**NORMAL PHYSIOLOGY 2**

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| **N** | **Themes** | **Hours** |
|
| **1.** | **Respiration**. Mechanism of inspiration and expiration. Negative pressure in pleural cavity and its significance. Respiratory volumes. Functional system maintaining the normal level of gases necessary for the metabolism of organism. Transport of gases by the blood, oxygen capacity of blood. Respiratory center. Neuro-humoral regulation of respiration. Role of cerebral cortex in the regulation of respiration. Hypoxia. Respiration under different atmospheric pressures. Compensation of functions at the base of functional system of respiration. | **2** |
| **2.** | **Digestion**. Functional system of digestion. Systemic mechanisms of hunger and satiety. Endogenous and exogenous nutrition. Sensory and metabolic satiety. Methods of investigation of the gastrointestinal tract function. Digestion in the oral cavity. Swallowing. Digestion in the stomach. Methods of investigation of the gastric juice secretion. Composition of gastric juice. Phases of gastric juice secretion. Inhibitory mechanism of gastric secretion. Evacuation of food from the stomach into duodenum. Digestion in duodenum. Pancreatic juice, composition and regulation. Functions of liver. Digestion in the small and large intestines. Mechanism of absorption. Digestion in small and large intestines. Functional system regulating the defecation. **Metabolism and energy exchange** as a base of vital processes of organism. Biocalorimethry, energetic balance, respiratory coefficient and basal metabolism.**.** | **2** |
| **3.** | **Excretory system.** Subsystems of excretory functional system. Functional system of urine formation. Mechanism of urine formation: filtration, reabsorption, secretion. Functional evaluation methods of renal activity. Self regulation of renal blood flow. Role of kidneys in the different functional systems. Mechanism of urine excretion. Amount, content and physical-chemical peculiarities of urine. Artificial kidney. Physical-chemical regulation of body **temperature**, physiological basis of hypo- and hyperthermia. Functional system maintaining constancy of body temperature. | **2** |
| **4.** | **Hormones.** General properties of hormones. Formation and action dynamics of hormones. Interaction of hormones with the target cells. Hormonal functions of hypophysis. Functions of thyroid and parathyroid glands. Hormones of adrenal cortex and adrenal medulla. Hormonal functions of pancreas, sexual glands, thymus and epiphysis. Tissue originated biologically active substances. Role of endocrine glands in the organism functional systems.  |  |
| **5.** | **Analysers**. Role of analyzers in systemic organization of behavior. Tactile, vestibular, olfactory and gustatory analyzers. Visual reception. Optic system of eye. Structure of retina and its functions, myopia and presbyopia. Electroretinography. Auditory analyzer. Pain reception. Neurochemical mechanisms of pain. Endogenous antinociceptive system.  | **2** |
| **6.** | **Movement.** Role of reverse afferentation in the regulation of movement. Vegetative and endocrine components of behavioral acts. **Higher nervous system.** Conditioned and unconditioned reflexes. Inhibition in the cerebral cortex. Afferent synthesis, decision making, acceptor of action result, estimation of result. Medical aspects of systemic organization of behavior. Types of higher nervous activity, experimental neurosis.  | **2** |
| **7.** | **Motivation.** Classification of motivation, theories, pathological motivations.**Emotion**. System mechanisms of emotion, physiological basis, theories about emotions, emotional stress. Architectonics of psychical activity. Dynamics of mental activity.**Memory** and types (short-term and long-term memory). Formation of memory engram. **Sleep.** Biological significance of sleep, objective manifestations, neuro-physiological bases of sleep, role of biologically active substances in the mechanism of sleep, sleep disorders, situations like sleep.**Sexual functions.** General characteristics. Sexual hormones, hormonal functions of male and female organisms, fertility. | **2** |

**NORMAL PHYSIOLOGY 2**

**LECTURE 1**

**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 pleural 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).

1. 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.
2. 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 inspiratory capacity (3500 ml) equals the tidal volume plus the inspiratory 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 spirometer, it cannot be used in a direct way to measure the functional residual capacity. Therefore, to measure this important index, the spirometer is used in an indirect manner, usually by means of a helium dilution method.

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** (VA) is the total volume of fresh air entering the alveoli (and other adjacent gas exchange areas) each minute:

VA = (VT - VD) . F

 VT - is the tidal volume, VD - 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**  | **O2**  | **CO2**  | **N2 and inert gases**  | **H2O**  |
| 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 pulmonary 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 pressure 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 PO2, PCO2 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., PO2, PCO2 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 (PH2O) 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**  | **O2**  | **CO2**  | **N2 and inert gases**  | **H2O**  |
| 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 quantitive 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 conditions 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 12001300 ml/min. mm Hg during exercise.

The PO2 of the gaseous oxygen in the alveolus averages 104 mm Hg, whereas the PO2 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 capillary is 64 mm Hg.

The PCO2 of the venous blood entering the pulmonary capillaries equals 45 mm Hg, whereas PCO2 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 alveoli. 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 (VA) 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 (VA/Q) is determined. The normal ventilation-perfusion ratio is equal to 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 CO2and 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 1.34-1.36 milliliters of oxygen (1.39 ml when the hemoglobin is chemically pure, but this is reduced by impurities such as met hemoglobin). 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 anhydrase catalysis 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 HCO3  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 NaHCO3 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 (HHb). Carbon dioxide reacts directly with hemoglobin to form the compound carbaminohemoglobin (CO2HHb).

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 Po2is still 95 mm Hg. The Po2in the interstitial fluid averages only 40 mm Hg. The normal intracellular Po2ranges 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 Po2provides 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%:

= 25.8 %

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

 =77.3%

When oxygen is used by the cells most of it becomes carbon dioxide, and this increases the intracellular PCO2 which is about 46 mm Hg. Interstitial Pco2 is about 45 mm Hg. Pco2 of the arterial blood entering the tissues is 40 mm Hg. So, carbon dioxide diffuses by the gradient (4645-40 mm Hg) from the cells into the interstitial fluid and then into the blood of tissues capillaries.

**Regulation of Respiration. Peculiarities of Breathing under Different Conditions. Respiratory Defense Reflexes. Artificial Respiration**

The nervous system adjusts the rate of alveolar 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 essentially. 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 dispersed 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 pneumotaxic 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 mid region, 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 increase of pulmonary ventilation and hypocapnia results in respiratory center activity weakening and decrease of ventilation.

Using the cross circulation method, Frederic 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.**

Excess 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 appropriate 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 Pco2or 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 Pco2increases, so also does the Pco2of 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 receptors, mechanoreceptors, chemoreceptors, olfactory receptors), 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 inhibition 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 respiratory 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 defense 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 indices 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 competition has not begun 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 Po2, Pco2and 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 characterized by slowly waxing and waning respiration, occuring over and over again approximately every 4060 seconds. The main cause of periodic breathing is decrease of excitability 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 ventilation), the respiration is weakened and temporarily stopped. 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 organism and may reach up to 120-150 litres per minute (10-20 folds of the norm). Heart rate increases 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 sickness 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 mountainous 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 conditions 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 characterized 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 decompression 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 decompression 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.

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.

**LECTURE 2**

# DIGESTION

**Significance of Digestion and Methods of Investigation of Digestive Tract Functions. Secretion of Saliva. Chewing. Swallowing. Gastric Digestion. Emptying of the Stomach. 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, and dissolving. The chemical processing consists of successive stages of hydrolytic splitting of proteins, fats, carbohydrates by hydrolyzing enzymes (protease, lipase, and 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, glycerin and fatty acids). These can be absorbed 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.

**Proper** digestion – is realized by enzymes synthesized in the organism itself.

**Autolytic** digestion – is realized by exogenous hydrolyses of food.

**Symbiotic** digestion – is realized by enzymes synthesized by bacteria and unicellular organisms.

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, somatostatin, encephalin, 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 peculiarities 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.

El**ectrogastrography** 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 peristaltic 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=1.51.8). 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 cholecystokininpancreozymin 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 intestine 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

**2)** gastric

**3)** intestinal

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 cephalic 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 accommodated 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:

* 1. - The simple monophase waves of low amplitude (5-8 mm Hg) and the duration of each wave - 5-20 seconds;
	2. - also simple, but more prolonged (12-60 seconds) waves with comparatively higher amplitude;
	3. - 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:

1. the phase contractions of peristaltic character of short duration (3 contractions per minute);
2. 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, aceelerate 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.

**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 carboxypolypeptidase. 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-, HCO3-).

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 contractions 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 duodenum 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 motility 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 vegetative 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, bradykinin, 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 propulsion 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.

**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 absorbed.

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 transport of the substances through the membrane against concentration, osmotic and electrochemical gradients with the expenditure of energy (**primary active**) and with the participation of the special systems (mobile carriers, transport membrane canals – **secondary active**).

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 another 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 square 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 epithelium, 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 monosaccharides 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 H2O and CO2. 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 quantities).

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, methylation, acetylation and conjugation 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 rhythmic 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.

Appearance 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 food and 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 operates primarily by inhibiting the feeding center.

The actual mechanisms of feeding are controlled by centers in the brain stem. If the brain is sectioned below hypothalamus but above the mesencephalon, the animal can still perform the 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 overeating 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 vagus to suppress the feeding center, thereby reducing 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, preventing 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 excessively 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 slightly 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.

**Nutrition** is the process of providing or obtaining the food necessary for health and growth. There are endogenous and exogenous nutrition.

***Endogenous nutrition*** is the assimilation by the body of substances that constitute the organism itself, as in starvation and hibernation. Endogenous nutrition involves the breakdown of carbohydrates, fats, and proteins in certain tissues, for example, fatty and muscle tissues.

***Exogenous nutrition*** is the process whereby substances entering the body from the environment are assimilated. Ingested food is broken down into comparatively simple chemical compounds, which are absorbed and then used to build tissues and organs and to regulate functions.

**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 lipids 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 triglycerides 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 (160180 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 glycosuria, 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-.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 B12 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 membrane 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.

**Energy Metabolism. Nutrition**

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 (t2 - t1) the amount of the heat, given off by the organism (Q), is calculated by well - known in physics formula: Q = cm (t2 - t1).

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.

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 (18-20oC) 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;

 - 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 CO2, H2O and NH3, 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 assimilability 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.

**LECTURE 3**

# EXCRETORY PROCESSES

**Homeostatic Functions of Kidneys. Glomerular Filtration and Tubular Reabsorption**

The basic function of excretory organs is to maintain the constancy of composition and volume of fluids of internal environment of organism and first, 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 intracellular 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.

1. 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.

1. 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 alreadly 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.

1. 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.

1. 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.
2. Kidneys take part in the regulation of metabolism of proteins, lipides and carbohydrates.
3. 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. Reninangiotensin system causes the vasoconstriction. In the kidneys vasodilative substances (medullin, prostaglandins) are also synthesized.
4. Kidneys take part in the erythropoiesis. They secrete erythropoietin which stimulates the bone marrow to produce red blood cells.
5. 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 complex 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 over reabsorption 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 cotransported 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:

 Urine flow (ml/min) × Concentration in urine

Plasma clearance (ml/min) =

 Concentration in plasma

**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 (Pin) 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 calculated. Since the amount of inulin in filtrate (F×P in ) is equal to that of in urine (V×U in ), we have the following equation from which the volume of the filtrate can be determined:

F×Pin=V×Uin F= V×Uin/P 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×Pin ) and the part of it that was excreted in urine (V×U in ) is equal to the volume of tubular reabsorption (R): R = F×P g - V×U g

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×U d ) and in the filtrate (F×P d ):

S = V×U d - F×P d

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 - Ppah, in urine - Upah and the volume of excreted urine - V, then the amount of PAH flowing into the kidneys is - C×Ppah and its amount in the urine - V×Upah . Since these are equal, we have an equation from which the flow of plasma through the kidneys may be determined:

C×Ppah = V×Upah

C = V×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 desoxyco rticosterone), 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 membranesemipermeable thin spirial 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:

1. excrete from the organism the waste products of metabolism;
2. take part in temperature regulation;
3. excreting 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 50-60o 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 electrical 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.

**Temperature regulation**

Unlike the **poikilothermal** (cold-blooded) animals, the body temperature of the **homoiothermal** (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 - 38oC) 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 - 33.9oC).

Usually the temperature is measured in the axillary cavity where it is equal to 36.5-36.9oC and in the rectum (especially in children) where it is 37.2 - 37.5oC. 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 18-20oC when one is dressed and 28o 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 receptors 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 20-30oC, and for warmth receptors-within 38-43oC.

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 supercooling (hypothermia) occur.

**The hypothermia** is the state when the body temperature is lower than 35oC. 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 30-32oC 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 conductivity greatly depresses body metabolism.

The **hyperthermia** is the state when the body temperature is higher than 37oC. 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 40-41oC 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. Often 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.

# LECTURE 4

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# ENDOCRINE SECRETION

**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 endocrine glands.

A hormonal (Gr. hormao - 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 certain activity of executive organs);
4. correcting effects (changing the intensity of function of organs and tissues).

The characteristic property of hormones is that their physiological activity is very high. For instance, 1 g of insulin is enough to decrease the blood sugar 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 secrete the adrenocortical hormones; the ovarian hormones have specific effects on the female sex organs, as well as on the secondary sexual characteristics of the female 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 (thyroxin 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 (especially 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:

1. Follicle stimulating hormone (FSH).
2. 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:
8. somatostatin or growth hormone inhibitory hormone (GHIH);
9. prolactostatin or prolactin inhibitory factor (PIF);
10. 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 controller 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.

**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 thyroxin (T4) and 10% is triiodothyronine (T3). But most of the thyroxin 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 thyroxin. But it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxin.

Thyroxin 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.

Thyroxin and triiodothyronine are iodine containing hormones of the thyroid gland. To form normal amount of thyroxin 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 thyroxin activity begins: after injection of a large amount of the thyroxin 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 1012 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 thyroxin 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 thyroid 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 thyroid 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 thyroxin 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 adenohypophysis 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 1416 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 mucous 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, Pamir, Urals, Tien Shan, Caucasus) insufficient 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 thyroxin 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 erythrocytes 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 concentration 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 effects 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.

 **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 pubertal 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 (ChG)), 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 simultaneous 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 several 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.

**LECTURE 5**

# SENSORY PHYSIOLOGY

**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 “analyzer”. 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 analyzers: 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 analyzers 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 analyzers. Transmission, transformation and coding of signals are realized in all analyzer 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 arterial blood, osmolality of the body fluids, carbon dioxide concentration, etc.;
3. thermoreceptors detecting changes in temperature (cold receptors and warmth receptors);
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
6. contact receptors–are sensitive only to stimuli from objects directly applied to them (tactile, pain, taste receptors);
7. distance receptors –are sensitive to stimuli arising from objects at a considerable distance from organism (visual, hearing, 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 order to be perceptible (differentational threshold) must exceed the stimulus already acting by a definite proportion:

∆I/I = const

In this formula I is the stimulus and ∆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 (∆ I) must be added:

 const = = 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, analyzers 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 neighboring 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 distinct reaction to the superlow or supershort 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 analyzers 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 analyzers.

The ultimate and most intricate operation of analyzers 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 analyzer 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 neurons.

Then, the “dendritic tree” (neuron inputs) have synaptic contacts with axons of several cells of the preceding layer. Therefore, all the neurons of analyzer have the totality of neurons at the next and higher levels of the analyzer 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 analyzers and provides them with high adaptability to changing environmental conditions. The inhibitory interaction in analyzer 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 mechanoreceptors 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 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 45oC 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 (A 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 substance 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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. Ishemia 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-defense 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 latterin 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 ampulla, 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 220cm/sec2. This is difference threshold of acceleration. The differrence threshold of inclination of the head is about 1o to the side and 1.5-2o 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 sec2 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.

**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 prolongated 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 30oC and left hand in that of heated to 20o C. Then both hands are put into the water heated to 25o 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 mm2, and the area of the tympanic membrane is 70 mm2. 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 1x10-9erg/cm2x 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).

**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 aqueous humor, the crystalline lens, vitreous 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 accommodation. Accommodation 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 accommodation 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 accommodation.

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 accommodation 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 accommodation, and cannot see clearly objects nearer than 10cm even with maximum contraction of the ciliary muscle, that is, at the great effort of accommodation.

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 accommodation. 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 cerebral 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 periphery.

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 opposide 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 42o, inward by 45 o, upward by 54 o and downward by 57 o.

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 (1.10-10-1.10-11erg/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 sensititvity 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 dispersing (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 o outward, 70 o downward, 60 o 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) yellowgreen 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.

# LECTURE 6

# HIGHER NERVOUS ACTIVITY

 **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 defense 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. descriptive 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.

Rehearsal 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 coordination 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.

**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 defense 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 switching 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 part ways) 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 unconditioned 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 humors” (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 inhibitionI  | 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.

Overst rain 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:
5. narcotic phase- cessation of responses to weak, average and at last, to strong stimuli;
6. 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 hierarchical gradation of needs (lower and higher needs) exists, and their satisfaction 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.



**Subconsciousness and Consciousness**

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 receptors, 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 realized 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 automatism. 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.

**LECTURE 7**

**Emotions and Motivations. Sleep**

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 hierarchical 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 river.

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 dishonorable 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.