**PATHOPHYSIOLOGY OF TISSUE GROWTH. TUMOR.**

**EXTREME STATES OF ORGANISM.**

The normal growth of the body promotes adaptation of the organism to the external environment. The pathological growth is the state in which the growth of the whole organism or of its different cells, tissues or organs ceases to promote the existence of the organism in the environment, that is, weakens its adaptability and becomes harmful for it.

The disorders in the development at the postnatal period are divided into two groups:

1. Hypobiotic processes- inhibition of the tissue growth (dissimilation preponderates).

2. Hyperbiotic processes- acceleration of the tissue growth (assimilation preponderates).

Both hypobiotic and hyperbiotic processes may embrace the whole body

(accordingly – growth inhibition and rapid growth )or separate tissues and organs.

Growth inhibition of the body is caused by the following factors:

1-hypofunction of the anterior lobe of the hypophysis (hypophyseal nanism);

2-hypofunction of the thyroid gland (cretinism );

3-some hereditary diseases ( Down’s syndrome,Shereshevsky-Turner syndrome, chondrodystrophic nanism);

4-damage to diencephalon;

5-protracted defective nutrition (alimentary dystrophy).

**Hypobiotic processes of separate tissues and organs include dystrophy and atrophy.**

Pathological processes of different character that are connected with the disturbances of the intracellular metabolism, are called dystrophy Gr.dysdisturbance; trophe-nutrition) or degeneration.

Atrophy is the pathological process which is characterized by diminution of the volume of cells, tissues or organs. Physiological atrophy and pathological atrophy are distinguished.

The physiological atrophy includes;

a)obliteration of the umbilical artery and Botallo’s duct in newborns;

b)atrophy of sexual glands in old persons;

c)diminution of the volume of intervertebral cartilage, etc.

The most frequent causes of the pathological atrophy are: malnutrition, dysfunction of the endocrine glands, damage to the central and peripheral nervous system, intoxications. When not very profound, the pathological atrophy is reversible process.

The following types of the atrophy are distinguished:

1. Dysfunctional atrophy-develops as a result of inactivity (metabolism in tissues is weakened, blood supply is decreased):in bone fractures, in diseases disturbing movements in joints, in tooth sockets after extraction of teeth, in optic nerve after removal of the eye, in skeletal muscles of cosmonauts under the conditions of the weightlessness, etc. In experiment this type of atrophy is produced by the way of dissection of muscles’ tendons.

2. Neurotic atrophy- develops as a result of disturbances in the innervation of tissues and organs (disorders in the nervous regulation of the metabolism and weakening of the organs’ activity).

3. Atrophy connected with the circulatory insufficiency – as a result of hypoxia, activity of cells is weakened, their volume is diminished, fibroblasts are proliferated and tissues are sclerosed.

4.Atrophy resulted from the protracted mechanical pressure on the tissues and organs (disturbances in blood supply of the cells which cause hypoxia): atrophy of nerve cells in hydrocephalus, atrophy in kidneys as a result of urinary obstruction, etc.

5.Atrophy caused by the physical, chemical and pharmacological agents: ionizing radiation more easily causes atrophy of bone marrow and sexual glands, thiouracil -that of the thyroid gland, alloxan - of the β cells in the insular apparatus, etc.

**Hyperbiotic processes** of separate tissues and organs include hypertrophy, hyperplasia, regeneration and tumors. Transplantation (gtrafting of the organs and tissues ) may be also classified as hyperbiotic process (autotransplantation, homo-or allotransplantation and heterotransplantation).

Increase of the volume of the tissue or organ is called hypertrophy. In hypertrophy the mass of the organ or tissue is increased which leads to its hyper-function. The volume of the tissue is increased as a result of increase of the volume of its cells.

Hypertrophy of tissues is often accompanied by their hyperplasia. In hyperplasia volume of tissues is increased as a result of increase of their number (division of cells). However, sometimes hyperplasia is limited only by the increase of the intracellular organoids- the number of cells does not increase, but the volume is increased.

Taking into account predominant development of the parenchymal or interstitial elements, two types of the hypertrophy are distinguished:

1) true hypertrophy-uniform enlargement of all constituent parts of an organ, including its specific parenchymal elements (the functional capacity of the organ is

increased ); true hypertrophy is characterized by the similarity of the newly formed

tissue with the normal tissue from which it has been formed;

2) false hypertrophy (pseudohypertrophy )-enlargement of the organ, due to increase in intermuscular cellular tissue, adipose tissue, etc., whereas the parenchyma remains normal or even is atrophied (the function of the organ is diminished ).

Under physiological conditions physiological hypertrophy develops. Physiological hypertrophy includes true hypertrophy of skeletal muscles as a result of increased work load (physical training), of the uterus during pregnancy, of breasts in nursing mothers, etc.

More often hypertrophy and hyperplasia develop under pathological conditions. Pathological hypertrophy is an adaptative reaction compensating the functional insufficiency of an organ or tissue.

Hypertrophy resulting from an increased work load is called work hypertrophy. Work hypertrophy may be physiological as well as pathological.

Hypertrophy which adapts an organ to increased functional requirements is called adaptive hypertrophy (hypertrophy of the heart in valvular defects, hypertrophy of the smooth muscles of the intestines and urinary bladder in cases of constrictions or calculi). Hypertrophy which follows destruction or injury in the opposite paired organ or in another part of the same organ with the remaining organ or part of organ taking over the total function is called compensatory hypertrophy. From the pathogenic point of view the compensatory hypertrophy may be regarded as a kind of the work hypertrophy. The following types of the compensatory hypertrophy are distinguished:

a) regenerative hypertrophy –increase of the remaining part of the organ (liver, spleen, pancreas)after removal of its another part;

b) vicarious hypertrophy –increased volume of the remaining organ after removal of the opposite paired organ (kidneys, lung, adrenal gland);

c) correlative hypertrophy –is observed in the organs that are connected functionally (increase of hypophysis after removal of thyroid gland ).

Congenital hypertrophies are also distinguished which are associated with disturbances in embryonal development (special form of hypertrophy of the breasts, congenital ichthyosis or hypertrophy of the corneal layer of the epidermis).

Hypertrophy is important for the organism, it promotes compensation of disturbed functions of organs and tissues. But hypertrophies that result from inflammations and neurohumoral disorders may harm the organism; sometimes they may cause even development of tumors.

Regeneration is restoration of destructed or lost tissues, organs or parts of the organism. It is new tissue growth stimulated by injury or destruction of tissues. Regeneration is one of the forms of the organism’s adaptation. The following types of the regeneration are distinguished:

1) physiological regeneration;

2) reparative regeneration;

3) pathological regeneration;

The physiological regeneration is restoration of tissue elements destroyed under normal conditions, that is, replacement of outlived elements by new ones (regeneration of the epidermis, glandular cells, blood cells). Some cells (for instance, ganglion cells of the brain) do not reproduce by the way of fission. Physiological regeneration of these cells is realized by the way of continuous renewal of intracellular organoids and membranes. Besides, in all tissues and cells of the organism biochemical regeneration occurs.

The reparative regeneration occurs in the pathological processes accompanied by the damage to tissues and cells. It may be complete (perfect) or incomplete (imperfect ). Complete regeneration (restitution) is characteristic of tissues with high ability to reproduce (mucous membranes, skin) ,and elements of the new formed tissue do not differ from the tissue that was at that area before injure. Incomplete regeneration (substitution) occurs in tissues whose ability to proliferation is weak; in the damaged area cicatricial tissue (connective tissue) develops.

**So, depending on their capacity to regenerate, 3 types of the parenchymal cells of the body are distinguished:**

a) labile cells –continue to multiply throughout life under normal physiological conditions(surface epithelial cells of epidermis, alimentary, respiratory, urinary tracts, vagina, cervix, uterine endometrium, hemopoietic cells of bone marrow, cells of lymphnodes and spleen);

b) stable cells-decrease or lose their ability to proliferate after adolescence but retain the capacity to multiply in response to stimuli throughout adult life (parenchymal cells of liver, pancreas, kidneys, adrenal and thyroid glands, mesenchymal cells like smooth muscle cells, fibroblasts, vascular endothelium, bone and cartilage cells);

c) permanent cells-lose their ability to proliferate around the time of birth (neurons of nervous system, skeletal muscle and cardiac muscle cells).

The pathological regeneration includes distorted forms of the regenerative processes:

a) hyperregeneration –at the site of regenerated tissue excessive amount of the new tissue is formed;

b) hyporegeration –at the site of regenerated tissue small amount of the new tissue is formed;

c) metaplasia(transformation of one form adult tissue into another)- at the site of regenerated tissue another type of tissue is formed (keloid cicatrix, very large callus, metaplasia of the epithelial tissue in the process of the chronic inflammatory processes).

Some exogenous and endogenous, general and local factors influence the rate and quality of the regeneration. The general factors include age and constitution of the organism, the functional state of the nervous system, character of the nutrition, the state of the metabolism, hemopoietic, endocrine systems, blood and lymph circulation,character of the pathological process, etc.

The rate of regeneration is higher in children and young people, then come elderly and old people. In the tissues with disturbed innervation, in the animals after removal of hypophysis, thyroid and sexual glands regeneration is weak. Glucocorticoids weaken the regeneration, whereas thyroxin and mineralocorticoids stimulate it.

Some local factors are of importance in origin of neurohumoral changes in the damaged tissues. Leukocytes are destroyed in damaged areas of tissues and excrete necrohormones or trephons which accelerate regeneration.In the regenerated tissues of tadpoles desmons, that is, specific stimulators were revealed.

The factors inhibiting regeneration were also revealed in tissues. In the cells which reproduce by the way of mitosis, keylons are synthesized. These are substances which inhibit proliferation. When part of tissues perishes, in healthy part amount of keylons is decreased, and regeneration is accelerated. Adrenalin decreases activity of keylons. Stimulating action of the central nervous system on the regeneration may be connected with this fact.

High-quality nutrition (sufficient quantitity of proteins and vitamins) influences regeneration positively, whereas deficiency of the vitamins (especially C and D) has negative effect.

Wound healing is the typical example of the pathological regeneration occurring after the damage to tissues. Healing by first intention (primary union) and healing by second intention (secondary union) are distinguished.

Healing by first intention is defined as healing of a wound which is clean, uninfected, surgically incised, without much loss of cells and tissues; edges of wound are approximated by surgical sutures.

Healing by second intention is defined as healing of open with a large tissue defect, at times infected wound having extensive loss of cells and tissues; the wound is not approximated by surgical sutures.

The edges of the wound are stuck together by fibrin that comes out into the wound with blood and lymph. Large amounts of fibrin form crust under which the healing occurs. Under the edges of the wound leukocytes are accumulated (slight inflammation develops). They excrete the substances stimulating reproduction of connective tissue cells-histiocytes which are converted into fibroblasts. These form collagenous and elastic fibers gradually filling the tissue defect. Epithelial cells reproduce, fill the defect, tighten it.

Healing by second intention is characterized by formation of granulation tissue resulted from reproduction of histiocytes and fibroblasts. This is protective barrier against infection. After the healing by second intention epithelization of the wound does not occur, and the scar (especially on the skin) is visible for many years.

**Tumor (neoplasm) is noncontrollable by the organism rapid, abnormal, excessive, uncoordinated and purposeless proliferation (reproduction) of cells with comparatively autonomous metabolism and essential differences in structure and properties.** The branch of science dealing with the study of neoplasms is called oncology (Gr. onkos-tumor; logos-study, science).

Tumor is local manifestation of the general biological phenomenon characteristic of all living beings. But in highly developed organisms more types of tumors are observed.

In connection with the working and living conditions of human beings the number of types of tumors and the frequency of cases is highest in man. Even the domesticated animals get the tumors more frequently than the wild animals of the same species. Taking into consideration existence of carcinogenic substances (chemical and radioactive substances, X-rays, etc.) in a number of branches of modern industry, tumors are classified as civilization diseases.

Depending on the working, living and domestic conditions, character of nutrition of people, different localizations of tumors predominate, for instance, in European countries carcinoma of the stomach and lungs are more frequent, whereas in India carcinoma of the liver is prevailing.

The tumoral cells differ not only from the normal cells, but also from the cells that are observed in other pathological processes. As distinct from the proliferative inflammation, hyperplasia, regeneration, etc., in which the cells also reproduce rapidly, in tumors reproduction of cells does not depend on regulative mechanisms of the organism.

The second main property of the tumors **is atypicalness**, that is, differences in structure, functions, reproduction, differentiation and metabolism of tumoral cells from the normal cells. Loss of differentiation of the cells and change of their structure and biological properties is called anaplasia or cataplasia. In the tumoral cells the following forms of atypicalness are observed:

1.Morphological atypicalness- may be of two forms: cell atypicalness and tissue atypicallness.

The tumoral cells differ from the ordinary cells by their form, size, strucure. This is called the cell atypicalness. The tumoral cells are larger than the normal cells. When the atypicalness is strongly expressed, the structure of the tumoral tissue becomes simpler, and it consists of cells of the same type (especially in malignant tumors). The tumoral cells differ from the ordinary cells also by their ultra-structural properties (there are more ribosomes, form and size of mitochondria are changed, nucleus is large, etc.). Owing to the changes in cell membrane the passage of substances through the membrane, its irritability, nutrition of cells are changed.

Changes in the structure of the tissue from which the tumor develops, is called tissue atypicalness. From this point of view two types of tumors are distinguished:

a) homotypical tumors-differ insignificantly from the normal tissues by the structure of their stroma and parenchyma;

b) heterotypical tumors-the tissue atypicalness is so strong that it is impossible to determine from which tissue the tumor has originated.

2. Biochemical atypicalness-expresses difference of metabolism in tumoral cells from that of in normal cells. For instance, in tumoral cells activity of the tissue respiration enzymes (cytochrome oxidase, catalase) is lower, and therefore, anaerobic glycolysis predominates. Content of cholesterol, glycogen, nucleic acids is higher than in normal cells.

3.Histochemical atypicalness-tumoral tissues differ from the normal tissues by their histochemical properties. For instance, in prostate cells acid phosphatase and nonspecific exonuclease activity is high, but is still more higher in the cells of tumors originating from this gland.

4. Antigenic or immunogenic atypicalness-is connected with antigens that are revealed in tumoral tissues and which influence the organism’s immune reactivity.5 types of antigens were discovered in tumoral cells:

a) antigens which are formed under the influence of cancerogenic substances;

b) antigens which are formed with participation of viruses;

c) transplantation isoantigens;

d) embryonal antigens;

e) heteroantigens-are organospecific antigens, but they do not correspond to the organ and tissue from which the tumor develops (for instance, in the persons with carcinoma of the liver specific renal antigens were found ).

Usually development of the tumor begins from certain proliferative center whose cells acquire the ability to rapid reproduction. The tumoral tissue grows incoherent of the surrounding tissues and the organism’s functional state. Two kinds of neoplastic growth are distinguished:

1.Expansive growth-is charecteristic of benign tumors. They grow in relative isolation, seperated by a capsule from the surrounding tissues from which nerves and blood vessels penetrate into the tumors. Tumors with expansive growth do not invade the surrounding tissues, but merely move them aside, and this may cause dysfunction by compression. They are distinctly seperated from the healthy tissues.

**2.Infiltrative growth** –is observed in malignant tumors. It is characterized by invasion into the surrounding tissues with obliteration of the borderline between the tumor and normal tissue; the safety of organs is disturbed. It is difficult to isolate them completely from the organism by the operative way.

Higher the extent of tumor’s atypicalnes, more rapidly it grows, but the extent of cell differentiation is lower. In such tumors blood vessels develop poorly, tissue nutrition (especially in the central part ) is weak and formation of the necrotized areas is observed.

According to the clinic course of the tumors they are divided into two groups:

1)benign tumors;2)malignant tumors. Sometimes benign tumors convert into malignant tumors. This process is called malignancy. There are the following differences between the benign and malignant tumors:

1) in benign tumors only tissue atypicalness occurs, whereas in malignant tumors cell atypicalness as well as tissue atypicalness are observed;

2) benign tumors are enveloped into capsule, whereas malignant tumors do not have capsule;

3) benign tumors are characterized by the expansive growth, but malignant tumors-by the infiltrative growth;

4) for malignant tumors metastatic spreading is characteristic, whereas benign tumors do not metastasize (capsule prevents this process; besides, cells in benign tumor are connected with each other more tightly);

5) recidivations are rare in benign tumors and frequent in malignant tumors;

6) metabolism in benign tumors does not differ from that of in normal tissues, whereas in malignant tumors metabolism is inversed;

7) malignant tumors cause cachexia in the organism, whereas in benign tumors cachexia is not observed (they do not exert toxic action on the organism ).

The harmful influence of the benign tumors on the organism is connected with compression of tissues and organs. Therefore, outcome of benign tumors depend on their localization (sometimes benign tumors in the brain lead to death ).

The tumors that develop from immature cells grow more rapidly, destroy surrounding tissues, metastasize and are inclined to recidivation.

Modern classification of tumors is based on their tissue structure. The names of tumors are formed by adding the ending “oma “(from the word “blastoma”)to the names of tissues from which they develop (myoma, osteoma, chondroma, fibroma).

The names of immature tumors are formed from the names of cells from which they originate (for instance, myoblastoma develops from myoblasts).The names of some tumors are connected with the names of organs where the tumors develop(hepatoma, thymoma, meningioma).Malignant tumors of the epithelial tissue are called cancer or carcinoma, of connective tissue –sarcoma.

The malignant tumors metastasize, that is, the cells of blstomatous tissue are transferred to distant sites where they form foci of new neoplastic growth (metastases). Tumoral cells metastasize by 3 ways:

1) lymphogenous;

2) hematogenous;

3) tissue contact.

More frequently metastases are spread by the lymphogenous way. Therefore, often they are found in the regional lymph nodes. For instance, in the cancer of the mammary gland metastases are found in axillary lymph nodes, cancer of the lower lip metastasizes into the submandibular lymph nodes. Sarcoma usually metastasisez through blood vessels.

The tumoral cells spread through lymph and blood vessels in the form of emboli. To change into metastases, the emboli must contain sufficient number of the cells and enter the vascular wall. Large tumoral emboli stick in small vessels, and thrombi are formed.

Formation of metastases depend also on the state of the tissue or organ into which the tumoral cells get. For instance, metastases are formed in spleen with difficulty, the cancerous metastases are rare inside muscles.

Frequently tumors of some organs selectively metastasize into certain organs. For example, malignant tumors of the prostate, mammary, thyroid glands often produce metastases (besides regional lymph nodes) in bones, cancer of lungs-in the brain and adrenal glands.

Frequently the metastasis of tumor depends on the direction of the vessels. For instance, tumors of the stomach metastasize into the liver (through the blood current). But the spread and localization of metastases are determined also by the properties of the organs into which they gain entrance.

One of the peculiarities of the neoplastic growth is tumoral progression. Tumoral progression is totality of all morphological, biochemical, functional and other changes of the tumor attained in the process of its growth. This means steady rise in malignant properties of the tumor in the course of its growth in the organism. Tumoral progression manifests itself in increased morphological anaplasia (atypicalness) of the tumoral cells, acquiring of more autonomy by them, invasive, infiltrative growth, increased capacity to metastasize.

The tumoral progression is connected with continuous division of tumoral cells, the process in the course of which the cells appear that differ from the initial tumoral cells by their properties.

The extent to which the tumor is able to perform the specific functions of the tissue and organ from which it has developed, depends on the degree of the morphological and biochemical cataplasia (atypicalness). Highly differentiated tumoral cells possess the functional properties of the tissue from which they have developed. For instance, in some tumors rising from the pancreatic island insulin is synthesized; some tumors of the adrenal glands and hypophysis produce a large amount of hormones. Tumors of the hepatic cells excrete bilirubin, and cancer cells in the pylorus excrete mucus.

Non-differentiated tumors may completely lose the functions of the tissues from which they have been originated. For example, sometimes the renal carcinoma cells produce thyroxin, and in the primary cancer of lungs corticotropin is synthesized.

The factors that participate in the mechanism of general changes caused by the tumor in the organism may be divided into 2groups:

1) changes connected with the competition of the tumoral cells with other cells of the organism in assimilating nutritive matters;

2) disturbances resulted from the changes in the biological character of the tissue from which the tumor has been originated.

The factors causing these changes are interconnected.

Tumors (especially malignant tumors ) cause profound metabolic changes in all tissues of the organism. Disturbances in carbohydrate metabolism are characteristic of malignant tumors. In tumoral cells carbohydrates are broken down rapidly and glucose easily passes from the membranes of the tumoral cells into cytoplasm. This results in decrease of blood sugar.

Hypoglycemia is the main motive factor of metabolic disorders in the organism where the malignant tumors grows. As a compensatory reactions, the organism’s glycogen reserves are rapidly broken down and consumed, production of glucocorticoids is increased which results in acceleration of gluconeogenesis. Besides the carbohydrate metabolism, different changes occur in the catabolism of nitrogen-containing organic substances and lipides, as well as in the hormonal balance of the organism, etc.

Acceleration of the anaerobic glycolysis is one the main signs of the intracellular metabolism in tumoral tissues. In normal tissues good oxygen supply leads to deceleration of anaerobic glycolysis (because 19 times more energy is produces when the glucose is broken down in the presence of oxygen than in anaerobic glycolysis). This is called Pasteur’s effect. In tumoral cells Pasteur’s effect is weak. In the presence, as well as in absence of oxygen a large amount of lactic acid is accumulated in tumoral cells and acidosis develops.

As a result of changes in the regulation of the genetic apparatus activity in the tumoral cells the synthesis of some proteins is decreased, whereas other proteins are synthesized more rapidly. Frequently they produce the proteins that are not found in normal cells. Some of proteins that are synthesized in the tissues of the fetus at the intrauterine period are found also in the tumoral cells.

The tumoral cells are called figuratively “a trap for amino acids”, because they absorb amino acids of blood with a great intensity. Some of glucose that enter these cells is also used for the synthesis of amino acids. One of the main biochemical peculiarities of the tumoral cells is rapid synthesis of nucleic acids.

In the organism with growing malignant tumor disorders in the hepatic function lead to disturbance of ammonia’s decontamination. Excretion of nitrogen-containing substances from the organism is still accelerated. At the same time a large amount of underoxidized anitrogenous organic compounds (especially fatty acids) are excreted in urine. Therefore, quantity of carbon in the urine and the carbon/nitrogen (C/N) ratio is increased up to 0.9 and more (in norm –0.7-0.8). This is called deoxydative carbonuria.

Lipide metabolism is also thoroughly changed. One of the compensatory reactions caused by hypoglycemia is hyperlipemia (lipolysis is accelerated and fatty acids are used as an additional source of energy). As a result of accelerated peroxide oxidation of lipids quantity of free radicals in blood and tissues is increased, which damage cell membranes (lysis of erythrocytes causes anemia).

Some physiologically active substances of tissue origin influence reproduction and growth of the tumoral cells. Such local substances include keylons, prostaglandins, cyclic nucleotids.

In the mechanism of the general changes caused by tumor in the organism, hormones and other physiologically active substances synthesized in its cells play a great part. For example, tumors of the anterior lobe of the hypophysis cause gigantism or acromegaly; in pheochromocytoma (tumor of the chromaffin cells of the adrenal glands) a large amount of adrenalin is synthesized, which causes increased blood pressure, etc.

Cachexia is caused by rapid metabolic processes in tumoral tissue (tumor deprives the organism’s healthy tissues of plastic and power materials) and influence of the toxic substances (toxohormones) that are formed in tumoral tissue.

According to modern ideas the normal cell turns into the tumoral cell as a result of changes in its genetic apparatus (somatic mutations). More than 90% of cancerogenic factors are of mutagenous character (they change structure and functions of the nucleic acids in cells). At first one or several cells are changed which then participate as “initiators” in the development of tumors. Owing to autonomy the tumor cells reproduce rapidly. In the process of reproduction by the way of fission they are exposed to next conversions. Cancerogenic substances exert additive action ,that is, even their smallest dozes do not vanish completely. Therefore, from the moment of the first influence of the cancerogenic factor on the organism up to the manifestation of signs of the disease different space of time may pass (from several weeks up to 30-40 years).

Presence of factors causing tumors and even inclusion of mechanisms of carcinogenesis are not sufficient for tumors to come into existence and develop. Decrease of antiblastomic resistance of the organism is also necessary. Antiblastomic resistance is resistance of the organism to origination and development of tumors. According to the stages and factors of carcinogenesis the following mechanisms of the antiblastomic resistance are distinguised:

1.Anticarcinogenic mechanisms, addressed to the stage of interaction of carcinogenic factor with cells, organellas, micromolecules:

a) acting against chemical carcinogenic factors;

b) acting against biological carcinogenic factors;

c) acting against physical carcinogenic factors.

2.Antitransformational mechanisms, inhibiting the stage of transformation of normal cells into the tumoral ones.

a) antimutation;

b) antioncogenic.

3.Anticellular mechanisms addressed to the stage of transformation of formed single tumoral cells into the cellular colony, that is, tumor :  
 a) immunogenic;

b) non-immunogenic.

**EXTREME STATES OF ORGANISM**

Extreme states of the organism are the pathological states caused by extremely strong stimuli and are characterized by overstrain or breakdown of the organism's adaptation mechanisms. They include pain, stress, shock, syncope, collapse, coma. The extreme states differ from the terminal state, that is, the final stage of diseases.

**Stress is totality of the nonspecific reactions which arise under the influence of different injurious factors and serve for adaptation of the organism to the action of these factors.**

Often the nonspecific reactions that come into being under the influence of different factors (mechanical and psychical traumata, radioactive rays, cold, warm, toxic and infectious agents, etc.) are alike. In a number of cases they are manifested more strongly than specific reactions. Usually the nonspecific reactions are of protective character, serve for adaptation of the organism to the action of the injurious agents and play decisive role in the course and outcome of the disease.

The nonspecific adaptative reactions which occur in the organism under the influence of extremely powerful stimuli were called by the Canadian scientist H. Selye "the general adaptation syndrome". The agents which cause in the organism changes of stereotype character, that is, extremely powerful stimuli, were called by him "stress factors" and the reactions caused by these factors - "stress".

The developmental mechanism of the general adaptation syndrome is connected with activity of the anterior lobe of the hypophysis and adrenal cortex. In the organism of the animals that were subjected to the influence of the extremely powerful injurious stimuli, hypertrophy of the adrenal glands (especially that of adrenal cortex) and their hypersecretion were observed.

There are 3 stages in the course of the general adaptation syndrome (stress):

I - alarm;

II - resistance;

III - exhaustion.

The stage of alarm is characterized by activation of hypophysis and adrenal cortex under the influence of unfavourable factors, hypersecretion of adrenocorticotropic hormone and glycocorticoids. In this stage 2 phases are distinguished: 1) shock, 2) antishock. At the first phase some functions of the organism are disturbed (hypothermia, hypotension, leukopenia, hypovolemia, etc.), whereas at the second phase activation of the hypophysis - adrenal gland system results in development of adaptative reactions, and the conditions come into being to restore the constancy of the organism's internal environment.

At the stage of resistance adrenal glands are hypertrophied, increased content of glycocorticoids circulating in the blood result in development of the organism's resistance against pathogenic stimuli. The circulating blood volume, arterial pressure are increased. These changes are due to the direct action of corticosteroids as well as activation of the sympathetic nervous system. If the influence of the stress factor is ceased or it is weak, above - mentioned changes in the organism are gradually eliminated.

However, powerful or protracted influence of the pathogenic factor on the organism causes exhaustion of the adrenal cortex function, sufficient amount of the glycocorticoids (which are, according to Selye, hormones of adaptation, that is, protective hormones) is not produced, and the organism's state is getting worse. These changes form the basis of the third stage of the general adaptation syndrome. The strong pathogenic factors may cause death at this stage.

So, at the second stage adaptation occurs ("eustress syndrome"), and at the third stage the general adaptation syndrome acquires the pathological character ("dystress syndrome"). Figuratively speaking, eustress is the relish of the life. It mobilizes the protective powers of the organism, ensures its response to the pathogenic factors.

The diseases resulted from the dystress syndrome were called by Selye "adaptation diseases". These include the diseases in whose pathogenesis disturbances of the processes of adaptation play an important part (rheumatism, bronchial asthma, some diseases of the skin, kidneys, cardiovascular diseases, etc.). The role of different factors of the external and internal environment, including occupational factors, in the formation of these diseases is also great.

The theory of Selye about the general adaptation syndrome exercised a great influence on the development of medicine. This theory attracted attention of practical physicians to the organism's protective - adaptive reactions and played an important part in the theoretical substantiation of the medicinal action of some nonspecific methods of treatment (blood - letting, autohemotherapy, acupuncture, etc). But Selye overestimated the role of nonspecific reactions and underestimated the role of specific reactions of the organism. This leads to a kind of banality in the activity of the physicians. Actually Selye turns out to be the supporter of the conditionality.

The second shortcoming of this theory is overestimation of the endocrine system's significance and underestimation of the role of the nervous system, especially that of the higher nervous system. So, Selye becomes the advocate of the theory of unconscious. True, after the criticism of his theory, to the end of his life Selye studied the role of the hypothalamus-hypophysis-adrenal gland system in the stress pathology.

The changes that occur in the hypothalamus under the impulses coming from the cerebral cortex, reticular formation and limbic system form the initial stage of the stress reaction. The neurosecretory nuclei of the hypothalamus secrete neurohormones (liberins and statins) into the blood which regulate secretion of the hormones in the anterior lobe of the hypophysis.

Pain, trauma, loss of blood, hyperthermia, hypothermia, some intoxications, infectious diseases and emotional strain cause hypersecretion of the adrenalin by the reflex way. Adrenalin, reaching the hypothalamus in the blood, causes hypersecretion of the corticoliberin which raises secretion of the adrenocorticotropic hormone. This hormone, in its turn, stimulates activity of the adrenal cortex.

**Shock is reflex disturbance in the organism's neurohumoral regulating mechanisms which arises under the influence of extraordinary stimuli and develops in several stages.** It is characterized by the decreased blood supply of tissues, hypoxia, sharply weakened vital functions. In shock deep changes occur in activity of the central nervous system, endocrine system, as well as in the general and local blood circulation, respiration, metabolism.

Shock may be regarded as the complex of passive protective reactions directed to preservation of the organism's life in the extremal conditions.

According to the classification of the shock based on the etiologic and pathogenetic signs, different types of the shock are divided into 4 groups:

1. shock connected with the exogenous pain - occurs under influence of the damaging factors of the external environment (mechanical trauma, burns, electric trauma, etc.);
2. shock connected with the endogenous pain-is resulted from the internal diseases (cardiogenic shock, nephrogenic shock, abdominal shock, the shock connected with the hepatic colic, etc.);
3. shock connected with the humoral factors - by the developmental mechanism is like collapse (posttransfusion shock, anaphylactic shock, hemolytic shock, the shock connected with the traumatic toxicosis, etc.);
4. psychoemotional shock.

According to the time of origination 2 types of the shock are distinguished:

1. early (primary) shock - arises in the period of damage or immediately after it;
2. late (secondfary) shock - develops several hours after the influence of the extremal agent (as a result of neurohumoral changes caused by the toxic products formed in the injured tissues).

According to the gravity of the clinic manifestations (decrease of the systolic arterial pressure -SAP and diastolic arterial pressure - DAP) the following degrees of the shock are distinguished:

Two stages are distinguished in the course of the shock which differ sharply from one another:

1. erectile
2. torpid

The erectile stage occurs in the period of influence of the extremal agent on the organism. Since its duration is very short (several minutes), frequently the physician does not see this stage. At the erectile stage powerful motor and psychical excitation is observed. Activity of the hypothalamus and sympathetic nerve centers, as well as tension of the bulbar vasomotor centers rise. A large amount of catecholamines is excreted into the blood which cause increase of the arterial pressure and hyperglycemia.

Secretion of cortioliberin in the hypothalamus is accelerated which results in increased secretion of adrenocorticotropic hormone in hypophysis and, in its turn, hypersecretion of glycocorticoids in adrenal cortex. So, in the organism the changes occur which are characteristic of stress reaction. Activation of the sympathoadrenal system results in increased heart rate; deep and frequent respiration is observed.

The changes occur in the morphological composition and coagulability of the blood: increased number of erythrocytes in the blood, leukopenia and then leukocytosis, decreased number of eosinophils, intravascular aggregation of the blood cells (especially thrombocytes), accelerated convertion of the fibrinogen into fibrin.

The torpid stage of the shock is more long and lasts from several hours to several days. At this stage activity of the central nervous system is inhibited. At first the patient distinctly answers the weak stimuli and whisper whereas the powerful stimuli frequently do not arouse the reaction. Then inhibition in the cerebral cortex becomes deeper and gradually spreads all over the subcortical structures. Blood pressure is decreased, reflex tachycardia (the compensatory reaction to the decreased blood pressure), in severe cases - infrequent respiration and periodic breathing are observed. Paralysis of the respiratory center may cause death.

Disturbed blood supply of the kidneys results in disorders in renal activity: oliguria and anuria, hypersecretion of renin (the compensatory reaction directed to normalization of the blood pressure). The deposited blood begins to circulate, and this results in leukocytosis. As a result of increased capillary permeability and passage of blood proteins into intercellular space, traumatic edema develops.

In the state of shock severe disorders occur in the metabolism. Hypoxia results in acceleration of the anaerobic glycolysis, accumulation of acid products of metabolism in the blood and tissues. Reserves of ATP are diminished. Heat production is decreased, and body temperature falls.

So, the processes taking place at the erectile stage of the shock are like those characteristic of stress, whereas torpid stage resembles parabiosis. Professor J.H. Tagdisi (1972) distinguished 3 phases in each of two stages of the shock.

In the erectile stage:

1. Mobilization - begins immediately after action of the agent causing shock and is characterized by mobilization of the organism's defensive reactions.
2. Resistance - the defensive powers of the organism are completely mobilized, and it is actively fighting against the agent causing the shock.
3. Overstrain - excitation in the cerebral cortex reaches the highest level. As a result of transition from quantity to quality the excitation is replaced by inhibition and the erectile stage - by the torpid stage.

In the torpid stage:

1. Beginning exhaustion - the organism's active defensive reactions are weakened .
2. Protective inhibition - since the process of inhibition is spread mainly in the cerebral cortex and still has not drawn in the subcortical centers, activity of heart and respiratory system are satisfactory.
3. Exhaustion - both active and passive protective possibilities of the organism are exhausted. This phase may result in death.

To cause shock in experiment, standard trauma is inflicted on the soft tissues of the thighs of the animal or they are squeezed by the special instrument. To cause shock in small animals (mice, rats) and to approve antishock remedies they are rapidly rotated in the special drums.

The pathological state caused by protracted compression of the organism's soft tissues during earthquake, war or in mines, mountains, is called traumatic toxicosis or compression (crush) syndrome. The changes in the organism in crush syndrome are connected with the following factors:

1. pain - causes neurohumoral and neuroendocrine disturbances characteristic of stress reaction;
2. toxemia - toxic products that are formed in damaged tissues are absorbed into the blood;
3. loss of blood and plasma - occurs as a result of development of edemas and hemorrhages in the damaged tissues.

Edemas and toxemia occur, usually after liberation of the damaged tissues from the pressure. Therefore, the clinical course of the traumatic toxicosis, although reminds that of traumatic shock, but differs from it. The substances passing from the damaged tissues into the blood in severe cases of the traumatic toxicosis, influence the parenchyma of kidneys and cause disturbances in the renal activity.

**Syncope is sudden loss of consciousness resulted from sharp disturbance of blood supply (hypoxia) of cerebral tissues.**

The following factors may cause syncope:

1. brief spasm of the cerebral blood vessels (pain, negative emotions);
2. excessive intake of some pharmacological (especially ganglioblocking) preparations;
3. sharp stimulation of a number of receptor zones (sinocarotid zone, vestibular apparatus, etc.);
4. sharp weakening of the heart systoles (heart block, compensatory pause after the extrasystole);
5. physical overstrain.

Usually syncope lasts no more than several minutes, during which the general state of the person is getting worse, he becomes restless, vascular tension and muscular tension are sharply weakened and he loses consciousness.

In the course of the syncope 3 stages are distinguished:

1. The stage of the initial manifestations - anxiety, general weakness, headache, nausea, unpleasant sensation in the area of the heart, vegetative vascular disturbances (decreased arterial pressure and muscular tension, pallor of skin and mucous membranes), buzzing in the ears, dimness in the eyes are observed.
2. Loss of consciousness - in several seconds above - mentioned changes become deeper, the person falls and loses consciousness.
3. The stage of recovery - the consciousness is restored from several seconds to several minutes depending on the gravity of the process.

**Collapse is acute vascular insufficiency resulted from decreased vascular tension and diminished circulating blood volume. The frequent causes of the collapse are the following:**

1. traumata,
2. intoxications,
3. acute infectious diseases,
4. loss of blood.

Inflow of the venous blood to the heart becomes difficult, arterial and venous pressures fall, blood supply of tissues and metabolism are disturbed, in brain hypoxia develops and the organism's functions are sharply weakened.

The clinical symptoms of the collapse are: sudden pallor, abrupt and weak pulse, decreased blood pressure, shallow and infrequent breathing, cyanosis, cold sweat, coldness in limbs, fall of body temperature, inhibition of the higher nervous activity, sometimes - the slight disturbance of the consciousness.

By its clinical manifestations collapse is very like shock. But in collapse in the first place the function of the cardiovascular system is changed, whereas in shock the function of the nervous system is disturbed first.

**Coma is the pathological state which is connected with sharp inhibition of the central nervous system's functions and is characterized by disturbances in organism's regulating mechanisms, loss of consciousness and reflexes to the external stimuli.**

Coma is one of the dangerous complications of different diseases and, in its turn, exercises severe influence on their outcome. The following etiologic factors cause different types of the coma:

1. traumata and diseases of the central nervous system (insult, epilepsy, craniocerebral injuries, inflammatory diseases and tumors of the brain);
2. endocrine diseases - hyposecretion of hormones (diabetic coma, hypocorticoid coma, hypothyroid coma, hypopituitary coma), hypersecretion of hormones or excessive intake of hormonal preparations (hypoglycemic coma, thyrotoxic coma);
3. loss of electrlytes, water and energy (for example, as a result of hunger and projectile vomiting);
4. disturbances in the gaseous exchange - decreased content of oxygen in inspired air and asphyxia, sharp changes in the function of the respiratory system, anemia and acute circulatory insufficiency;
5. exogenous and endogenous intoxications, toxoinfections.

The types of coma with different etiology differ also from the pathogenetic point of view. Nevertheless, there are also some common aspects in their developmental mechanisms. All types of coma are resulted from the disturbances in the functions of the cerebral cortex, subcortical nuclei, brain stem, which cause loss of consciousness. Disturbance in activity of the reticular formation and weakening of its activating influence on the cerebral cortex, disturbance of the reflex activity of the brain stem and weakening of the vegetative centers play an important part in the pathogenesis of coma. These disturbances may occur by the following pathogenetic mechanisms:

1. Hypoxemia, anemia, disturbance of the cerebral blood circulation cause hypoxia in the nerve cells, disturbance of biological oxidation and energy metabolism. Quantity of the adenosine triphosphate and creatine phosphate is decreased but that of adenosine diphosphate, lactic acid and ammonia is increased.
2. Disturbances in the electrolyte balance and osmotic pressure are of great importance in the pathogenesis of the diabetic, uremic, chloropenic, hepatic comas; sodium, potassium, calcium, magnesium metabolism in nerve cells is disturbed, acid - base equilibrium is thoroughly changed.
3. Hormonal disturbances, disturbances in the amino acid metabolism (in hepatic coma), hypoxia and some cellular poisons decrease the rate of formation and secretion of mediators in the synapses of the central nervous system.
4. In the pathogenesis of comas caused by craniocerebral injuries, intracranial hemorrhages, tumors of the brain and meninges, mechanical injuries of nerve cells play a main part. Edema and tumor in brain and meninges cause increase of intracranial pressure, disturbances in the cerebral blood circulation and movement of the liquor. Hypoxia in the nerve cells becomes more severe and their physiological activity becomes lower.

Each of these mechanisms may be decisive in different types of coma, but in a number of cases they influence together. In deep comatose states disturbances in regulating mechanisms of the vegetative functions make the metabolic diseases more severe and lead to formation of vicious circle.

In connection with the common aspects in the pathogenesis of extreme states, the therapeutic measures in these cases are similar. But in each concrete case the etiologic factor, specific peculiarities of the pathogenesis and concomitant diseases must be taken into consideration.

The first medical aid in extreme state must be directed to elimination of hypoxia and functional disorders which cause immediate danger for the organism. Then the factor responsible for the extreme state and vicious circle must be eliminated.

Thus, above - mentioned extreme states are alike in many aspects, and many of their peculiarities are common. But each of them has its special features. The principal differences between these extreme states become more distinct in comparison of their definitions which reflect the essence of each concrete state.

Pain is complicated psychophysiological state arising under the influence of the injurious factors causing organic and functional changes in tissues.

Stress is totality of the nonspecific reactions which arise under the influence of different injurious factors and serve for adaptation of the organism to the action of these factors.

Shock is reflex disturbance in the organism's neurohumoral regulating mechanisms which arises under the influence of extraordinary stimuli and develops in several stages.

Syncope is sudden loss of consciousness resulted from sharp disturbance of blood supply (hypoxia) of cerebral tissues.

Collapse is acute vascular insufficiency resulted from decreased vascular tension and diminished circulating blood volume.

Coma is the pathological state which is connected with sharp inhibition of the central nervous system's functions and is characterized by disturbances in organism's regulating mechanisms, loss of consciousness and reflexes to the external stimuli.