesis is completed by the decision taking and formation of a program of action consisting of 2 elements, differing in principle:

1) action program;
2) acceptor of the result of action, that is, a neuronal model of the anticipated result brought by a given action.

Accomplishment of the action program leads to a definite sequence of a set of neural command (efferent excitations) passing to effectors. The result of their action is evaluated by the organism according to their parameters through the feedback afferenttation. The information on the actually obtained result is compared with the acceptor of the result of action- coded prognosis. If the obtained result corresponds to the anticipated one, a given functional system ceases to exist.

Otherwise, all the process is repeated until the goal set before the organism is accomplished. So, the functional system is a union of various elements of the nervous system- from the receptors to the executive devices, which appears to accomplish a concrete task.

Thus, behaviour is built by the principle of continuous circular interaction between the organism and its environment rather than by the stimulus- reaction type.

Feedback afferentation

Situational afferentation

Triggering stimulus

Memory

Dominant motivation

Decision taking

Acceptor of the result of action

Action program

Parameters of the result

Result of the action

Action

Afferent synthesis

Efferent excitations
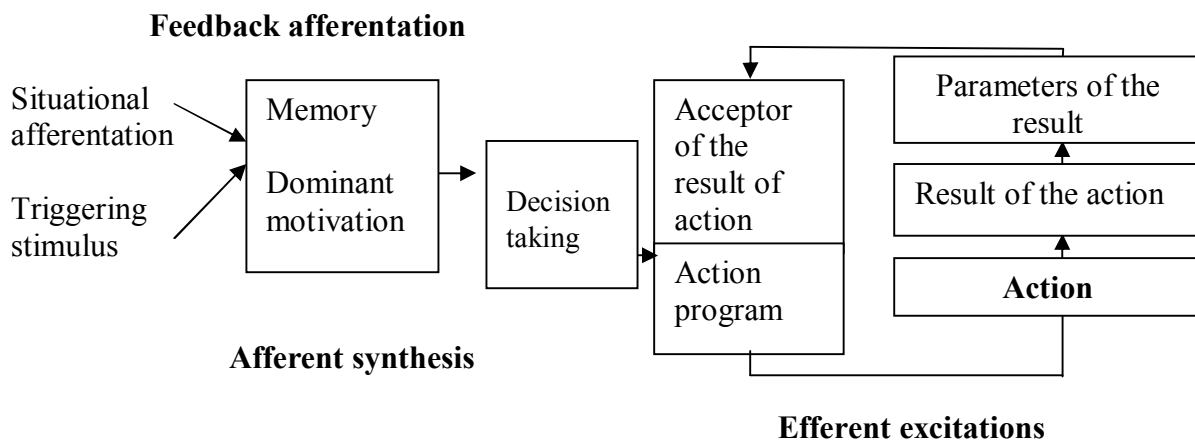
Lecture 48

Subconsciousness and Consciousness. Emotions and Motivations. Sleep

Consciousness, as the function of the human brain, consists essentially in the reflection of reality and directed regulation of interrelation between personality and the external world. The use and improvement of labour tools in the process of joint activity of people promoted development of consciousness. The material form of consciousness expression is language.

Consciousness is not the congenital brain function; congenital is only the possibility of consciousness evolvement. This is determined by the definite structure of the nervous system and becomes a reality, that is, consciousness is taking shape, only under conditions of social life.

Human brain receives information in the form of signals, most commonly in the form of words. Each signal is a material information carrier, which, acting on the recaptors, gives rise to material nervous processes or physiological phenomena that reflect perception, transmission, processing and storage of information in the brain. The content of information itself is also determined by the whole past life history and working activity of a subject and his association with other people, that is, by his consciousness.

So, consciousness is simultaneously the product of the brain and the product of man's social life, his living experience which is imprinted by means of the conditioned reflexes. A conditioned reflex is that "brick" whose totality makes the basis for the formation of the intricate structure of consciousness. But this construction is not reduced to the sum of conditioned reflexes.

It was long believed that consciousness is underlined by the activity of the cerebral cortex, the highest part of the central nervous system, whereas subconscious reactions are accomplished by its lower divisions (the spinal cord and brain stem structures). But the brain was found to operate as a single whole, without being separated into "storeys". Cerebral cortex can take part in all reflex reactions.

The answer to the question related to the difference between processes underlying the emergence of consciousness and those, which are accomplished at the subconscious level, has a methodological significance. Because certain researchers believed that subconscious reactions and uncomprehended forms of mental activity could not be integrated into the principle of determinism. And this gives way to idealism and mysticism.

The physiological facts enable one to reveal the difference and the common character of neurophysiological processes, which determine emergence of conscious and subconscious manifestation of the human higher nervous activity.

Any stimulus by causing excitation in any receptor gives rise to the appearance of afferent signals that reach the cortex and induce primary electric response, which can be recorded even in sleeping state, that is, it is realised unconsciously. The latent period of this electrical reaction is equal to 9-20 msec.

As soon as this information has been assessed by the brain, the response reaction to it can proceed by one of the following three types:

1. If the coming signal is lacking any information necessary for the organism, the program formed at the subconscious level includes inhibition of the external response reactions to given signal. That is, the signal elicits a primary bioelectric response and secondary bioelectric activity without signal comprehension and organism's other reactions.

2. If primary evaluation of signal at the subconscious level indicates that it requires a standard, well-known response the developing reaction is accomplished by the type of automotism. In this case also there is no need in the conscious activity and the automatized response is accomplished at the subconscious level (especially during sleep) with a limited number of the central nervous system neurons involved in activity

3. If primary assessment of a signal at the subconscious level gives evidence that the arriving information is important for organism, then a command is formed in the cerebral cortex at the subconscious level, which induces general cerebral activation through the reticular formation. The entire central nervous system becomes involved in activity. The "reaction of awakening" arises that is expressed in EEG desynchronization. Only in this case the signal is comprehended and further response to it proceeds at a conscious level. A minimal latent period of consciousness switching in a sleeping person is over 100 msec. Taking a moment subjectively, in fact this is a sufficient period of brain activity, which involves a number of essential neurophysiological processes.

Some facts indicate that both conscious and subconscious manifestations of higher nervous activity in man can be expressed by the same structures of the entire brain and not only by any of its parts. Any conditioned –reflex reactions (including those arising with the participation of the second signaling system) can occur at the subconscious level. The brain is able to analyse any signals (including verbal) until consciousness has been involved in activity. The secondary bioelectric response (which reflects the analyses and processing of information and decision making) is accomplished unconsciously and can be recorded in any part of the brain. So, the difference between the comprehended and uncomprehended reactions consists in the degree of activation of the brain, that is, the number of its neuronal structures involved in a reaction. If a small number of cortical and subcortical neurons take part in a reaction, it proceeds as a subconscious one. When the whole enormous super system of cortical and subcortical neuron "ensembles" is involved in a response reaction, that is, it occurs with "global" activation of the entire central nervous system, then the reaction is accomplished with the participation of consciousness.

Reactions occurring at the subconscious level are more economical. The subconscious (automatized) reactions are the most fast response reactions and their latent periods are less prolonged in contrast to reactions proceeding at the conscious level.

Thus, the entire higher nervous psychic activity of man has a double-member structure constantly proceeding at two levels - subconscious and conscious. This gives the human organism certain advantage and ensures a continuous interaction between the organism and its environment. Although the man has only one brain and one consciousness, a multitude of automatized reactions may simultaneously take place at the level of subconsciousness.

Consciousness may be disengaged from the habitual situation of the surroundings and be directed to deep comprehension essence of events. The derangement of incessant interaction between the organism and its environment may cause death. But this does not happen because subconsciousness is always on the guard even when consciousness is disengaged or switched over to solution of abstract problems.

There is a dynamic equilibrium between processes occurring at a subconscious level and those that are responsible for the origination of consciousness. If the continuous activity of subconsciousness involved in analyses and processing of information entering the brain is stopped, the function of consciousness becomes impossible. On the contrary, continuous weak stimuli activate the cortex and increase its working capacity.

The conditioned-reflex regulation of activity of visceral organs proceeds at the subconscious level. Signals entering the cerebral cortex from interceptors cause conditioned reflexes that change the organism's behaviour though the subject himself remains unaware of the emergence of such reactions. Occasionally, various feelings of uneasiness, that is, not

sufficiently differentiated sensations appear, which promote the idealistic concepts with "premonitions", "divine intuition" or "providential aspiration". When such stimuli grow in intensity, they are perceived by consciousness in the form that point out to some trouble in the corresponding part of the body.

Subconsciousness stores information accumulated in the course of living experience, that is, all which becomes the basis for the organism's behavioural reactions or the foundation of personality.

Subconscousness is not in conflict with consciousness. The relationship between them is similar to that existing between a part and the whole. It is the first step, the first link (though not independent) of all the organism's reactions. Its activity is directed by consciousness and subordinated to it since it is exactly consciousness that is the highest regulator of human behaviour.

Subconscious reactions, like all the other forms of behaviour and mental activity, are subordinated to the low of cause and effect relationship. This is the essence of intuition, guesses, creative impulses and premonitions based on the subject's past experience and on the influences of the external and internal environment acting on him at given moment.

One of the manifestations of the human higher nervous activity are emotions, the organism's reactions to the action of external and internal stimuli.

Emotions (Lat. emovere -to excite, agitate) are the reactions in the form of the subjectively coloured experience (feeling) of the individual, which reflect the significance for him of the acting stimulus or the result of the own action (satisfaction or non -satisfaction). Emotions embrace all kinds of sensitivity.

All the totality of emotions is divided into two groups: the positive emotions in the form of pleasant experience of the satisfaction of some needs and the negative emotions in the form of unpleasant experience of non- satisfaction of any need.

The biological emotions connected with the satisfaction (or non-satisfaction) of the physiological needs (hunger, thirst, sexual drives) and the higher emotions connected with the satisfaction of the spiritual (social, moral, cognitive, aesthetic) needs, are distinguished.

The emotions, whose external manifestation must be suppressed by the individual for some (usually social) reasons, are called the detained emotions. They may cause the focus of the pathological congestive excitation. The state of emotional stress is accompanied by essential functional changes of certain organs and systems, which can reach such a high degree of intensity that they appear to be real "vegetative storm." But there is a definite order, that is, only those organs and systems are involved in intensive activity by emotions, which can ensure a better interaction between the organism and environment: blood content of adrenaline, heart activity, blood pressure, rate of gas exchange, intensity of oxidative and energy processes in the body are increased as a result of strong excitation of the symphatetic nervous system. Separate groups of muscle fibers all come into play simultaneously. All the organism's reserves are instantaneously mobilized. At the same time, its reactions and functions, which are not vital at a given moment, are inhibited, in particular those associated with processes of energy accumulation and assimilation, while processes of dissimulation grow in intensity to supply the organism with necessary energy resources.

Evolutionally emotions were formed as the mechanism of adjustment. But emotional reactions with an extraordinary degree of expression may prove to be harmful to the organism and provoke certain ailments.

Emotions arise in cases when the organism lacks sufficient reserves to solve the task or to achieve some goal set before it. The means to achieve the goal include the information, skills, experience (I), energy (E) and time (T).Goal can be achieved on condition that objectively necessary information, energy and time (In, En, Tn) are available. If the amount of the existing information, energy and time (Ie, Ee, Te) possessed by the organism is less than necessary, the

state stress (SS) comes into being. More important the goal (G) and greater the effect of necessary means, greater is the expression acquired by SS:

SS = fG (In. En. Tn - Ie. Ee. Te).

Emotions occur when SS attains a definite strength, four stages (degrees) of which are distinguished:

SS - I - the stage of attention, mobilization and activity (AMA) - is characterized by the increase in working capacity, augmentation of functioning of organs and systems ensuring the solution of a given task. This state is useful since it trains the organism and increases its working fitness.

SS - II - sthenic negative emotions (SNE) - appears in insufficient mobilization of the organism's reserves in SS-1 as a paroxysm of rage (anger, indignation) attended by extraordinary increase in the activity of organs and systems responsible for the interaction between the organism and environment, the reaction aimed at a maximal increase of the organism's reserves and solution of the task.

SS - III - asthenic negative emotion(ANE) arises when the task requires far more resources for its solution than the organism possesses even in maximal mobilization of its strength; this is the state of fright (fear, frustration).

Functional changes in SS-III are opposite to those typical for SS - II: mental and energy reserves are sharply reduced by inhibition of corresponding reactions (as that of immune reactions and compensatory processes). Fear, frustration and anxiety destruct the body and open way to various illnesses.

SS - IV- is a hopeless condition, neurosis, that is, a morbid condition or the breakdown of a number of regulatory mechanisms.

A state of stress of any degree may appear directly from a "start", without involvement of the preceding stage. The four stages of the SS are rarely encountered in a pure form. For instance, only mental functions can be inhibited with a full maintenance and even increase of energy reserves in the stage between SS-II and SS- III: a person seized by fear and out of mind commits unreasonable acts in panic spending enormous energy. For other transitional states reduction of only energy reserves is typical: a fear -stricken person is aware of the approaching danger, but cannot move a finger to escape it.

Emotional stress has a greater degree of expression in weak and ill-informed persons than in strong and self -possessed ones - strong persons rely upon themselves, while weak and diffident people constantly need support in the form of emotional stress and because of that they are always agitated.

Positive emotions accompanied by the feeling of joy are important in man's life and play the role of a life stimulus responsible for the regulation of behaviour and activity. They also help high working capacity and health.

Emotions induce changes in man's subjective status: functioning of intellect and memory acquires a more refined pattern and perception of the environment influences becomes particularly bright. Emotion is a state of the highest aspiration of man's mental and physical powers, causing the creative activity.

The achievement of goal, satisfaction of needs or solution of task are accompanied by positive emotions. More difficult the task, more complex the goal or stronger the need-higher is the degree of the state of stress and stronger a positive emotion that can relieve or reduce stress.

The hierarchial gradation of needs exist. Satisfaction of biological needs (minimum of conditions needed by the organism for survival) has a definite limit. The limit of satisfaction from the perceived information is much higher and cannot be attained even during the whole life span with an optimal rate and rhythm of information arrival. Under these conditions a given source of positive emotions is practically inexhaustible.

A constant "information hunger" had been laid by nature in every organism. A rat put in

cage supplied with all necessary things for its biological needs (food, water, even a creature of an opposite sex) eagerly explores its new surroundings. After being used to them, it begins to search for a small well-hidden opening for escaping. Even if the new surroundings threaten with danger and the animal has a risk to perish, it will, nevertheless, leave the cage.

The emotions are inseparably linked with motivations. The enjoyment from satisfaction of any of the human needs is greater-stronger its motivations.

Motivation is subjectively coloured state originated on the basis of the activation of the cerebral structures, which impels the individual to accomplish actions directed to the satisfaction of organism's vital needs. So, motivations are inborn reactions-drives which force the individual to certain purposeful activity leading to the removal of the state which caused it.

Lower, higher and social motivations are distinguished. The lower (biological, primary, visceral, unconditioned) motivations depend on the inborn mechanisms and ensure the conditions of the normal metabolism in organism. The higher (complex) motivations originate on the basis of lower motivations and habits acquired during the individual life. The social motivations are higher motivations originating under the influence of the social factors. Motivations present the second stage of the organization of the purposeful behaviour after the actualization of the need.

The limbic system provides most of the drives for setting the other areas of the brain into action and even provides the motivational drive for the process of learning. The reward and punishment centers constitute one of the most important of all the controllers of bodily activities,drives, aversions and motivations.

The physiological mechanism of motivations is based on the interaction of the conditioned direct connections and feedbacks. In this case the conditioned feedback means influence of the reinforcing reflex on the functional state of the structures which perceive the conditioned signal and realize the action that is followed by reinforcement.

Sleep is indispensable requirement for the organism of higher animals and man. It is a period of rest for the body and mind. Man spends a third of his life in a state of periodically recurring sleep.

Sleep is defined as unsconsciousness from which the individual can be aroused by sensory or other stimuli (unlike the coma, which is unconsciousness from which the person cannot be aroused).There are multiple stages(from very light to very deep) of sleep.

Several different types of sleep are known:
1) periodic diurnal;
2) periodic seasonal (winter or summer hibernation of animals);
3) narcotic;
4) hypnotic;
5) pathological.

Periodic diurnal and seasonal types are forms of physiological sleep. Narcotic sleep can be induced by various chemical or physical agents (by inhaling ether or chloroform vapours, intake of alcohol, injection of morphine, an intermittent electric current (electronarcosis). Hypnotic sleep is suggested sleep. Pathological sleep develops in cerebral ischemia, in compression of the brain by tumors of the cerebral hemispheres or in lesions of certain parts of the brain stem. It may last for days, months or even years (lethargic sleep).

Sleep is characterized by lowering of the nervous system activity (especially that of the cerebral cortex), dissociation from the environment, reduction of muscle tone and all types of sensibility. Conditioned reflexes are inhibited and unconditioned reflexes are considerably weekend. To cause a reaction in a sleeping person much stronger stimulus is required than that when he is awake, because the thresholds for stimulations are elevated and the latent periods are prolonged. Breathing is more slow and quiet, the heart rate, blood pressure, metabolic rate, body temperature, diuresis are decreased.

In the transition from wakefulness to sleep instead of the alpha-waves quick beta-wakes and desynchronization typical for the waking state, high-amplitude slow theta and delta waves appear in the electroencephalogram.

Deep sleep has two stages that alternate with each other during each night:

1) slow wave sleep;

2) rapid eye movement (REM) sleep.

The slow wave sleep or non-rapid eye movement (NREM) sleep in adults accounts for about 75-80% of the sleep duration each night. The remaining period of sleep (20-25%) is REM sleep.

Slow wave sleep is the deep, restful type of sleep that the person experiences during the first hour of sleep after having been kept awake for many hours.REM sleep is not so restful, and it is usually associated with dreaming. Episodes of this type of sleep occur periodically during the sleep and recur about every 90 minutes.

Although slow wave sleep is often called "dreamless sleep", dreams and even nigthmares occur during this type of sleep. But the dreams of REM sleep are remembered whereas those of slow wave sleep usually are not remembered. This means that during slow wave sleep the process of consolidation of the dreams in memory does not occur.

The person is even more difficult to arouse by sensory stimuli during REM sleep than in slow wave sleep, and yet person usually awakens in the morning during an episode of REM sleep.

During REM sleep the muscle tone throughout the body is exceedingly depressed (strong inhibition of the spinal projections from the excitatory areas of the brain stem). But despite the extreme inhibition of the peripheral muscles, a few irregular muscle movements occur (especially rapid movements of the eyes). The heart rate and respiration become irregular (which is characteristic of the dream state).

In REM sleep the brain is highly active (brain metabolism may be increased as much as 20%). The pattern of brain waves is similar to those that occur during wakefulness. So, in REM sleep the brain is quite active, but its activity is not channelled in the proper direction for persons to be fully aware of their surroundings. Since it is paradox that a person can still be asleep despite marked activity in the brain this type of sleep is also called paradoxical sleep. Children have polyphasic sleep, while in adults monophasic (once in 24 hours) and in rarer cases diphasic sleep are observed.

Duration of sleep depends on age: it is 21 hours in the newborn, whereas adults sleep 7-8 hours.

Breaking of the organism's contact with the outside world usually occurs quickly and is just quickly replaced by wakefulness, that is, resumption of the activity of the nervous system and normal contact with the environment.

In long spell of complete wakefulness for 3-5 days and nights an irresistible desire to sleep sets in, which is uncontrollable by the will. The onset of sleep can be prevented only by strong painful stimuli (pricking with a needle, electric shock).

The subjective sensations in forced deprivation of sleep for 40-80 hours are very unpleasant and distressing (slowing down of psychical reactions, fatigability, less accuracy in mental work).

The depth of sleep reaches its maximum during the first 2-3 hours, then is gradually reduced, though in some individuals sleep again deepens in the sixth and seventh hours.

Some types of cortical activity and reactions to definite stimuli can be preserved during normal periodic sleep (partial wakefulness). Stimuli to which reactivity is retained and which rapidly cause awakening refer to the signals of high biological or social value for a given individual. For example, partial wakefulness of the cerebral cortex can be observed in a mother who is awakened even by faint groan of her child, but remains unresponsive to other (much

louder) sounds. A person on duty is awakened by a telephone ring, serviceman jumps immediately he hears the sound of a bugle, etc.

Pavlov regarded sleep as a conditioned (internal) inhibition, that is, widespread, irradiated (general) inhibition extending over the entire cerebral cortex and descending to the lower-lying parts of the brain.

The sleep developing under the influence of conditioned inhibitory stimuli was called active sleep in contrast to passive sleep arising upon cessation (or sharp reduction) of the inflow of different signals to the cerebral cortex.

Sechenov confirmed the importance of afferent signalization in maintaining the waking state. For instance, in a patient from all the sense organs only one eye and one ear could function, and he was awake as long as the eye could see and the ear could hear. But as soon as these sole means of contact with the outer world were closed, he would immediately fall asleep. A female patient retained only tactile and muscle sensation in one hand. She slept most of the time and woke only when her hand was touched.

Similar results were obtained in experiment, that is, sleep developed in animals after surgical destruction of the peripheral parts of the visual, auditory and olfactory analysers.

To Pavlov's theory was counterposed the theory of the sleep center. Hess discovered that electrical stimulation of definite points in the anterior portion of the brain stem (in cats) evoked sleep. After fidgeting for a few minutes, the animal chose a place to lie down and purring like a normal cat, fell asleep.

These findings agreed with the observations of neuropathologists and results of histological studies of the brains of victims of lethargic encephalitis. Sleep disorders during this disease are characterized either by pathological sleep lasting for days or by pathological wakefulness (insomnia). Economo discovered changes in different areas of the brain in cases with pathological sleep and those of pathological wakefulness, and considered the existence of the sleep center and the center of wakefulness.

All these facts found new explanation after the functional significance of the reticular formation had been established and the interaction between this structure and the cerebral cortex was fully defined.

Afferent signals passing into the cerebral cortex through the reticular formation of the midbrain and the non-specific thalamus nuclei (reticular activating system) exert an activating influence on the cortex and maintain active waking state. Its elimination (affection of several receptor systems, destruction of the reticular formation or suppression of its functions under the action of narcotics) induces deep sleep. The brain stem reticular formation, in turn, is under continuous activating influence of the cerebral cortex.

Two mutually antagonistic systems responsible for the waking and sleeping state exist in the brain stem. Maintenance of the waking state is associated with the activity of rostral parts of the brain stem reticular formation. Sleep is initiated by the excitation of structures located in the definite areas of the thalamus, hypothalamus and in the caudal parts of the reticular formation that are called hypnogenic.

Almost natural sleep is caused by stimulation of the raphe nuclei in the lower half of the pons and in the medulla oblongata (a thin sheet of nuclei located in the midline). Nerve fibers from these nuclei spread widely in the reticular formation and also upward (into the thalamus, neocortex, hypothalamus, limbic system) and downward (into the spinal cord, terminating in the posterior horns where they can inhibit incoming pain signals). Discrete lesions in the raphe nuclei lead to state of wakefulness.

Many of the endings of fibers from these raphe neurons secrete serotonin. On the other hand, when a drug that blocks formation of the serotonin is administered to an animal, it cannot sleep for the next several days. Therefore, it is assumed that serotonin is the major transmitter substance associated with production of sleep.

Other possible transmitter substances related to sleep were also found: muramyl peptide that accumulates in the cerebrospinal fluid and in the urine in animals kept awake for several days, a nonapeptide isolated from the blood of sleeping animals, etc.

It is possible that prolonged wakefulness causes progressive accumulation of a sleep factor in the brain stem or in the cerebrospinal fluids that leads to sleep.

The origin of dreams is a Fairyland for many people. Up to data the interpreters of dreams are publishing their commentaries. This is intolerable. Because there is nothing mysterious or supernatural in the mechanism of the dreams. The night-time dreams reflect the day- time activity and thoughts of the person. Even, the most fantastic dreams are combinations of the real events.

Dreams are caused by stimulations influencing on the body during the sleep or traces of the stimulations that had influenced before. This was proved by numerous experiments. Even the stencils are known how to cause some dreams. For instance. if the red light rays are directed on the face of the sleeping person, in most of cases he will see a fire in his dream If the tap is opened and the water is flowing- he will see ariver.

Many persons affirm that their dreams are unexpected and far from their thoughts.

In the mechanism of such dreams great is the role of the events that are engraved on one's memory subconsciously. These and also the ability to think logically and draw a true conclusion (to find a sound decision) are responsible for the prophetic dreams.

For a long time sleep was regarded as a rest, full suppression of activity necessary for recovery of the organism's working capacity. But for the brain activity sleep is not simply rest and inhibition though it ensures rest for the skeletal muscles.

During sleep cortical neurons of the motor, visual and other areas are in a state of rhythmic activity the rate of which is not lower, but occasionally even higher than that during the waking state. Only the character of the cortical activity is changed: continual neuron discharges typical for the waking state are replaced by brief group discharges separated from each other by long periods of inactivity. In the period of NREM sleep these group discharges are synchronized (slow waves on the EEG), whereas during REM sleep they are synchronized (more frequent waves on the EEG).

So, cortical inhibition during sleep is not interpreted as the absence of activity, but as transition of this activity to a new regimen in which brain cells are switched off from the peripheral stimuli, and processing of information supplied to the brain during a waking state becomes possible. This process seems to take place in the period of REM sleep, which is deeper than NREM sleep.

The most interesting and incomprehensible type of sleep for the general public is the hypnotic sleep, that is, the suggested sleep. Hypnosis is one of the endless possible suggested states. Some investigators consider that there is no hypnosis at all and there is only the suggestion, and suggestion acts through auto- suggestion.

The hypnotic sleep is caused by the hypnotizing soporific action of a situation or (more frequently) by the manipulations of a hypnotist suggesting a need for sleep. During hypnotic sleep voluntary cortical activity may be suppressed, while partial contact with surroundings and sensomotor activity are retained. Hypnotist may cause by the way of suggestion complete inhibition or excitation of the nerve centers of the muscular system.

There is no physiological phenomenon that could not be caused by the suggestion, and sleep is not an exception, The suggestion is based on the knowledge of life that is impressed in the memory. For instance, a person which has no notion of the Papuans, cannot be suggested that he is one of them.

In the psychoterapeutic practice the hypnosis is used with a great success. But it is a pity that many dishonourable people which have nothing in common with medicine use hypnosis as well as ideomotor acts (the slight muscular movements appearing in body when one is thinking

of the concrete object or living being that is before his eyes) for their mercenary ends and harm the people. These adventurers call themselves parapsychologists (telepaths, extrasenses and so on). It is a duty of every medical man to be well informed of particulars of the tricks of parapsychologists and struggle against them mercilessly.

EXAMPLES OF TESTS

41. Fill the blanks. After the first ligature of Stannius activity of sinus venosus is…., contractions of atria and ventricle are
a) stopped, continued
b) continued, stopped
c) stopped, also stopped
d) continued, also continued

42. Choose the theories explaining the nature of heart automatism
a) monocausalism
b) myogenic
c) vascular
d) nutritional
e) neurogenic
f) constitutionalism

43. Arrange in due order the phases of blood coagulation
a) formation of fibrin
b) formation of thrombin
c) formation of prothrombin activator (prothrombinase)

44. Fill the blanks. Fall of leukocytes number as lower as ……in 1 mcl causes death.
a) 4000-9000
b) 3000-5000
c) 500
d) 1000-3000

45. Fill the blank. Allergic states, helminthic invasion, antibacterial therapy lead to ….
a) basophilia
b) neutrophilia
c) eosinophilia
d) monocytosis

46. The blood of how many people is Rh-positive and how many people have Rh-negative blood?
a) 50% and 50 %
b) 85% and 15%
c) 75% and 25%
d) 15% and 85%

47. Fill the blanks. The persons whose blood belongs to the …group, are called the universal donors, and those who have the … group blood - the universal recipients
a) I, IV
b) IV, I
c) I, II
d) II, III

48. Which is the normal number of erythrocytes in 1 mcl of blood for men and women?
a) 4 - 4.5 and 4.5 - 5 millions
b) 4.5 - 5 and 4 - 4.5 thousands
c) 5 - 6 and 6 - 7 millions
d) 4.5 - 5 and 4 - 4.5 millions

49. Loss of which part of blood mass results in death?
a) 1/3 - 1/2
b) 1/5 - 1/4
c) 1/9 - 1/7
d) 1/10 - 1/8

50. When the first physiology chair was founded in Azerbaijan?
a) 1930
b) 1920
c) 1950
d) 1940

51. Arrange in due order (I- III) the standard leads.
a) left arm - left leg
b) right arm - left arm
c) right arm - left leg

52. The weak stimulation does not cause contraction of myocardium, whereas if the stimulation is strong enough, the heart muscle responds with all its strength. How is this called?
a) staircase phenomenon
b) Frank - Starling law
c) the law "all or nothing"
d) Anrep phenomenon

53. Which is the normal clotting time by Mas and Magro method?
a) 6-12 min
b) 1-3 min
c) 12-15 min
d) 6 -12 sec

54. Which cells are inactivated or destroyed by acquired immunodeficiency syndrome virus?
a) killer cells
b) helper T cells
c) suppressor T cells
d) cytotoxic T cells

55. *Fill the blanks. Increase of the number …is called shift to the left, and that of … shift to the right.*
a) juvenile and stab neutrophils, segmented neutrophils
b) segmented neutrophils, juvenile and stab neutrophils
c) segmented neutrophils, basophils   d) juvenile neutrophils, monocytes

56. *Which is the normal number of leukocytes per microliter of the blood?*
a) 4-5 millions   b) 4000 - 9000   c) 2000 - 4000   d) 200000 – 400000

57. *Which is the minimal and maximal resistance of normal erythrocytes?*
a) 0.24% and 0.34% NaCl   c) 0.54% and 0.40% NaCl
b) 0.40% and 0.34% NaCl   d) 0.34% and 0.40% NaCl

58. *Which is the normal absolute content of hemoglobin for men and women?*
a) 13 - 16 and 12 - 14 gm/dl   c) 12 -14 and 10 - 12 gm/dl
b) 12 - 14 and 13 - 16 gm/dl   d) 16 - 18 and 13 - 16 gm/dl

59. *How much blood is in the healthy adults organism?*
a) 9 -12 litres   b) 2.25 - 3 litres   c) 12 - 13 litres   d) 4.5 - 6 litres

60. *Who creates a well-balanced doctrine of higher nervous activity?*
a) Pavlov   b) Descrates   c) Sechenov   d) Anokhin

61. *In which lead of ECG the largest waves are recorded?*
a) III   b) II   c) I

62. *Arrange in due order the phenomena that accompany strong stimulation of the heart in diastole.*
a) compensatory pause   b) compensatory systole   c) extrasystole

63. *Which is the normal number of thrombocytes in 1 mcl of the blood?*
a) 100000 - 200000   b) 200000 - 400000   c) 400000 - 600000   d) 4000 – 9000

64. *Which type of leukocytes are "the yard-keepers of organism"?*
a) lymphocytes   b) neurtrophils   c) monocytes   d) basophils

65. *Which type of leukocytes produce histamine, heparin, bradykinin and serotonin?*
a) eosinophils   b) neutrophils   c) lymphocytes   d) basophils

66. *Arrange in due order the agglutinogens in the I - IV blood groups.*
a) AB   b) A   c) B   d) 0

67. *Which is the normal colour index?*
a) 0.8 - 1   b) 0.5 - 0.8   c) 1 - 3   d) 5

68. *Which is the normal active reaction of the arterial and venous blood?*
a) 7.4 and 7.35   b) 7.8 and 7.0   c) 7.0 and 7.8   d) 7.35 and 7.4

69. *Choose the excitable tissues.*
a) epithelial   b) nervous   c) muscular   d) glandular   e) connective

70. *Who discovered the reflex and formulated the principle of reflex activity of nervous system?*
a) Descartes   b) Galvani   c) Pavlov   d) Sechenov

71. *Which change in ECG witnesses aggravation of atrioventricular conduction?*
a) increase of PQ interval
c) increase of ST interval
b) increase of QS interval
d) deep Q wave

72. Arrange in due order periods of changes in the heart muscle excitability.
a) period of exaltation   b) relative refractory period   c) absolute refractory period

73. Which is formula to calculate the number of leukocytes?

a) $L = \dfrac{L \cdot 4000 \cdot 20}{25 \cdot 16}$

c) $L = \dfrac{L \cdot 400 \cdot 20}{25 \cdot 16}$

b) $L = \dfrac{L \cdot 4000 \cdot 200}{25 \cdot 16}$

d) $L = \dfrac{L \cdot 4000 \cdot 20}{5 \cdot 16}$

74. Which is the normal nuclear shift index?
a) 0.1 – 1   b) 5 - 10   c) 0.01 - 0.05   d) 0.05 – 1

75. Arrange in due order the agglutinins in the I - IV blood groups.
a) β   b) 0   c) αβ   d) α

76. By the help of which apparatus is ESR determined?
a) Melangeur b) Sahli's hemometer c) Goryayev's camera   d) Panchenkov's apparatus

77. Choose the formula to calculate number of erythrocytes

a) $E = \dfrac{e \cdot 400 \cdot 200}{25 \cdot 16}$ b) $E = \dfrac{e \cdot 4000 \cdot 200}{5 \cdot 16}$ c) $E = \dfrac{e \cdot 400 \cdot 20}{5 \cdot 16}$ d) $E = \dfrac{e \cdot 400 \cdot 20}{25 \cdot 16}$

78. Which is the normal viscosity of the blood and plasma?
a) 5; 1.7 - 2.2   b) 1; 0.5   c) 0.5; 1   d) 1.7 - 2.2; 5

79. By which feedback operate mainly all the control systems of the body?
a) Positive   b) negative, positive c) negative

80. From which year dates existence of the physiology as an independent science?
a) 1528 b) 1828 c) 1728 d) 1628

81. Arrange in due order the phenomena that accompany strong stimulation of the heart in diastole.
a) compensatory pause   b) compensatory systole   c) extrasystole

82. *Which is the normal number of erythrocytes, leukocytes and thrombocytes in 1 mcl of the blood?*
a) 200000-400000; 4000-9000; 4-5 millions
c) 4-5 millions; 200000-400000; 4000-9000
b) 4000-9000;200000-400000;4-5 millions
d) 4-5 millions; 4000-9000; 200000-400000

83. Which type of leukocytes produce histaminase?
a) agranulocytes   b) eosinophils   c) neutrophils   d) basophils

84. Which is the normal absolute content of hemoglobin for men and women?
a) 13-16 and 12-14 gm/dl
c) 12-14 and 10-12 gm/dl
b) 12-14 and 13-16 gm/dl
d) 16-18 and 13-16 gm/dl

85. Which is duration of: systole of atria, systole of ventricles, pause?
a) 0.1-0.4-0.3 sec   b) 0.3-0.4-0.1 sec   c) 0.4-0.1-0.3 sec   d) 0.1-0.3-0.4 sec

86. With which discovery existence of physiology as an independent science is connected?
a) discovery of reflex by Descartes
b) discovery of bioelectrical phenomena by Galvani
c) discovery of greater and lesser circulation by Harvey
d) discovery of inhibitory effect of the vagus nerve by Weber brothers

47. In which lead of ECG the largest waves are recorded?
a) III   b) II   c) I

48. Arrange in due order parts of the specialized excitatory and conductive system of the heart
a) left and right bundles of Purkinje fibers   d) atrioventricular node
b) sinus (sinoarterial) node   e) atrioventricular bundle (bundle of His)
c) internodal pathways

89. Choose the physiological combinations of hemoglobin:
a) oxyhemoglobin   c) carboxyhemoglobin   e) methemoglobin
b) reduced hemoglobin   d) carbohemoglobin

50. Which are the normal osmotic and oncotic pressures of the blood?
a) 3-5 and 3-4 atm   c) 1-2 and 0.03-0.04 atm
b) 13-15 and 2.5-3.5 atm   d) 7.6-8.1 and 0.03-0.04 atm

51.Who discovered reflex arc and formulated the principle of reflex activity of nervous system?
a) Descartes   b) Galvani   c) Sechenov   d) Pavlov

52.Which change in ECG witnesses aggravation of atrioventricular conduction?
a) increase of PQ interval   c) deep Q wave
b) increase of QS interval   d) increase of ST interval

93. Which T cells are inactivated or destroyed by acquired immunodeficiency syndrome virus?
a) killer   b) helper   c) suppressor   d) cytotoxic

94. Fill the blank. Allergic states, helminthic invasion, antibacterial therapy lead to …
a) basophilia   b) neutrophilia   c) eosinophilia   d) monocytosis

95. Arrange in the following order: leukocytosis, leukopenia, leukosis (leukemia)
a) excessive increase of the leukocytes number
b) decrease of the number of leukocytes
c) increase of the number of leukocytes

96. Fill the blank. To convert the absolute content of hemoglobin into relative content one must multiply it by … and vice versa.
a) 9   b) 5   c) 6   d) 16

97. Which is the normal viscosity of the blood and plasma?
a) 5 and 1.7-2.2   b) 1 and 0.5   c) 0.5 and 1   d) 1.7-2.2 and 5

1. Which hormones possess the permissive effect?
a) catecholamines   b) peptide hormones   c) steroids   d) epinephrine

2. Which of the following disturbances causes diabetes insipidus?
a) hypofunction of posterior pituitary gland   c) hypofunction of anterior pituitary gland
b) hyperfunction of posterior pituitary gland   d) hyperfunction of anterior pituitary gland

3. Choose the excitable tissues.
a) connective   b) epithelial   c) nervous   d) muscular   e) glandular

4. What is the time during which the stimulus of double rheobase must infuence the tissue to cause excitation?
a) effective time   b) chronaxy   c) useful time   d) refractory period

5. What is the highest number of the action potentials that the excitable tissue is able to generate in 1 second?
a) refractory period   b) rheobase   c) lability   d) chronaxy

6. Arrange in due order phases of the solitary contraction.
a) period of contraction   b) latent period   c) period of relaxation

7. Choose the laws of conduction of excitation.
a) "all or nothing"   c) isolated conduction   e) physiological electrotonus
b) physiological safety   d) Two-way conduction

8. Which transmitters cause most of acute response of the nervous system?
a) neuropeptide transmitters   c) pituitary peptides
b) small-molecule transmitters   d) substance p

9. Arrange the parts of reflex arc in due order.
a) afferent nerve   c) receptor   e) efferent nerve
b) nerve center   d) working organ

10. Who discovered the feedback in the reflex arc?
a) Pavlov   b) Sechenov   c) Anokhin   d) Descartes

68. Which are the second messengers?
a) steroid hormones   b) AMP and GMP   c) catecholamines   d) proteine hormones

69. Choose the diseases caused by hypothyroidism.
a) cretinism   c) endemic goiter   e) diabetes insipidus
b) Myxedema   d) Basedow's disease

70. Who discovered the "animal electricity?"
a) Harvey   b) Descrates   c) Galvani   d) Sechenov

71. At the moment of closing of the circuit excitation occurs under the cathode, and at the moment of breaking it - under the anode. Which rule is this?
a) polar rule of excitation
b) local reply
c) physiological electrotonus
d) Pfluger's rule of contraction

72. Which of the following processes is responsible for diminution of the total length of the muscle?
a) increase of I discs   c) disappearance of I discs
b) disappearance of A discs   d) increase of A discs

73. Arrange the following structures in order in which the fatigue occurs:
a) muscle   b) nerve center   c) neuromuscular synapse

74. Choose the main characteristics of synapses.
a) two-may conduction   c) one-way conduction   e) physiological safety
b) synaptic delay   d) isolated conduction

75. Whose is the following principle: Whatever smal-molecule transmitter and neuroppeptides are released at one terminal of the neuron, the same transmitters will be released at all other terminals of the same neuron.
a) Pavlov's   b) Prochaska's   c) Dale's   d) Sechenov's

76. Who the first introduced the idea of reflex activity principle of the nervous system?
a) Descartes   b) Pavlov   c) Sechenov   d) Anokhin

77. When the first reflex reactions of the human fetus are revealed?
a) in the II half of the III month of the intrauterine life
b) in the II half of the IX month of the intrauterine life
c) in the I week of the intrauterine life
d) in the IV week of the intrauterine life

78. Choose the parahormones.
a) gastrin   c) villikinin   e) norepinephrine
b) enkephalin   d) renin   f) histamine

79. Which hormones maintain the blood calcium level?
a) parathyroid hormone, calcitonin   c) insulin, parathyroid hormone
b) calcitonin, insulin   d) parathyroid hormone, oxytocin

80. What is characteristic of action potential?
a) stream of sodium ions out of cells   c) stream of potassium ions out of cells
b) stream of potassium ions into cytoplasm   d) stream of sodium ions into cytoplasm

81. When the direct current flows through the nerve or muscle fiber, its excitability and conduction change. How is this phenomenon called?
a) physiological electrotonus   c) local reply
b) polar rule of excitation   d) Pfluger's rule of contraction

82. Which is the ability of smooth muscle to preserve the length given by stretch without changing the tension?
a) refractory period   b) lability   c) rheobase   d) plasticity

83. Where is the saltatory conduction realized?
a) myelinated fibers   b) unmyelinated fibers   c) smooth muscles   d) skeletal muscles

84. Arrange the nerve fibers in the following order: motor, sensory, preganglionic, postganglionic.
a) B   b) C   c) Aα d) Aβ, Aγ, AΔ

85. Who and when discovered the central inhibition?
a) Sechenov, 1861   b) Pavlov, 1861   c) Vvedensky, 1930   d) Ukhtomsky, 1910

86. Who the first proved the reflex nature of the psychical activity?
a) Prochaska   b) Anokhin   c) Descartes   d) Sechenov

87. Choose the spinal reflexes.
a) pupillary   c) rubbing   e) plantar   g) vomiting
b) flexor   d) scratch   f) knee

88. Which of the following growth hormone secretion disturbances causes acromegaly?
a) hypersecretion after adolescence
c) hypersecretion in childhood
b) hyposecretion in childhood
d) hyposecretion after adolescence

89. In which of the following cases the "moon face" is observed?
a) excess of cortisol secretion
c) hypersecretion of epinephrine
b) hyposecretion of cortisol
d) hyposecretion of thyroxin

90. What is characteristic of excitation?
a) hyperpolarization
c) long-term delolarization
b) depolarization
d) repolarization

91. Choose the electrophysiological proofs of inhibition
a) Polarization
c) Depolarization
e) Repolarization
b) Hyperpolarization
d) Protracted depolarization

92. How many muscle fibers have eyeball and gastrocnemius muscle in a motor unit?
a) several hundreds, less than 10
c) 1 and 10
b) less than 10, several hundreds
d) 50 and 5

93. Choose the advantages of the saltatory conduction:
a) decrease of the velocity of conduction
d) the conduction is isolated
b) increase of the velocity of conduction
e) the physiological safety is provided
c) the energy is conserved for the axon

94. Arrange in due order the stages of parabiosis.
a) paradoxical
b) inhibitory
c) provisory

95. In which cerebral structure did Sechenov first discover the central inhibition?
a) cerebral cortex
b) hypothalamus
c) medulla oblongata
d) thalamus

96. Who discovered the conditional reflexes?
a) Anokhin
b) Descartes
c) Sechenov
d) Pavlov

97. Choose the bulbar reflexes:
a) sucking
b) vomiting
c) micturition
d) corneal
e) defecation

98. Thanks to which method it is possible to study the higher nervous activity without hurting the organism?
a) electroencephalography b) radiotelemetry   c) conditioned reflex d) electromyography

99. How much sweat is secreted daily?
a) 100 ml
b) 500 ml
c) 1000 ml
d) 1500 ml

100. Which is the action of antidiuretic hormone on the permeability of collecting ducts wall and volume of excreted urine?
a) increases, decreases b) decreases, increases   c) increases, increases d) decreases, decreases

101. How much definitive urine is removed from the organism daily?
a) 200 ml
b) 0.5 ml
c) 1-1.5 ml
d) 3 ml

102. Which mechanism of thermoregulation is important: in warm and cold?
a) chemical, chemical
c) physical, physical
b) chemical, physical
d) physical, chemical

103. Put in the missing phrase: The ratio of volume of the carbon dioxide given off by the organism to the volume of the oxygen consumed by the organism is called…

a) caloric equivalent of oxygen
b) caloric / thermal coefficient of nutritive matter
c) amortization coefficient
d) respiratory coefficient

104. Choose the "contra-insular" hormones:

a) glucagon
b) adrenalin
c) glucocorticoids
d) enterogastrone
e) somatotropic hormone
f) gastrin
g) thyroxin

105. Arrange in due order phases of pancreatic secretion

a) gastric
b) intestinal
c) cephalic

106. How much is daily gastric secretion?

a) 500 ml
b) 1000 ml
c) 1500 ml
d) 3 l

107. By which gradient does carbon dioxide diffuse from the cells into the interstitial fluid and then into the blood of tissues capillaries?

a) 46→45→40 mm Hg
b) 95→40→23 mm Hg
c) 100→60→40 mm Hg
d) 50→25→15 mm Hg

108. How much are: the minute respiratory volume, the dead space air?

a) 8l; 150 ml
b) 800 ml; 150 ml
c) 15 l; 500 ml
d) 3 l; 300 ml

109. The person is balance on the scales and when he is intensively thinking over the problem his head becomes heavier and the balance is disturbed. Whose experiment is this?

a) Walter
b) Mosso
c) Claude Bernard
d) Descartes

110. Which is the nature of vasoconstrictors and vasodilators?

a) adrenergic, cholinergic
b) cholinergic, adrenergic
c) cholinergic, cholinergic
d) adrenergic, adrenergic

111. Which is blood flow velocity (mm/sec) in the aorta and in capillaries?

a) 33 and 0.3
b) 0.3 and 33
c) 3.3 and 0.03
d) 330 and 3

112. When is the heart stopped as a result of stimulation of sympathetic and vagus nerves?

a) systole, systole
b) diastole, diastole
c) systole, diastole
d) diastole, systole

113. Arrange in due order phases of systole of ventricles:

a) slow ejection
b) rapid ejection
c) asynchronous contraction
d) isometric contraction

114. Fill the blanks. The secretory nerves of sweat glands are the … nerves and mainly … is secreted in their nerve endings.

a) sympathetic, acetylcholine
b) vagus, acetylcholine
c) sympathetic, adrenalin
d) vagus, adrenalin

115. How much is the normal glomerular filtration rate for two kidneys?

a) 100 ml/sec
b) 100 ml/min
c) 125 ml/min
d) 250 ml/sec

116. How much are the optimal daily norms of: prteins, fats, carbohydrates?

a) 80-100 g, 70 g, 400-450 g
b) 70 g, 400-450 g, 80-100 g
c) 80-100 g, 400-450 g, 70 g
d) 400-450 g, 70 g, 80-100 g

117. Put in the missing word: Amount of heat released when 1 litre of oxygen is consumed is called…
a) caloric equivalent of oxygen
b) caloric/thermal coefficient of nutritive matter
c) respiratory coefficient
d) oxygen index

118. How much is the amortization coefficient?
a) 0.028 – 0.075
b) 0.28-0.75
c) 2.8-7.5
d) 28-27

119. During which time do the mixed food remain in the stomach?
a) 30 minutes
b) 1 hour
c) 6-10 hours
d) 2 days

120. How much gastric juice is secreted daily?
a) 100-25 ml
b) 0.5 l
c) 1-1.5 l
d) 2-2.5 l

121. By which gradient does oxygen diffuse from the blood into the interstitial fluid and then into the cells?
a) 95→40→23 mm Hg
b) 100→60→40 mm Hg
c) 46→45→40 mm Hg
d) 95→60→23 m Hg

122. Choose the components of the vital capacity:
a) inspiratory reserve volume
b) residual volume
c) tidal volume
d) expiratory reserve volume
e) total lung capacity

123. How much is the coronary blood flow in norm and during physical work?
a) 200-250 ml and 3-4 l
b) 65-70 ml and 3-4 l
c) 5 l and 15 l
d) 200-250 ml and 500-600 ml

124. In whose experiment the vasoconstrictive effect of the sympathetic nerves was first revealed?
a) Pavlov
b) Ovsyannikov
c) Claude Bernar
d) Walter

125. Which are the maximal linear velocity of blood flow and that of pulse wave spreading (m/sec)?
a) 3-5 and 55-95
b) 0.55-0.95 and 0.03-0.05
c) 0.3-0.5 and 5.5-9.5
d) 5.5-9.5 and 0.3-0.5

126. Which are parasympathetic and sympathetic mediators?
a) adrenalin and norepinephrine; acetylcholine
b) norepinephrine; adrenalin and acetylcholine
c) adrenalin; norepinephrine
d) acetylcholine; adrenalin and norepinephrine

127. Arrange in due order phases of the diastole of ventricles:
a) slow filling of ventricles
b) presystole
c) isometric relaxation
d) protodiastole
e) rapid filling of ventricles

128. How much is the coronary blood flow in norm and during physical work?
a) 200-250 ml and 3-4 l
b) 65-70 ml and 3-4 l
c) 5 l and 15 l
d) 200-250 ml and 500-600 ml

129. How do the painful stimulation effect the diuresis?
a) increase
b) do not change
c) decrease or stop
d) do not change or stop

130. Which is the effect of small and large doses of adrenalin on the glomerular filtration?
a) decreases, increases   b) increases, decreases   c) decreases, decreases   d) increases, increases

131. At which volume of urine and level of pressure does the micturition reflex occur?
a) 250-300 ml; 15-16 cm of water column   c) 1-1.5 l; 15-16 mm Hg
b) 15-30 ml; 15-16 mm Hg   d) 0.5-1 l; 250-300 mm Hg

132. Which is the order of the calorifi coefficient of fats, proteins, carbohydrates (kcal)?
a) 9.3-9.3-4.1   b) 4.1-4.1-9.3   c) 9.3-4.1-4.1   d) 4.1-9.3-4.1

133. Fill the blank. Amount of heat released when 1 g of nutritive matter is burnt in the organism is called……
a) caloric equivalent of oxygen   b) caloric / thermal coefficient of nutritive matter
c) respiratory coefficient   d) oxygen index

134. On which level of the hydrostatic pressure (mm Hg) the absorption is stopped?
a) 8-10   b) 20-30   c) 80-100   d) 100-120

135. To which phase of gastric secretion belongs secretion of the gastric juice during the sham feeding of the dog with esophagotomy?
a) cephalic   b) intestinal   c) gastric

136. Which is shortcoming of Heidenhain's method of isolated stomach?
a) gastric juice secretion by the reflex way is disturbed
b) gastric juice secretion by the humoral way is disturbed
c) gastric juice secretion by the reflex as well as humoral way is disturbed
d) the juice is mixed with the food

137. How much is the pressure difference (mm Hg) causing the carbon dioxide diffusion from the pulmonary capillaries into the alveoli?
a) 45-40=5   b) 45-5=40   c) 100-40=60   d) 100-60=40

138. How much is the pressure (mm Hg) in the pleural cavity during the expiration and inspiration?
a) (-6) and (-3)   b) (-3) and (-6)   c) 3 and 6   d) 6 and 3

139. Choose the vasodilative substances:
a) angiotensin   c) acetylcholine   e) prostaglandins   g) histamin
b) epinephrine   d) medullin   f) bradykinin

140. Arrange in the order of recording of a, c, v waves on phlebogram.
a) contraction of ventricles   b) contraction of atria
c) pulsation in the common carotid artery

141. Which are normal systolic, diastolic and pulse pressures (mm Hg)?
a) 35-40; 60-80; 110-125   c) 150-170; 110-115; 60-80
b) 110-125; 60-80; 35-40   d) 60-80; 35-40; 15-20

142. Which are actions on heart activity of potassium and calcium ions?
a) strengthen, weaken   c) weaken, weaken
b) weaken, strengthen   d) strengthen, strengthen

143. Which are the normal stroke index and cardiac index?
a) 65-70 ml and 5 l/min   c) 5 l and 3 l/min
b) 3 l/min and 7 l   d) 45-55 ml/m^2 and 3 l/min

144. How do the painful stimulation effect the diuresis?
a) increase   b) do not change   c) decrease or stop   d) do not change or stop

145. Which is the effect of aldosterone?
a) decreases resorption of calcium in tubules
b) increases resorption of potassium in tubules
c) decreases reabsorption of sodium and potassium in tubules
d) increases reabsorption of sodium in tubules

146. How much is the specific gravity of urine?
a) 1.012-1.020   b) 0.012-0.020   c) 1.090   d) 1.025-1.035

147. How much is the filtration pressure?
a) 50-(20+10)= 20 mm Hg   c) 70-(20+30)=20 mm Hg
b) 100-(70+20) = 10 mm Hg   d) 70+(20+30) = 120 mm Hg

148. How much is the respiratory coefficient for carbohydrates, fats, proteins?
a) 0.8-1-0.7   b) 0.7-1-0.8   c) 1-0.7-0.8   d) 0.8-0.7-1

149. Fill the blank. The mineral substances which compose less than …% of body mass are called microelements or trace elements.
a) 1   b) 0.1   c) 0.01   d) 0.001

150. Where is the process of absorption mainly realized?
a) oral cavity   b) stomach   c) jejunum and ileum   d) duodenum

151. Arrange in due order the phases of gastric secretion.
a) intestinal   b) cephalic   c) gastric

152. Which type of breathing is characterized by slowly waxing and waning respiration, occurring over and over again approximately every 40-60 seconds?
a) Biot   b) Cheyne-Stokes   c) Cussmaul   d) Agonal

153. How much is the initial pressure (mm Hg) difference forcing oxygen to diffuse into the pulmonary capillaries?
a) 64-40=24   b) 104-40=64   c) 104-64=40   d) 64-24=40

154. How much lymph returns into the blood through the thoracic duct daily?
a) 100-300 ml   b) 0.5-1 l   c) 1-3 l   d) 3-5 l

155. Choose the vasoconstrictive substances
a) norepinephrine   c) vasopressin   e) serotonin   g) prostaglandins
b) epinephrine   d) angiotensin   f) medullin

156. How much is the time of the complete circuit of the blood?
a) 10-13 sec   b) 1-2 min   c) 2-3 sec   d) 20-23 sec

157. Which is the action of cathecholamines on heart activity directly and through the vagus nerve center?
a) strengthen, inhibit   c) strengthen, strengthen
b) inhibit, strengthen   d) inhibit, inhibit

158. Which are the normal values of cardiac output an stroke volume?
a) 5 l and 65-70 ml   b) 5 l and 1 l   c) 65-70 ml and 5 l   d) 1 l and 5 l

159. When the heart activity is stopped as a result of long stimulation sympathetic and vagus nerves?
a) systole, systole   b) diastol, diastol   c) systole, diastole   d) diastole, systole

160. How much is the minute respiratory volume?
a) 800 ml   b) 8 l   c) 15 l   d) 3 l

161. How much is the normal utilization coefficient?
a) 75-100%   b) 3-5%   c)50-60%   d) 25-35%

162.How much is the normal daily secretion of saliva?
a) 300-500 ml   b) 80-150 ml   c) 2 l   d)800-1500 ml

163. Where is the process of absorption realized mainly?
a) oral cavity   b) stomach   c) jejunum and ileum   d) duodenum

165. Choose the "contra-insular" hormones.
a) glucagon   b) adrenalin   c) glucocorticoids   d) enterogastrone
e) somatotropic hormone   f) gastrin   g) thyroxin

165. How much are the optimal daily norms (g) of proteins, fats, carbohydrates?
a) 80-100; 70; 400-450   b) 70; 400-450; 80-100
c) 400-450; 80-100; 70   d) 80-100; 400-450; 70

166. Put in the missing word. When the blood supply of kidneys is getting worse, in their juxtraglomerular cells…is synthesized.
a) gastrin   b) medullin   c) prostaglandins   d) renin

167.Arrange effects of the extracardial nerves on heart activityin the following order:chronotropic, inotropic, bathmotropic, dromotropic.
a) on the conduction of myocardium   b) on the excitability of myocardium
c) on the rate of the heart beat   d) on the strength of heart muscle contraction

168. Choose the properties of the lymph
a) alkaline   d) does not coagulate
b) acid   e) lesser than blood viscosity   g) contains erythrocytes
c) coagulates   f) more than blood viscosity   h) does not contain erythrocytes

169. How much is the initial pressure (mm Hg) difference forcing oxygen to diffuse into the pulmonary capillaries?
a) 64 - 40 =24   b) 104 - 40 = 64   c) 104 - 64 = 40   d) 64 - 24 = 40

170. How much is the specific gravity of saliva?
a) 0.001-0.017   b) 0.020-0.040   c) 1.001-1.017   d) 1.020-1.040

171. Which function of the liver is demonstrated by the method of Ecc?
a) participation in the carbohydrate metabolism   c) barrier function
b) participation in the protein metabolism   d) d) participation in the fat metabolism

172. How much is the daily balance of sodium?
a) 4-5 g (10-12.5 g NaCl)   c) 2-2.5 g (5-6.25 g NaCl)
b) 8-10 g (20-25 g NaCl)   d) 12-15 g (30-37.5 g NaCl)

173. How much is the respiratory coefficient when the mixed food is taken?
a) 1   b) 0.85-0.9   c) 0.7   d) 0.8

174. Which mechanism of thermoregulation is important in warm and in cold
a) chemical, chemical b) chemical, physical   c) physical, physical   d) physical, chemical

175. Which is the quantity of glomerular filtrate formed each day?
a) 180 l   b) 18 l   c) 1. 8 l   d) 180 ml

176. Which heart sounds are heard in auscultation and which are not heard?
a) III, IV and I, II   b) I, II and III, IV   c) I, III and II, IV   d) II,IV and I, III

177. Arrange in due order the periods of the influence of the extracardial nerves stimulation on the heart activity
a) the period of action   b)the latent period   c)the period of afert- action

178. How much lymph returns into the blood through the thoracic duct daily?
a) 0.5-1 l   b) 100-300   c) 1000-3000 ml   d) 3-5 l

179. Choose the methods of investigation of the enteric secretion .
a) Thiry   b) Vella   c) Heidenhain   d) Basov   e) Pavlov

180. Which is the normal blood glucose level?
a) 0.44-0.67 mmol/l (8-12 mg%)   b) 44 - 67 mmol/l (800-1200 mg%)
c) 4.4- 6.7 mmol/l (80-120 mg%)   d) 6.7-8.4 mmol/l (120-160 mg%)

181. How much is the daily balance of iron?
a)10-30 mg   b) 20-60 mg   c) 1-3 mg   d) 1-3 g

182. How much is the normal basal metabolic rate?
a) 1700 cal   b)170 cal   c) 170 kcal   d) 1700 kcal

183. Put in the missing number. When water evaporates from the body surface, … .kcal of heat is lost for each gram of water that evaporates.
a) 5.8   b) 58   c) 0.58   d) 10

184. What becomes of filtration if the pressure inside the glomerular capillaries is as low as 50 mm Hg or the sum of capsular pressure is as high as 70 mm Hg?
a) is increased   b) is stopped   c) is decreased   d) does not change

185. Which is the effect of adrenalin's small and large doses on filtration?
a) decreases, increases   b) increases, decreases   c) decreases, decreases
d) increases, increases

186.Arrange in order where are auscultated: mitral valve, tricuspid valve, aortic valve, pulmonary valve.
a) in the II intercostal region, at the right age of the breast bone
b) in the II intercostal region, at the left edge of the breast bone
c) over the apex of the heart
d) on the xiphoid process of the breast bone

187.Which are 1) parasympathetic and   2) sympathetic mediators?
a) 1) adrenalin, noradrenalin 2) acetylcholine
b) 1) norepinephrine, adrenalin 2) acetylcholine
c) 1) adrenalin 2) norepinephrine
d) 1) acetylcholine 2) adrenalin, norepinephrine

188.How much is the dead space air?
a) 500 ml   b) 3-5 l   c) 150 ml   d) 1500 ml

189.How much is the normal ventilation-perfusion ratio?
a) 8 b) 0.08   c) 5   d) 0.8

190. By which methods absorption is studied?
a) angiostomy (London)   d) vividiffusion (Abel)
b) Basov   e) isolated stomach (Heidenhain)
c) isolated stomach (Pavlov)   f) sham feeding (Pavlov)

191. Choose the humoral stimulants of bile formation.
a) bile   c) glucagon   e)cholecystokinin-pancreozymin
b) secretion   d) gastrone   f) trypsin

192. Which level of hyperglycemia causes glucosuria?
a) 89-100 mmol/l (1600-1800mg%)   b) 10-20 mmol/l (180-360 mg%)
c) 0.89 - 1 mmol/l (16-18 mg%)   d) 8.9-10 mmol/l (160-180 mg%)

193. How much is the calorific coefficient of fats, proteins, carbohydrates (kcal) ?
a) 9.3 - 9.3 - 4.1   b) 4.1 - 4.1- 9.3   c) 9.3 - 4.1 - 4.1   d) 4.1 - 9.3 - 4.1

194. How much is the specific gravity of urine?
a) 1.012 - 1.020   b) 0.012 - 0.20   c) 1.090   d) 1.025 - 1.035

194.   Which property of nerve centers does the following experiment demonstrate? Stimulation of the spinal cord's posterior root causes the action potential in the anterior root, whereas no action potential is recorded in the posterior root when the anterior root is stimulated.
a) two-way conduction   b) one-way conduction c) delay of conduction d) summation

195. The reflex reaction during simultaneous stimulation of two nerve fibers is weaker than the sum of reactions caused by separate stimulation of these fibers. What is this?
a) inhibition   b) facilitation c) occlusion   d) potentiation

196. When a spinal dog is suspended by the trunk, pressure applied to one of its paws elicits reflex movements of a walking type in all four legs. Which reflex is this?
a) scratch reflex   b) stretch reflex   c) Babinsky's reflex   d) Philippson's reflex

197. With which function are the red nucleus and the midbrain reticular formation closely connected?
a) regulation of optic function   b) regulation of auditory function
c) regulation of coordination   d) regulation of muscular tone

198. Choose the symptoms of disorders following excision of cerebellum.
a) atony   b) astasia   c) asthenia   d) hyperglycemia   e) ataxia
f) dysmetria g) disequilibration

199.   Which is the highest pain center?
a) medulla oblongata b) mesencephalon   c) thalamus   d) red nucleus

200. Which patients have mimic immobility of the face?
a) spinal   b)pallidal   c) bulbar   d) mesencephalic

201. Which changes are detected by muscle spindle and Golgi tendon?
a) muscle length, muscle tension b) muscle tension, muscle tension
c) muscle tension, muscle length d) muscle length, muscle length

202. Arrange in order of localization of the sweet and salty tastes, the bitter taste, the sour taste
a) posterior tongue and soft palate b) tip of the tongue c) two lateral sides of the tongue

203. What is myopia?
a) eyeball is too long   c) ability of lens to accommodation is increased
b) eyeball is too short   d) the lens is almost totally nonaccomodating

204. Which structures of the brain play the main role in the mechanism of the temporary connection?
 a) brain stem, spinal cord   c) cerebral cortex, pons
 b) cerebral cortex, spinal cord   d) cerebral cortex, brain stem reticular formation

205. Choose types of the conditioned inhibition.
a) delayed conditioned reflex b) extinction   c) differentiation
d) protective inhibition   e) conditioned inhibitor

206. Which is the principal mechanism of irradiation of excitation from one part of the cortex to another?
 a) subcortex-cortex-subcortex   c) cortex-subcortex-cortex
 b) horizontal   d) subcortex-cortex-cortex

207. Arrange in the following order: sanguine, phlegmatic, choleric, melancholic.
a) inert b) weak   c) pugnacious d) lively

208. When the first signs of development of the second signaling system appear?
a) during the second half of the first year of the infant's life
b) within a few days after the birth
c) at the moment of the birth
d) during the first half of the first year of the infant's life

209. How much time does transmission of excitation through one synapse require?
a) 15-20 msec b) 1.5-2 msec c) 15-20 sec d) 1.5--2 sec

210. Thanks to which process the principle of the final common path is possible?
a) facilitation b) convergence   c) potentiation d) occlusion

211. Which level of spinal cord transaction causes the spinal shock?
a) not higher than the IV-V cervical segments c) not higher than the IV-V thoracic segments
b) not lower than the IV-V cervical segments d) not lower than the IV-V thoracic segments

212. After destruction of which part of the brain the animal lapses into a deep sleep?
a) red nucleus   c) substantia nigra
b) medulla oblongata   d) reticular formation in the upper parts of the brain stem

213. Arrange in the following order: astasia, asthenia, ataxia, adiadochokinesis.
a) quick tiring
b) inability to perform quick movements with groups of antagonist muscles
c) disturbance of coordination of movements
d) continuous trembling or swaying of the animal's head, trunk, extremities

214. In which of hypothalamic nuclei are the center of hunger and the center of satiety situated?
a) lateral, lateral
c) lateral, ventromedial
b)ventromedial, lateral
d) ventromedial, ventromedial

215. By which waves are alpha waves replaced during deep sleep and under different stimulations?
a) beta; theta and delta
b) theta; beta and delta
c) beta and theta; delta
d) theta and delta; beta

216. Choose the nerve centers that are situated in the medulla oblongata.
a) urination   b) defecation   c) inhibiting heart activity   d) lacrimation
e) salivation   f) vasomotor   g) ejaculation

217. Where lie the far and near points of distinct vision for a normal eye?
a) 10 cm, infinity   b) 1 m, infinity   c) infinity, 10 cm   d) infinity, 1m

218. Which lenses must use a myopic person to see distant objects clearly?
a) cylindrical b) biconvex   c) concave

219. Which structure of the brain plays an important role in learning?
a) hippocampus
c) hypothalamus
b) medulla oblongata
d)mesencephalon

220. Where are the processes of analysis most developed?
a) receptors   b) hypothalamus   c) red nucleus   d) cerebral cortex

221. What is the expression of "reaction of awakening" in EEG?
a) synchronization   b) desynchronization c) alpha waves   d) theta waves

222. Choose the lower motivations.
a) biological   b) primary   c) social   d) visceral   e) unconditioned

223. How much is the time of knee reflex and that of wink reflex?
a) 20-24 msec; 50-200 msec   b) 50-200 msec; 20-24 msec
c) 20-24 sec; 50-200 sec   d) 2-4 msec; 5-20 msec

224. Who formulated the principle of dominant?
a) Ukhtomsky b) Vvedensky c) Sechenov   d) Pavlov

225. Which part of the brain participates in the coordination of all complex motor acts of the organism?
a) pons   b) cerebellum   c) medulla oblongata   d) spinal cord

226. Which is interrelation between the latent periods of evoked potentials in the cerebral cortex during stimulation of the specific (1) and non-specific (2) nuclei?
a) 1>2   b) 1=2   c) 1<2

227. Multiple small lesions in which structure do cause St Vitus' dance (chorea)?
a) caudate nucleus   b) medulla oblongata   c) pons   d) putamen

228. Choose the substances which do not pass through the haemato-encephalic barrier.
a) iodine compounds   c) immune bodies   e) alcohol
b) nitrates   d) antibiotics   f) strychnine

229. Which analyser supplies the brain with 90% of the information coming from all receptors?
a) gustatory   b) auditory   c) taste   d) visual

230. What is presbyopia?
a) the lens is almost totally nonaccomodating   c) eyeball is too short
b) ability of lens to accomodation is increased   d) eyeball is too long

231. Which is the sequence of conditioned and unconditioned stimulation for building conditioned reflexes?
a) simultaneous   b) unconditioned, conditioned   c) conditioned, unconditioned

232. Arrange in the following order: descriptive memory, emotional memory, verbal logical memory.
a) a similar situation elicits emotions that attended the previously experienced events
b) inherited only in man   c) reproduces the image of a vital object

233. In which phenomenon complex forms of cortical synthesis are expressed?
a) dynamic stereotype   b) irradiation   c) occlusion   d) facilitation

234. Arrange in due order the phases of neurosis.
a) inhibitory   b) paradoxical   c) equalizing   d) ultraparadoxical

235. Which lenses must a hypermetropic person use for reading?
a) cylindrical   b) biconvex   c) concave

236. Fill in the blanks: Stimulation of specific nuclei causes..., whereas stimulation of non-specific nuclei causes...
a) activation reaction, primary responses   b) primary responses, activation reaction
c) both-primary responses   d) both-activation reaction

237. Choose the centers that are in the sacral segments of the spinal cord.
a) urination   b) defecation c) erection   d) ejaculation e) lacrimation f) salivarion

238. How much is the refractive power of the human eye for viewing distant and near objects?
a) 59 and 70.5 D   b) 70.5 - 59 D   c) 5 and 7 D   d) 7 and 5 D

239. What is hypermetropia?
a) eyeball is too long   c) ability of lens to accomodation is increased
b) eyeball is too short   d) the lens is almost totally nonaccomodating

240. Choose the characteristics of conditioned reflexes.
a) inborn   b) acquired   c) individual d) specific   e)unstable   f) stable
g) can be realized at the level of the brain stem and spinal cord
h) are the function of the cerebral cortex

241. Arrange in due order stages of memory.
a) recollection   b) remembering   c) storage of experience

242. What forms the basis for development of various habits (skills), automatic actions and a definite system of behaviour?
a) dynamic stereotypeb) occlusion   c) facilitation d) irradiation

243. When formation of temporary connections of the first signaling system in the cerebral cortex of a full-term baby begins?
a) within a month after the birth   b) within a few days after the birth
c) at the moment of the birth   d) within two weeks after the birth

245. Choose the parts of the functional system by Anokhin.
a) afferent synthesis   b) decision taking   c) acceptor of the result of the action
d) feedback afferentation   c) temporary connection

246. What is unconsciousness from which the individual can be aroused by sensory or other stimuli?
a) consciousness   b) motivation c) emotion   d) sleep

247. Choose the factors which promote filling of the heart by blood.
a) remainder of the motive power created   d) additional sucking force in ventricles
  by preceding systole of ventricles   e) additional sucking force in atria
b) positive pressure in the chest   f) valves in vein
c) negative pressure in the chest   g) valves in arteries

248.   Arrange in due order the I-IV heart sounds.
a) vibrations of the ventricles' valves in the presystolic period
b) simultaneous slapping of the leaflets of the mitral and tricuspid valves
c) vibrations of the ventricles' walls in the phase of their rapid filling
d) simultaneous sudden closure of the aortic and pulmonary valves

249.   Arrange the Holtz reflex arch in due order
a) vagus nerve   c) celiac plexus   e) vagus nerve nuclei
b) splanchnic nerve   d) heart

250.   Choose the methods of the enteric secretion investigation.
a) Thiry   b) Vella   c) Heidenhain   d) Basov   e) Pavlov

251.   Which is the action of atropine on the salivation?
a) is increased   b) is decreased   c) is not changed   d) is stopped

252. Put in the missing phrase: The power expenditures of the organism in resting state, on an empty stomach and at the temperature of comfort is called...
a) caloric coefficient of nutritive matter   c) respiratory coefficient
b) basal metabolic rate   d) amortization coefficient

253. Which nutritive substances are subjected to the chemical processing in the oral cavity?
a) proteins   b) fats   c) proteins, fats   d) carbohydrates

254. Put in the missing phrase: Amount of the heat released when 1 g of nutritive matter is burnt in the organism, is called...
a) caloric equivalent of oxygen
b) caloric (thermal) coefficient of nutritive matter
c) respiratory coefficient

255. How much is the normal basal metabolic rate?
a) 1700 cal   b) 170 cal   c) 170 kcal   d) 1700 kcal

256. Which mechanism of thermoregulation is important: in warm, in cold?
a) physical, chemical   b) chemical, chemical   c) chemical, physical   d) physical, physical

257.How much is the total surface of the glomerular capillary walls?
a) 0.15-0.2 m^2 b)15-20 m^2 c)1.5-2 m^2 d) 4-5 m^2

258.How much is the normal glomerular filtration rate for two kidneys?
a) 250 ml/min   b) 25ml/min   c)125 ml/min   d)100 ml/sec

259.Which is the protodiastolic period?
a) the time from the beginning of the relaxation of the ventricles to the slapping of the tricuspid valve
b) the time from the beginning of the relaxation of the ventricles to the slapping of the semilunar valves
c) the time from the beginning of the period of ejection to the slapping of the semilunar valves
d) the time from the beginning of the period of tension to the slapping of semilunar valves

260.Arrange in the following order: phonocardiography, electrokymography, ballistocardiography, dynamocardiography.
a) electrical recording of the movements of cardiac shade outline on the screen of the X-ray apparatus
b) recording of vibrations of all the body resulted from the jet propulsions
c) recording of the heart sounds
d) recording of displacement of the chest's centre of gravity, caused by movements of the heart

261.How much is the minute respiratory volume?
a) 800 ml   b) 8 l   c) 15 l   d) 1 l

262.Choose the factors inhibiting the gastric secretion.
a) the fatty food   b) enterogastrone   c) gastrin   d) gastrone
e) urogastrone   f) acetylcholine   g) epinephrine

263.Choose the states when the nitrogen balance is positive.
a) growth of the organism   d) protein deprivation
b) pregnancy   e) increase of the musculature mass
c) recovery after severe disease   f) deficiency of amino acids

264.Which is the normal blood glucose level?
a) 0.44 - 0.67 mmol/l (8-12 mg %)   c) 4.4-6.7 mmol/l (80-120 mg %)
b) 44-67 mmol/l (800-1200 mg %)   d) 6.7 - 8.4 mmol/l (120-160 mg %)

265.Put in the missing phrase: Amount of the heat released when 1 litre of oxygen is consumed by the organism, is called...
a) calorific equivalent of oxygen
b) caloric (thermal) coefficint of nutritive matter
c) respiratory coefficient

266.Arrange in the following order: Dagnini-Aschner reflex, Holtz reflex, Bainbridge reflex.
a) decrease of pulse rate after pressing of eyeballs
b) strengthening of heart activity as a result of the venous congestion
c) cardiac arrest or marked decrease of heart rate after trashing of the stomach.

267.Which is characteristic of salivation in response to stimulation of the parasympathetic nerve fibers?
a) a large amount of thick saliva   c) a large amount of watery saliva
b) a small amount of thick saliva   d) a small amount of watery saliva

268.During which time does the mixed food remain in the stomach?
a) 6-10 hours   b) 1 hour   c) 30 minutes   d) 2 days

269. At which body temperature heat stroke occurs?
a) 38 ^{O}C
b) 39 ^{O}C
c) 39-40 ^{O}C
d) 40-41 ^{O}C

270. How much is the coronary blood flow in norm and during the physical work?
a) 200-250 ml and 3-4 l
b) 65-70 ml and 3-4 l
c) 5 l and 15 l
d) 200-250 ml and 500-600 ml

271. Which is the blood flow velocity in the aorta and in capillaries (mm/sec)?
a) 33 and 0.3
b) 0.3 and 33
c) 3.3 and 0.03
d) 330 and 3

272. Which is effect of stimulation of the vagosympathetic fascicle in frog on its heart activity?
a) inhibition, then excitation
b) excitation, then inhibition
c) inhibition
d) excitation

273. Which is the effect of aldosterone?
a) decreases resorption of sodium in tubules
b) increases reabsorption of potassium in tubules
c) decreases reabsorption of sodium and potassium in tubules
d) increases reabsorption of sodium in tubules

270. Choose the advantages of the saltatory conduction:
a) decrease of the velocity of conduction
b) increase of the velocity of conduction
c) the energy is conserved for the axon
d) the conduction is isolated
e) the physiological safety is provided

271. How many muscle fibers have eyeball and gastrocnemius muscle in a motor unit?
a) several hundreds, less than 10
b) less than 10, several hundreds
c) 1 and 10
d) 50 and 5

272. Choose the electrophysiological proofs of inhibition:
a) polarization
b) hyperpolarization
c) depolarization
d) protracted depolarization
e) repolarization

273. What is characteristic of excitation?
a) hyperpolarization
b) depolarization
c) long-term depolarization
d) repolarization

274. Which of the following growth hormone secretion disturbances causes acromegaly?
a) hypersecretion after adolescene
b) hyposecretion in childhood
c) hypersecretion in childhood
d) hyposecretion after adolescence

279. At the moment of closing of the circuit excitation occurs under the cathode, and at the moment of breaking it - under the anode. Which rule is this?
a) polar rule of excitation
b) local reply
c) physiological electrotonus
d) Pfluger's rule of contraction

276. Who discovered the feedback in the reflex arc?
a) Pavlov
b) Sechenov
c) Anokhin
d) Descrates

277. Which transmitters cause most of acute response of the nervous system?
a) neuropeptide transmitters
b) small molecule transmitters
c) pituitary peptides
d) substance P

278. Choose the laws of conduction of excitation:
a) "all or nothing"
b) physiological safety
c) isolated conduction
d) two-way conduction
e) physiological electrotonus

279. Arrange in due order phases of the solitary contraction:
a) period of contraction   b) latent period   c) period of relaxation

280. What is the highest number of the action potentials that the excitable tissue is able to generate in 1 second?
a) refractory period   b) rheobase   c) lability   d) chronaxy

281. What is the time during which the stimulus of double rheobase must influence the tissue to cause excitation?
a) effective time   b) chronaxy   c) useful time   d) refractory period

282. Choose the excitable tissues:
a) connective   b) epithelial   c) muscular   d) glandular   e) nervous

287. Which hormones possess the permissive effect?
a) cathecholamines   b) peptide hormones   c) steroids   d) epinephrine

284. Choose the distant receptors:
a. tactile   b. pain   c. visual   d. acoustic   e. olfactory   f. taste

285. Where are the processes of analysis most developed?
a. receptors   b. hypothalamus   c. red nucleus   d. cerebral cortex

286. Which structures of the brain play the main role in the mechanism of temporary connection?
a. brain stem, spinal cord   c. cerebral cortex, pons
b. cerebral cortex, spinal cord   d. cerebral cortex, brain stem reticular formation

287. How is the adaptability of the nerve centers and changeability of their functional significance called?
a. facilitation   b. convergence   c. plasticity   d. potentiation

288. Which lenses must a hypermetropic person use for reading?
a. cylindrical   b. biconvex   c. concave

289. Which level of spinal cord transection causes the spinal shock?
a. not higher than the IV-V cervical segments
b. not lower than the IV-V cervical segments
c. not higher than the IV-V thoracic segments
d. not lower than the IV-V thoracic segments

English-Azerbaijani-Russian dictionary of physiological terms

ENGLISH	AZERBAIJAN	RUSSIAN
Ablation	Kənar etmə, ekstirpasiya, amputasiya	Удаление, экстирпация, ампутация
Abrupt pulse	Sürətli (sıçrayan) nəbz	Скорый (подскакивающий) пульс
Absorption	Absorbsiya, sorulma, sorma, hopma	Абсорбция, всасывание, поглощение, впитывание
Acceleration	Akselerasiya, sürətlənmə	Акцелерация, учащение
Acclimatization	Akklimatizasiya, iqlimə uyğunlaşma, adaptasiya	Акклиматизация, адаптация
Acid-base balance	Turşu-qələvi müvazinəti	Кислотно-щелочное равновесие
Action potential	Fəaliyyət potensialı	Потенциал действия
Activate	Fəallaşdırmaq, oyatmaq, radioaktiv etmək	Активировать, возбуждать, придавать радиоактивность
Active rest	Fəal istirahət	Активный отдых
Adapt	Uyğunlaşmaq, uyğunlaşdırmaq	Приспосабливаться,приспосабливать
Adaptability	Uyğunlaşma qabiliyyəti	Приспособляемость
Adaptation	Adaptasiya, uyğunlaşma	Адаптация, приспособление
Adherent	Bitişmiş, yapışqan	Сращенный, клейкий
Adjustment	Uyğunlaşma, tənzim etmə, qurma, sazlama	Приспособление, регулировка, установка, настройка
Administration	Təyin etmə, qəbul etmə, tətbiq etmə, yeritmə (dərman), yardım göstərmə (xəstəyə)	Назначение, прием, применение, введение (лекарства), оказание помощи (больному)
Afterdischarge	Qıcıq kəsildikdən sonra iz reaksiyası	Следовая реакция после прекращения раздражения
After-image	İşıq kəsildikdən sonra görünən xəyal	Последовательный образ
After potential	İz potensialı	Следовой потенциал
Age physiology	Yaş fiziologiyası	Возрастная физиология
Aggravate	Pisləşmək, kəskinləşmək, güclənmək (xəstəlik)	Ухудшаться, обостряться, усиливаться (болезнь)
Aggravation	Aqqravasiya, pisləşmə (sağlamlıq vəziyyəti), kəskinləşmə (xəstəlik)	Аггравация, ухудшение (состояния здоровья), обострение (болезни)
Allied reflexes	Müttəfiq (əlaqədar) reflekslər	Аллированные (союзные) рефлексы
"All or nothing" principle	«Hamı ya heç» qanunu	Закон «Все или ничего»
Altitude (mountain) sickness	Yüksəklik (dağ) xəstəliyi	Высотная (горная) болезнь
Ambient temperature	Ətraf mühitin temperaturu	Температура окружающей среды
Amortization coefficient	Aşınma əmsalı	Коэффициент изнашиваемости
Amplification of potentials	Potensialların gücləndirilməsi	Усиление потенциалов
Analyze (analyse)	Analiz etmək, təhlil etmək, ətraflı tədqiq etmək	Анализировать, подвергать анализу, подробно исследовать
Annihilate	Məhv etmək, qırmaq	Уничтожать, истреблять
Anxiety	Narahatlıq, həyəcan, qorxu	Тревога, страх, боязнь
Appetite juice	İştaha mədə şirəsi	Запальный (аппетитный) сок
Artificial respiration	Süni tənəffüs	Искусственное дыхание
Atrial fibrillation	Qulaqcıqların səyriməsi	Фибрилляция (мерцание) предсердий
Atrial flutter	Qulaqcıqların titrəməsi	Трепетание предсердий
Attach	Bərkitmək, birləşdirmək, fiksə etmək, yayılmaq (şiş)	Прикреплять, присоединять, фикси-ровать, распространяться (опухоль)
Attention	Diqqət	Внимание
Background electrical activity	Fon elektrik fəallığı	Фоновая электрическая активность
Baldness	Dazlıq	Алопеция, облысение
Basal metabolism (basal metabolic rate)	Əsas mübadilə	Основной обмен
Beaker	Menzurka, laboratoriyada işlədilən dimdikli stəkan	Мензурка, лабораторный стакан
Behaviour	Davranış	Поведение

Biconvex	İkitərəfli qabarıq (linza)	Двояковыпуклый
Bile	Öd	Желчь
Biological constant	Bioloji sabit	Биологическая константа
Biological expediency	Bioloji məqsədəuyğunluq	Биологическая целесообразность
Biological reaction	Bioloji reaksiya	Биологическая реакция
Biological unit	Bioloji vahid	Биологическая единица
Bitter	Acı	Горький
Bleeding	Qanaxma, qanı axan	Кровотечение, кровоточащий
Blink	Göz qırpmaq, gözlərini qıymaq	Мигать, щуриться
Blood alkali reserve	Qanın qələvi ehtiyatı	Щелочной резерв крови
Blood circulation	Qan dövranı	Кровообращение
Blood clotting factor	Qanı laxtalandıran amil	Фактор свертывающей системы крови
Blood coagulation	Qanın laxtalanması	Свертывание крови
Blood count	Qanın formalı elementlərinin sayı, hemoqram	Число форменных элементов крови, гемограмма
Blood flow	Qan cərəyanı	Кровоток
Blood pressure	Qan təzyiqi	Кровяное давление
Blood supply	Qan təchizatı, qanla təmin olunma	Кровоснабжение
Blood typing (determination of blood groups)	Qan qrupunun müəyyən edilməsi	Определение группы крови
Blood viscosity	Qanın suvaşqanlığı	Вязкость крови
Bolus of food	Qida kütləsi	Пищевой комок
Breathing	Tənəffüs	Дыхание
Bronze disease	Tunc (Addison) xəstəliyi	Бронхзовая (аддисонова) болезнь
Calorific equivalent of oxygen	Oksigenin kalorik ekvivalenti	Калорический эквивалент кислорода
Cannula	Kanyula, mənfəzi olan iynə, borucuq	Канюля
Cardiac beat	Ürəyin yığılması	Сердечное сокращение
Cardiac cycle	Ürək tsikli (ürək fəaliyyəti dövrü)	Сердечный цикл
Cardiac index	Ürək indeksi	Сердечный индекс
Cardiac output	Ürəyin dəqiqəlik həcmi	Минутный объем сердца
Cardiopulmonary preparation	Ürək-ağciyər preparatı	Сердечно-легочный препарат
Carnivorous animal	Ətyeyən heyvan	Плотоядное животное
Castration	Axtalama	Кастрация
Cellular physiology	Hüceyrə fiziologiyası	Физиология клетки
Central inhibition	Mərkəzi ləngimə	Центральное торможение
Centrifugal	Mərkəzdənqaçan, efferent	Центробежный, эфферентный
Centripetal	Mərkəzəqaçan, afferent	Центростремительный, афферентный
Cessation	Arası kəsilmə, saxlama, fasilə	Прекращение, остановка, перерыв
Chewing	Çeynəmə	Жевание
Child-bearing	Doğum, doğuş	Роды, родовой акт
Chyme	Ximus (horrayabənzər mədə və ya bağırsaq möhtəviyyatı)	Химус (кашицеобразное содержимое желудка или кишечника)
Circulating blood volume	Dövr edən qanın həcmi	Объем циркулирующей крови
Clamp	Sıxac, sıxıcı, metal bənd	Зажим, скобка
Clotting time	Qanın laxtalanması müddəti	Время свертывания крови
Cognitive control	İdraka nəzarət	Познавательный контроль
Collapse of lungs	Ağciyərlərin sıxılması (yaprıxması)	Спадение легких
Collision	Toqquşma, ziddiyyət	Столкновение, противоречие
Colour index	Rəng göstəricisi	Цветной показатель
Comparative physiology	Müqayisəli fiziologiya	Сравнительная физиология
Compatibility	Uyğunluq, uyuşma	Совместимость
Compensative vessel	Kompensasiyaedici damar	Компенсирующий сосуд
Concave	çökük	Вогнутый
Conditional inhibitor	Şərtli tormoz (ləngidici)	Условный тормоз
Conditioned reflex	Şərti refleks	Условный рефлекс
Conditioned-reflex switching	Şərti reflektor dəyişdirilmə	Условнорефлекторное переключение
Conduction	Nəqlolunma, nəqletmə, nəqletmə qabiliyyəti (impulsu)	Проведение, проводимость

Cone	Kolbacıq (tor qişada)	Колбочка (сетчатки)
Conjugated reflexes	Əlaqədar (bağlı) reflekslər	Сопряженные рефлексы
Consciousness	Şüur, huş	Сознание
Consolidation	Bərkimə, konsolidasiya (sümüyün bitişməsi)	Затвердение, укрепление, консолидация (сращение кости)
Constipation	Qəbizlik	Запор
Contraction	Təqəllüs, yığılma, büzüşmə, daralma, sıxılma	Сокращение, сморщивание, сжатие
Consumatory behaviour	Qida davranışı	Пищевое поведение
Contractility	Yığılma qabiliyyəti	Сократимость
Control	Kontrol, nəzarət, tənzim, idarə etmə	Контроль, регуляция, управление
Convulsion	Konvulsiya, qıclıq, qıcolma	Конвульсия, судорога
Corneal reflex	Buynuz qişa refleksi	Роговичный (корнеальный) рефлекс
Coughing	Öskürək	Кашель
Cracking voice	Qırılan (dəyişilən) səs	Ломающийся голос
Craving for food	Qidaya meyllik	Стремление к пище
Crumbly	Ovulub tökülən, kövrək, tez ovulan, kövşək	Крошащийся, рассыпчатый, рыхлый
Cusp	Tay (ürək qapağında)	Створка (клапана сердца)
Damage	Zədə, zədələnmə, zərər, pozulma	Повреждение, поражение, нарушение
Dead space	Ölü sahə	Мертвое пространство
Deceleration	Yavaşıma, sürəti azalma, ləngimə	Замедление, торможение
Decerebrate rigidity	Deserebrasion rigidlik (qıclıq)	Децеребрационная ригидность
Decontaminate (render harmless)	Zərərsizləşdirmək, təmizləmək	Обеззараживать
Defence (defensive) reflex	Müdafiə (mühafizə) refleksi	Защитный рефлекс
Defibrinated blood	Fibrinsizləşmiş qan	Дефибринированная кровь
Deficient pulse	Nəbz defisiti	Дефицит пульса
Definitive urine	Son sidik	Конечная моча
Deglutition	Udma	Глотание
Dehydration	Dehidratasiya, susuzlaşma	Дегидратация, обезвоживание
Delayed (retarded) conditioned reflex	Şərti refleksin gecikməsi	Запаздывание условного рефлекса
Denticulated tetanus	Dişli tetanus	Зубчатый тетанус
Depolarization threshold	Depolyarizasiya həddi (qıcıq qapısı)	Порог деполяризации
Deprivation	Məhrum olma, itirmə	Депривация, лишение, утрата
Descriptive memory	Təsviri yaddaş	Описательная память
Deteriorate	Pisləşmək, korlanmaq, pozulmaq, dığılmaq	Ухудшаться, портиться, разрушаться
Diabetes insipidus	Şəkərsiz diabet	Несахарный диабет
Diabetes mellitus	Şəkərli diabet	Сахарный диабет
Differential blood count (leukogram)	Leykositlərin müxtəlif növlərinin sayılması (leykoqram)	Определение лейкоцитарной формулы (лейкограмма)
Differentiation of conditioned stimulus	Şərti qıcığın fərqləndirilməsi	Дифференциация условного раздражителя
Diffusing capacity of lungs	Ağciyərlərin diffuziya qabiliyyəti	Диффузионная способность легких
Digestion	Həzm, qidanı mənimsəmə	Пищеворение, усвоение пищи
Dilation	Genəlmə	Дилатация, расширение
Direct calorimetry	Vasitəsiz kalorimetriya	Прямая калориметрия
Disinhibition	Ləngimədən azad olma	Растормаживание
Dissection	Yarma, kəsmə	Рассечение, вскрытие
Distensibility	Elastiklik, genəlmə	Растяжимость, расширение
Distention	Dartılma, genəlmə	Растяжение, расширение
Diurnal animal	Gündüz fəaliyyətdə olan heyvan	Дневное животное
Dizziness	Başgicəllənmə	Головокружение
Doctrine of evolution	Təkamül nəzəriyyəsi	Эволюционное учение
Dormant	Mürgüləyən, yatmış, fəaliyyətsiz, gizli	Дремлющий, спящий, бездействующий, скрытый
Dream	Yuxu, röya, yuxu görmək	Сон сновидение, видеть сон

Drive	Meyl, istək, davranışın səbəbi, cəhd	Влечение, побеждение, мотив поведения, стремление
Dropped beat	Ürəyin fasiləli yığılması	Выпадение сокращения сердца
Drowsiness	Yuxuculluq, hipersomniya	Сонливость, гиперсомния
Dry residue	Quru qalıq	Сухой остаток
Dwarf	Karlik, cırtdan, cırtdanboy (adam)	Карлик
Dwarfism	Nanizm, cırtdanboyluq	Нанизм, краликовость, карликовый рост
Dysfunction	Disfunksiya, funksiyanın pozulması	Дисфункция, нарушение функции
Elastic draught of lungs	Ağciyərlərin dartı qüvvəsi	Эластическая тяга легких
Electrical activity	Elektrik fəallığı	Электрическая активность
Elicit	Almaq, əldə etmək, hasil etmək, törətmək, aşkar etmək, müəyyən etmək	Извлекать, выявлять, устанавливать
Emaciation	Arıqlama, üzülmə, əldən düşmə, kaxeksiya	Истощение, кахексия
Emotional memory	Emosional yaddaş	Эмоциональная память
End-plate	Uc lövhəcik, hərəki sinir ucu	Двигательная пластинка, окончание двигательного нерва
Enhance	Artırmaq, gücləndirmək, yüksəltmək	Увеличивать, усиливать, повышать
Environment	Ətraf mühit (şərait)	Окружающая среда, окружающие условия
Epileptic seizure	Epilepsiya tutması	Эпилептический припадок
Epinephrine	Adrenalin	Адреналин
Equalizing (provisory) phase	Bərabərləşdirici (provizor) faza	Уравнительная (провизорная) фаза
Equilibrium	Müvazinət, tarazlıq halı	Равновесие, равновесное состояние
Erythrocyte sedimentation rate (ESR)	Eritrositlərin çökmə sürəti (EÇS)	Скорость оседания эритроцитов (СОЭ)
Evoked potential	Törədilmiş potensial	Вызванный потенциал
Evolution	Təkamül	Эволюция
Evolutionary physiology	Təkamül fiziologiyası	Эволюционная физиология
Exacerbation	Sərtləşmə, kəskinləşmə (xəstəlik), güclənmə (ağrı), paroksizm	Обострение (болезни), усиление (боли), пароксизм
Excitability	Oyanıcılıq, oyanma qabiliyyəti	Возбудимость
Excitable tissues	Oyanıcı toxumalar	Возбудимые ткани
Excitation	Oyanma	Возбуждение
Excitation threshold	Oyanmanın qıcıq qapısı	Порог возбуждения
Excitatory postsynaptic potential (EPSP)	Oyadıcı postsinaptik potensial (OPSP)	Возбуждающий постсинаптический потенциал (ВПСП)
Exhaustion	Üzülmə, əldən düşmə, həddən artıq yorulma	Истощение, крайняя усталость
Exophthalmos	Ekzoftalm, gözlərin bərəlməsi	Экзофтальм, пучеглазие
Expenditure of energy	Enerji sərfi	Расход (потребление) энергии
Experience	Həyat təcrübəsi, təəssürat, təsadüf	Жизненный опыт, переживание, случай
Experimental animal	Təcrübə heyvanı	Подопытное животное
Expiratory gasp	Nəfəsvermənin çətinləşməsi	Затрудненный выдох
Expiratory reserve volume	Nəfəsvermənin ehtiyat həcmi	Резервный объем выдоха
Expire	Nəfəs vermək, son nəfəs vermək, ölmək	Выдыхать, скончаться
External environment	Ətraf mühit	Окружающая среда
Extinction	Sönmə, kəsilmə (qurtarma)	Угасание, потухание, прекращение
Extirpation	Ekstirpasiya, çıxırma, tam kənar etmə (orqanı)	Экстирпация, полное удаление (органа)
Extrinsic	Xarici, xas olmayan	Внешний, наружный, несвойственный
Eyeball protrusion	Gözlərin bərəlməsi	Пучеглазие
Facilitate	Yüngülləşdirmək, asanlaşdırmaq, kömək etmək	Облегчать, помогать, содействовать, способствовать
Facilitation	Yüngülləşmə, asanlaşma	Облегчение
Failure	Çatışmazlıq, qüsur, dekompensasiya,	Недостаточность, декомпенсация,

	pozulmaq, uğursuzluq, pis nəticə (müalicə)	нарушение, расстройство, неудача, неблагоприятный исход (лечения)
Fatigue	Yorğunluq, gücdən düşmə	Утомление, усталость
Feedback	Qayıdan əlaqə	Обратная связь
Feeding center	Qida mərkəzi	Пищевой центр
Feeding physiology	Qidalanma fiziologiyası	Физиология питания
Ferocious reaction	Qəzəb reaksiyası	Реакция ярости
Field of vision	Görmə sahəsi	Поле зрения
Filling of the ventricles	Mədəciklərin dolması	Наполнение желудочков
Final common path	Ümumi son yol	Общий конечный путь
Fit of rage	Hiddətlənmə, qəzəbin coşması	Приступ ярости
Flexor reflex	Bükmə refleksi	Рефлекс сгибания
Food reflex	Qida refleksi	Пищевой рефлекс
Frequent pulse	Sıx nəbz	Учащенный пульс
Full pulse	Dolğun nəbz	Полный пульс (пульс хорошего наполнения)
Functional residual capacity	Funksional qalıq tutum	Функциональная остаточная емкость
Functional system	Funksional sistem	Функциональная система
Fuse	Qovuşmaq, birləşmək	Сливаться, объединяться
Gestation	Hamiləlik	Беременность
Giant	Giqant, nəhəng	Гигант
Gigantism	Giqantizm, nəhənglik	Гигантизм
Gnawing feeling	Əzabverici (gəmirici) hissiyyat	Терзающее чувство
Goitrous	Urlu, urla xəstələnmiş	Зобный, страдающий зобом
Goose-skin	Qaz dərisi	Гусиная кожа
Gorayev's accounting camera	Qoryayevin say kamerası	Счетная камера Горяева
Grafting	Transplantasiya, implantasiya	Трансплантация, имплантация
Greater (systemic) circulation	Böyük qan dövranı	Большой круг кровообращения
Guarding reflex	Gözətçi (keşikçi) refleks	Сторожевой рефлекс
Habit	Vərdiş, adət	Привычка
Hard pulse	Sərt nəbz	Твердый пульс
Healthy	Sağlam	Здоровый
Hearing	Eşitmə, eşitmə qabiliyyəti	Слух, способность слышать
Heart activity	Ürək fəaliyyəti	Сердечная деятельность
Heart contraction	Ürəyin yığılması	Сокращение сердца
Heart murmur	Ürək küyü	Сердечный шум
Heart sound	Ürək tonu	Тон сердца
Heat loss	İstillik itkisi	Потеря тепла
Heat production	İstiliyin əmələ gəlməsi	Теплообразование
Hemocoagulation	Qanın laxtalanması	Свертывание крови
Herbivorous animal	Otyeyən heyvan	Травоядное животное
Heterologous	Yad, başqa növdən törənmiş, uyğun gəlməyən	Инородный, состоящий из разнород-ных элементов, несоответствующий
Hibernation	Qış yuxusu	Зимняя спячка
Higher nervous activity	Ali sinir fəaliyyəti	Высшая нервная деятельность
Homoiothermal (warm-blooded) animal	İstiqanlı heyvan	Теплокровное животное
Hormonal regulation	Hormonal tənzim	Гормональная регуляция
Human physiology	İnsanın fiziologiyası	Физиология человека
Humoral regulation	Humoral tənzim	Гуморальная регуляция
Hunched back	Donqar, qozbel	Горб, кифотическое искривление позвоночника
Hunger	Aclıq	Голод
Hunger pangs	Aclıqdan törənən qəfil kəskin ağrı	Внезапная острая боль, вызванная голодом
Husky voice	Xırıltılı (batıq) səs	Сиплый (охрипший) голос
Hyperacidity	Hiperxlorhidriya, mədə turşuluğunun artması	Гиперхлоргидрия, повышенная кислотность желудочного сока

Hypercoagulability	Hiperkoaqulyasiya, qanın laxtalanma qabiliyyətinin artmsı	Гиперкоагуляция, повышенная свертываемость крови
Hyperfunction	Hüperfunksiya, fəaliyyətin artması	Гиперфункция
Hypersecretion	Hipersekresiya, sekresiyanın artması	Гиперсекреция, повышенная секреция
Hyperthyroidism	Hipertireoz, qalxanabənzər vəzinin hiperfunksiyası	Гипертиреоз, гиперфункция щитовидной железы
Hypnotic suggestion	Hipnoz altında təlqin	Гипнотическое внушение
Hypoacidity	Hipoxlorhidriya, mədə turşuluğunun azalması	Гипохлоргидрия, пониженная кислотность желудочного сока
Hypocoagulability	Hipokoaqulyasiya, qanın laxtalanma qabiliyyətinin azalması	Гипокоагуляция, пониженная свертываемость крови
Hypofunction	Hipofunksiya, fəaliyyətin azalması	Гипофункция
Hyposecretion	Hiposekresiya, sekresiyanın azalması	Гипосекреция, пониженная секреция
Hypothyroidism	Hipotireoz, qalxanabənzər vəzinin hipofunksiyası	Гипотиреоз, гипофункция щитовидной железы
Image	Xəyal	Изображение
Immature	Yetişməmiş, inkişafdan qalmış	Незрелый, недоразвитый
Implanted microelectrode	İmplantasiya edilmiş mikroelektrod	Вживленный микроэлектрод
Inanition	Arıqlama, üzülmə (aclıq nəticəsində)	Истощение, изнурение
Incipient starvation	Aclığın erkən mərhələsi	Начальная стадия голодания
Indirect calorimetry	Vasitəli kalorimetriya	Непрямая калориметрия
Inflate	Üfürmək, hava ilə doldurmaq	Надувать, наполнять воздухом
Influence	Təsir, təsir göstərmək	Влияние, воздействие, оказывать влияние, воздействовать
Inhibition	Ləngimə, tormozlanma, ləngitmə, dayandırma	Ингибирование, торможение, задержка, подавление
Inhibitory postsynaptic potential (IPSP)	Ləngidici postsinaptik potensial (LPSP)	Тормозной постсинаптический потенциал (ТПСП)
Injure	Zədələmək, zərər vermək	Повредить, ушибить, ранить
Insomnia	Yuxusuzluq	Инсомния, асомния,бессоница
Inspiratory capacity	Nəfəsalmanın həcmi	Емкость вдоха
Inspiratory reserve volume	Nəfəsalmanın ehtiyat həcmi	Резервный объем вдоха
Inspire	Nəfəs almaq, ruhlandırmaq, təlqin etmək	Вдыхать, вдохновлять, внушать
Intracardiac reflexes	Ürəkdaxili (intrakardial) reflekslər	Внутрисердечные (интракардиальные) рефлексы
Internal environment of organism	Orqanizmin daxili mühiti	Внутренняя среда организма
Interrelation	Qarşılıqlı əlaqə, münasibət	Взаимосвязь, соотношение
Intrinsic	Daxili, xas olan, anadangəlmə, irsi	Внутренний, свойственный, врожденный, наследственный
Invade	Daxil olmaq, girmək, keçmək (virus), zədələnmək, yayılmaq (xəstəlik)	Внедряться, проникать (вирус), поражать, распространяться (болезнь)
Involuntary	Qeyri-iradi	Непроизвольный
Irreversible	Dönməyən, geri qayıtmayan, dönməz (proses)	Необратимый (процес)
Irritability	Qıcıqlanma qabiliyyəti, əsəbilik	Раздражимость, раздражительность
Irritant	Qıcıq, qıcıqlandırıcı	Раздражитель
Irritation	Qıcıqlanma	Раздражение
Jet	Fəvvarə, şırnaq, şırnaqla axmaq, reaktiv	Струя, бить струей, реактивный
Jujuba (unabi)	İnnab	Ююба, жужуба, унаби
Juvenile neutrophils	Cavan neytrofillər	Юные нейтрофилы
Knack	Səriştə, vərdiş, kəskin səs (şappıltı)	Сноровка, привычка, резкий звук (треск)
Knee jerk (patellar) reflex	Diz refleksi	Коленный рефлекс
Lability	Labillik	Лабильность
Labour physiology	Əmək fiziologiyası	Физиология труда
Laky blood	Lak (hemolizə uğramış) qan	Лаковая (гемолизированная) кровь

Lamellated	Lövhəşəkilli	Пластинчатый
Latch	Qıfıl, kilid, sürgü, rəzə	Запор, защелка, задвижка, щеколда
Latent period	Latent (gizli) dövr	Латентный (скрытый) период
Law "all or nothing"	«Hamı ya heç» qanunu	Закон «Все или ничего»
Law of the heart	Ürək qanunu	Закон сердца
Law of the isolated conduction	Təcrid edilmiş nəqlolunma qanunu	Закон изолированной проводимости
Law of the physiological safety	Fizioloji tamlıq qanunu	Закон физиологической целостности
Law of the two-way conduction	İkitərəfli nəqlolunma qanunu	Закон двусторонней проводимости
Lead	Aparma	Отведение
Leaflet	Tay (ürək qapağında)	Створка (клапана сердца)
Leak	Axıb tökülmə, itki (axıb tökülmə nəticəsində), sızma	Утечка, истечение, просачивание
Left-handed person	Solaxay adam	Левша
Lesion	Zədə, zədələnmə, zərər	Повреждение, поражение
Lesser (pulmonary) circulation	Kiçik qan dövranı	Малый круг кровообращения
Lick	Yalamaq	Лизать, облизывать
Life span	Ömür müddəti, yarımparçalanma dövrü (radioaktiv maddə)	Продолжительность жизни, период полураспада (радиоактивного вещества)
Ligate	Liqaturaya almaq, bağlamaq	Лигировать, накладывать лигатуру, перевязывать
Ligation	Liqaturaya alma, bağlama	Лигирование, наложение лигатуры, перевязка
Lively type	Diribaş tip	Живой тип
Local circuit	Lokal cərəyan	Локальный ток
Local reply	Yerli (lokal) cavab	Локальный ответ
Loose	Sərbəst, azad, tarım olmayan, laxlayan (diş), sallanan	Свободный, нетугой, шатающийся (зуб), болтающийся
Loss of blood	Qanitirmə	Кровопотеря
Loss of consciousness	Huşun itməsi	Потеря сознания
Lubrication	Sürtmə, yağlama	Смазка, смазывание
Maintain	Saxlamaq, kömək etmək, müdafiə etmək, tərəfdar olmaq	Поддерживать, защищать, сохранять
Mask-like face	Maskayabənzər sifət	Маскообразное лицо
Mastication	Çeynəmə	Жевание
Mature	Yetişmiş, yetkin, vaxtında doğulmuş (uşaq)	Зрелый доношенный (новорожденный)
Mean arterial pressure	Orta arterial təzyiq	Среднее артериальное давление
Measurement	Ölçmə, ölçü	Измерение
Melangeur	Melanjer	Меланжер, смеситель
Memory	Yaddaş	Память
Mental	Əqli, zehni, psixi, çənəyə aid	Умственный, психический, подбородочный
Merge	Qovuşmaq, birləşmək	Сливаться, соединяться
Meshwork	Torlu struktur	Сетчатая структура
Metabolic vessel	Mübadilə damarı	Обменный сосуд
Micturition	Sidik ifrazı	Мочеиспускание
Minute respiratory volume	Tənəffüsün dəqiqəlik həcmi, ağciyərlərin dəqiqəlik ventilyasiyası	Минутный объем дыхания, минутная вентиляция легких
Mobility	Hərəkilik, hərəkətlilik	Мобильность, подвижность
Moon face	Ayabənzər sifət	Лунообразное лицо
Motility	Hərəkətlilik, mütəhərriklik, yığılma qabiliyyəti, iradi hərəkətlərə qabillik	Подвижность, сократительная способность, способность к самопроизвольному движению
Motor function	Hərəki funksiya	Двигательная функция
Motor unit	Hərəki vahid	Двигательная единица

Muscle spindle	Əzələ iyi (mili)	Мышечное веретено
Muscle tone	Əzələ tonusu	Мышечный тонус
Muscular debility	Əzələ zəifliyi	Мышечная слабость
Muscular sluggishness	Əzələ süstlüyü	Вялость мышцы
Musk	Müşk, müşk ətri	Мускус, мускусный запах
Napkin	Salfet	Салфетка
Nausea	Ürəkbulanma, öyümə	Тошнота
Nauseate	Ürəyi bulanmaq (bulandırmaq)	Вызывать тошноту (рвоту)
Nerve center	Sinir mərkəzi	Нервный центр
Nerve impulse	Sinir impulsu	Нервный имплуьс
Nervousness	Əsəbilik, sinir sisteminin oyanıcılığının artması	Нервозность, повышенная возбудимость
Nervous regulation	Sinir tənzimi	Нервная регуляция
Neurohumoral mechanism	Neyrohumoral mexanizm	Нейрогуморальный механизм
Night-blindness	Hemeralopiya, şəbkorluq, toyuq korluğu	Гемералопия, ночная (куриная) слепота
Nitrogen balance	Azot balansı	Азотистый баланс
Nitrogen equilibrium	Azot müvazinəti	Азотистое равновесие
Nocturnal animal	Gecə fəaliyyətdə olan hevan	Ночное животное
Norepinephrine	Noradrenalin	Норадреналин
Nuclear shift index	Nüvə təmayülü indeksi	Индекс ядерного сдвига
Nutrition	Qidalanma, qida	Питание, пища
Nutritional reflex	Qidalanma refleksi	Питательный рефлекс
Obese	Kök, tosqun, piylənməsi olan	Страдающий ожирением
Oblivious	Huşsuz, yaddaşsız, hafizəsiz	Рассеянный, забывчивый
Observation	Müşahidə	Наблюдение
Observe	Müşahidə etmək	Наблюдать
Occlude	Tıxamaq, qapamaq, yummaq (dişləri)	Закупоривать, закрывать, смыкать (зубы)
Odoriferous	Ətirli	Дцшистый
Odour	Qoxu, ətir	Запах
Offspring	Nəsil, nəvə-nəticə, övlad	Отпрыск, потомок
Oncotic pressure	Onkotik təzyiq	Онкотическое давление
One-way conduction	Birtərəfli nəqlolunma	Односторонняя проводимость
Orientation reflex	Oriyentasiya (bələdləşmə) refleksi, istiqamətləndirici refleks	Ориентировочный рефлекс
Origin	Mənşə, mənbə, başlanğıc, ilk səbəb	Источник, начало, происхождение, первопричина
Osmotic pressure	Osmotik təzyiq	Осмотическое давление
Osmotic resistance of erythrocytes	Eritrositlərin osmotik rezistentliyi	Осмотическая резистентность эритроцитов
Overexertion	Həddən artıq gərginlik	Перенапряжение
Override	Üstün gəlmək, rədd etmək, qəbul etməmək	Брать верх, отвергать, не принимать во внимание
Oxygen capacity of blood	Qanın oksigen tutumu	Кислородная емкость крови
Oxygen-hemoglobin-dissociation curve	Oksihemoqlobinin dissosiasiyası əyrisi	Кривая диссоциации оксигемоглобина
Pacemaker of the heart	Ürəyin sinus düyünü	Пейсмекер, водитель ритма (очаг автоматии) сердца
Pain	Ağrı	Боль
Painful stimulation	Ağrı qıcığı	Болевое раздражение
Pallor	Solğunluq	Бледность
Panchenkov's apparatus	Pançenkov aparatı	Аппарат Панченкова
Paradoxical phase	Paradoksal (təəccüblü) faza	Парадоксальная (удивительная) фаза
Paroxysm	Paroksizm, tutma (xəstəlikdə), ürəkkeçmə	Пароксизм, приступ (болезни), припадок
Partial pressure	Parsial təzyiq	Парциальное давление
Pathogenic influence	Patogen (xəstəliktörədici) təsir	Патогенное (болезнетворное) влияние
Pathological process	Patoloji proses	Патологический процесс

Pathological voracity	Patoloji acgözlük	Патологическая прожорливость
Pattern	Pattern, xarakter, xüsusiyyət, struktur, konfiqurasiya, nümunə, model, şablon, sxem, diaqram	Паттерн, характер, особенность, структура, образец, модель, шаблон, схема, диаграмма
Pendulum – like contractions	Rəqqasi hərəkət (yığılmalar)	Маятникообразные сокращения
Perceive	Qavramaq, hiss etmək, dərk etmək	Воспринимать, ощущать, чувствовать, осознавать
Periodic breathing	Dövri tənəffüs	Периодическое дыхание
Period of action	Təsir dövrü	Период действия
Period of after-action	Təsirdən sonrakı dövr	Период последействия
Period of ejection	Qovma dövrü	Период изгнания
Period of relaxation	Boşalma dövrü	Период расслабления
Period of tension	Gərginlik dövrü	Период напряжения
Permeability	Keçiricilik	Проницаемость
Perspiration	Tərləmə, tər	Потоотделение, пот
Perversion	Təhrif, təhrif olma, normadan kənara çıxma, pozulma	Извращение, отклонение от нормы
Physiological function	Fizioloji funksiya	Физиологическая функция
Physiological solution	Fizioloji məhlul	Физиологический раствор
Pitch	Ucalıq, yüksəklik (ton, səs)	Высота (тона, звука)
Plantar	Ayaqaltı refleks	Подошвенный рефлекс
Plug	Tıxac, plomb, tampon, tıxacla bağlamaq, plomblamaq, tamponlamaq	Пробка, пломба, тампон, закупоривать, пломбировать, тампонировать
Poikilothermal (cold-blooded) animal	Soyuqqanlı heyvan	Холоднокровное животное
Polar rule of excitation	Oyanmanın qütb qanunu	Полярный закон возбуждения
Postsynaptic inhibition	Postsinaptik ləngimə	Постсинаптическое торможение
Pregnancy	Hamiləlik	Беременность
Premature beat	Ekstrasistola	Экстрастстола
Prepubertal	Cinsi yetişkənlik dövründən əvvəlki	Препубертатный
Presynaptic inhibition	Presinaptik ləngimə	Пресинаптическое торможение
Primary reply	Birincili cavab	Первичный ответ
Primary sexual characteristics	Birincili cinsi əlamətlər	Первичные половые признаки
Primary urine	İlk sidik	Первичная моча
Principle of the leading role of the head	Başın aparıcı rolu prinsipi	Принцип ведущей роли головы
Propagation of impulse	İmpulsun yayılması	Распространение импульса
Propensity	Meyllik, meyl, həvəs	Склонность, предрасположение, пристрастие
Proper reflexes	Xüsusi reflekslər	Собственные рефлексы
Propulsion	İrəliləmə, irəliyə doğru hərəkət, təkan	Продвижение, движение вперед, толчок
Psychic disorder	Psixi pozulma	Психическое рсстройство
Puberty	Yetişkənlik, cinsi yetişkənlik, cinsi yetişkənlik dövrü	Половое созревание, период полового созревания
Puffiness	Şişkinlik	Отечность, одутловатость
Pugnacious type	Hirsli (dalaşqan) tip	Безудержный (драчливый) тип
Pulse	Nəbz	Пульс
Pungent	Yeyici, kəskin (dad, qoxu)	Едкий, острый (вкус, запах)
Pupullary reflex	Bəbək refleksi	Зрачковый рефлекс
Purposeful activity	Məqsədyönlü fəaliyyət	Целенаправленная деятельность
Putrid	Çürüntülü, dağılan	Гнилостный, гниющий, распадающийся
Radiation sickness	Şüa xəstəliyi	Лучевая болезнь
Rare pulse	Seyrək nəbz	Редкий пульс
React	Reaksiyaya girmək, cavab vermək (təsirə), qarşılıqlı təsirdə olmaq	Реагировать, влиять, взаимодействовать

Reactivity	Reaktivlik	Реактивность
Rebound (recoil) phenomenon	Geriyə təpmə fenomeni	Феномен отдачи
Reciprocal innervation	Resiprok (çarpaz) sinirlənmə	Реципрокная (сопряженная) иннервация
Recurrent inhibition	Qayıdan ləngimə	Возвратное торможение
Redistribution	Yenidən bölüşdürülmə, yenidən paylanma	Перераспределение
Reflex arc	Refleks qövsü	Рефлекторная дуга
Reflex time	Refleks vaxtı (müddəti)	Время рефлекса
Regularity	Qanunauyğunluq	Закономерность
Regulation	Tənzim, nəzarət, tənzim etmə, idarə etmə	Регуляция, контролирование, регулирование, управление
Rehersal	Məşq, məşq etmə, təkrar etmə	Репетиция, повторение
Reinforcement	Möhkəmləndirmə (şərti refleksi), gücləndirmə	Подкрепление (условного рефлекса), укрепление, усиление
Rejuvenation	Cavanlaşma, cavanlaşdırma, bərpa olunma	Омоложение, восстановление сил, здоровья
Relative indefatigability of nerve	Sinirin nisbi yorulmazlığı	Относительная неутомляемость нерва
Relaxation	Boşalma, zəifləmə	Релаксация, расслабление
Removal	Kənar etmə, çıxarma, yerini dəyişmə	Удаление, устранение, перемещение
Render harmless	Zərərsizləşdirmək	Обезвреживать
Residual volume	Qalıq həcm	Остаточный объем
Resistibility	Müqavimət qabiliyyəti	Сопротивляемость
Resistive vessel	Rezistiv damar	Резистивный сосуд
Respiration	Tənəffüs	Дыхание
Respiratory arrhythmia	Tənəffüs aritmiyası	Дыхательная аритмия
Respiratory center	Tənəffüs mərkəzi	Дыхательный центр
Respiratory coefficient	Tənəffüs əmsalı	Дыхательный коэффициент
Respiratory defence reflexes	Tənəffüsün mühafizə refleksləri	Защитные дыхательные рефлексы
Respond	Reaksiya (cavab) vermək (qıcığa qarşı)	Реагировать, отвечать (на раздражение)
Resting (membrane) potential	Sükunət (membran) potensialı	Потенциал покоя, мембранный потенциал
Retain	Saxlamaq, tutub saxlamaq, kömək etmək	Удерживать, поддерживать, сохранять
Reticular formation	Torabənzər törəmə	Ретикулярная формация, сетевидное образование
Reversible	Dönən, donər, geri qayıda bilən (proses)	Обратимый (процесс)
Reward center	Mükafat (ləzzət) mərkəzi	Центр поощрения (удовольствия)
Pheoscopic paw	Reoskopik pəncə	Реоскопическая лапка
Righting (uprise) reflex	Düzləndirici refleks	Выпрямительный (установочный) рефлекс
Rod	Çöpcük (tor qişada)	Палочка (сетчатки)
Rubbing reflex	Silmə refleksi	Рефлекс потирания
Rule of average loads	Orta yük qanunu	Правило средних нагрузок
Sahli's hemometer	Sali hemometri	Гемометр Сали
Saliva	Ağız suyu	Слюна
Salivation	Ağız suyu ifrazı	Слюноотделение
Salty	Şor	Соленый
Satiation	Doyma	Насыщение
Satiety	Doyma	Насыщение, сытность
Satiety center	Doyma mərkəzi	Центр насыщения
Saturate	Doyurmaq, hopdurmaq	Насыщать, пропитывать
Scratch reflex	Qaşınma refleksi	Чесательный рефлекс
Second messenger	İkinci vasitəçi (bioloji aktiv maddə)	Второй посредник, второй посыльный (биологически активное вещество)
Secondary reply	İkincili cavab	Вторичный ответ

Secondary sexual characteristics	İkincili cinsi əlamətlər	Вторичные половые признаки
Self-stimulation	Özünüqıcıqlandırma	Самораздражение
Self-regulation	Özünütənzim	Саморегуляция
Self-restraint (self-control)	Özünü saxlaya bilmə, təmkinlilik	Самообладание, сдержанность
Semipermeable membrane	Yarımkeçirici membran	Полупроницаемая мембрана
Sensitivity	Həssaslıq	Чувствительность
Sexual reflex	Cinsi refleks	Половой рефлекс
Shallow breathing	Səthi tənəffüs	Поверхностное дыхание
Sham feeding	Yalan qidalandırma	Ложное кормление
Shift	Kənara çıxma, meyl, təmayül, yerdəyişmə	Отклонение, сдвиг, смещение
Shift to the left	Sola təmayül	Сдвиг влево
Shift to the right	Sağa təmayül	Сдвиг вправо
Shivering	Üşümə, titrəmə, titrətmə, tremor	Озноб, дрожь, дрожание, тремор
Skill	Məharət, bacarıq, səriştə, vərdiş	Мастерство, умение, сноровка, навык
Slap	Şapalaq, şappıldatmaq	Шлепок, шлепать
Sleep	Yuxu, yatmaq	Сон, спать
Slow pulse	Yavaş nəbz	Медленный пульс
Smell	İy, qoxu, iybilmə qabiliyyəti, iyi gəlmək	Запах, обоняние, обонять, пахнуть
Smooth tetanus	Hamar tetanus	Гладкий тетанус
Sneezing	Asqırma	Чиханье
Soft pulse	Yumşaq nəbz	Мягкий пульс
Solitary contraction	Tək təqəllüs	Одиночное сокращение
Somnolence	Yuxuculluq, yarımhüşsuz vəziyyət	Сонливость, полубессознательное состояние
Sound	Səs, küy, ton, zond, sağlam, zondlamaq, auskultasiya etmək	Звук, тон, шум, зонд, здоровый, зондировать, выслушивать
Sour	Turş	Кислый
Spatial summation	Məkan üzrə summasiya	Пространственная суммция
Species	Növ, cins	Вид, род
Spike	Spayk, fəaliyyət potensialı	Спайк, потенциал действия
Spurt	Şırnaq, şırnaqla axmaq	Струя, бить струей
Squeeze	Sıxılma, təzyiq etmə, sıxmaq, təzyiq etmək	Сжатие, сдавливание, сжимать, сдавливать
Stab (band, imamture) neutrophil	Çöpnüvəli neytrofil	Палочкоядерный нейтрофил
Staggering gait	Yırğalanan yeriş	Качающаяся походка
Staircase phenomenon	Pilləkən fenomeni	Феномен лестницы
Standstill	Dayanma, pauza, fasilə	Остановка, пауза
Starvation	Aclıq, acqalma	Голодание
Sthenic	Fəal, güclü, möhkəm	Активный, сильный, крепкий
Stimulant	Qıçıq, qıcıqlandırığı	Раздражитель
Stimulation	Stimulyasiya, qıcıqlanma, qıcıqlandırma	Стимуляция, стимулирование, раздражение
Stimulus	Stimul, qıcıqlandırıcı, qıcıq	Стимул, раздражитель
Stocky	Enlikürək (şəxs)	Коренастый, приземистый (человек)
Stretch	Dartma, uzatma, interval (vaxt), dartmaq, uzatmaq	Растягивание, удлинение, интервал (времени), вытгивать, удлинять
Stroke index	Sistolik indeks	Систолический индекс
Stroke volume of the heart	Ürəyin sistolik həcmi	Систолический (ударный) объем сердца
Subconsciousness	Təhtəlşüur	Подсознание
Subtreshold	Subliminal, qıcıq qapısıedan aşağı	Подпороговый
Sucking force	Sorucu qüvvə	Всасывающая сила
Suggested sleep	Təlqin edilmiş yuxu	Сон, вызванный внушением
Suggestion	Təlqin	Суггестия, внушение
Suprathreshold	Supraliminal, qıcıq qapısından yuxarı	Надпороговый
Surge	Şappıltı, təkan, tullanma, impuls,	Всплеск, толчок, выброс, импульс,

	pulsasiya, döyünmə, rəqs, rəqs etmək, döyünmək	пульсация, колебание, колебаться, пульсировать
Survival	Sağ qalma, sağqalma müddəti	Выживание, продолжительность существования, дожитие
Swallowing	Udma	Глотание
Sweating	Tərləmə	Потение, потоотделение
Sweet	Şirin	Сладкий
Synaptic cleft	Sinaps yarığı	Синаптическая щель
Synaptic delay	Sinaptik yubanma	Синаптическая задержка
Synaptic gutter (through)	Sinaps yarığı	Синаптическая щель
Target tissues	Hədəf toxumalar	Ткани-мишени
Taste	Dad, təm, dadmaq, dadina baxmaq	Вкус, вкусовое ощущение, ощущать вкус
Temporal summation	Zaman üzrə summasiya	Временная сумация
Temporary connection	Müvəqqəti əlaqə	Временная связь
Tension (of the gas)	Gərginlik (qaz)	Напряжение (газа)
Thermal coefficient of nutritive matter	Qida maddəsinin kalorik əmsalı	Тепловой (калорический) коэффициент питательного вещества
Thicken	Qatılaşmaq, qatılaşdırmaq	Сгущаться, сгущать
Thirst	Susuzluq, yanğı	Жажда
Thready pulse	Sapabənzər nəbz	Нитевидный пульс
Threshold of stimulation	Qıcıq qapısı	Порог раздражения
Tidal volume	Tənəffüs həcmi	Дыхательный объем
Time of complete circuit of the blood	Qanın tam dövr etməsi müddəti	Время полного кругооборота крови
Tissue	Toxuma	Ткань
Toadstool	Zəhərli göbələk	Поганка (гриб)
Total lung capacity	Ağciyərlərin ümumi tutumu	Общая (полная) емкость легких
Touch	Toxunma, toxunmaq	Осязание, осязать
Toxic goiter	Diffuz tireotoksik ur, Bazedov xəstəliyi	Диффузный тиреотоксический зоб, Базедова болезнь
Trace element	Mikroelement	Микроэлемент
Transection	Köndələn kəsik	Поперечное сечение
Transfusion of blood	Qanköçürmə	Переливание крови
Transmission of neural impulse	Sinir impulsunun nəql olunması	Передача нервного импульса
Transmitter	Mediator	Медиатор
Ultraparadoxical phase	Ultraparadoksal (həddən artıq təəccüblü) faza	Ультрапарадоксальная (чрезмерно удивительная) фаза
Unconditioned reflex	Şərtsiz refleks	Безусловный рефлекс
Uninhibition	Ləngimədən azad olma	Растормаживание
Unyielding	Bərk, əyilməyən	Твердый, несгибаемый
Urinary output	Diurez	Диурез
Urination	Sidik ifrazı, sidikburaxma	Мочеиспускание
Valvular pneumothorax	Qapaqlı pnevmotoraks	Клапанный пневмоторакс
Varicosity	Varikoz, venaların varikoz genəlməsi	Варикоз, варикозное расширение вен
Vasoconstrictive	Damarbüzücü, damardaraldan	Сосудосуживающий
Vasodilative	Damargenəldən	Сосудорасширяющий
Venous pulse	Vena nəbzi	Венный пульс
Ventilation – perfusion ratio	Ventilyasiya-perfuziya göstəricisi	Вентиляционно-перфузионный показатель
Ventricular fibrillation	Mədəciklərin səyriməsi	Фибриляция (мерцание) желудочков
Ventricular flutter	Mədəciklərin titrətməsi	Трепетание желудочков
Verbal logical memory	Söz-məntiqi yaddaş	Словесно-логическая память
Vicious circle	Qüsurlu dövran	Порочный круг
Viscosity	Suvaşqanlıq	Вязкость
Visual acuity	Görmə itiliyi	Острота зрения
Vital activity	Həyat fəaliyyəti	Жизнедеятельность

Vital capacity	Ağciyərlərin həyat tutumu	Жизненная емкость легких
Volatile	Uçucu	Летучий
Volumetric vessel	Həcm damarı	Объемный сосуд
Voluntary	İradi	Произвольный
Warm-blooded animal	İstiqanlı heyvan	Теплокровное животное
Web	Zar, membran	Перепонка, мембрана
Winking	Göz qırpma	Мигание, моргание
Withdrawal reflex	Bükmə refleksi	Сгибательный рефлекс
Worry	Narahatlıq, həyəcan, iztirab, narahat olmaq, iztirab çəkmək	Беспокойство, тревога, мучение, беспокоиться, мучиться

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