**CELL INJURY. PATHOLOGY OF MICROCIRCULATION. LOCAL CIRCULATORY DISORDERS.**

Cell injury is disturbance of cellular structure and function under the influence of different pathogenic agents. As a result of damage to the cells, interrelations between cells and intercellular substance is disturbed, functions of organs and systems are changed and diseases develop. At the same time cellular injury of any degree and intricacy immediately is accompanied by the development of the defence-compensatory processes in the cell. For instance, suppression of oxidative processes in damaged cell is usually accompanied by the activation of another source of energy-glycolysis.

In the damaged cells protease of lysosomas are activated; they digest injured cells and this way promote their removal from the organism.

**Cell injuries may be caused by exogenous and endogenous factors.** According to their causes and main signs cell injuries are divided into the following groups (types of cell injury):

1. Hypoxic cell injury. Hypoxia is the most common cause of cell injury and cell death resulting in disease. The various causes of hypoxia resulting in inadequate perfusion of cells and tissues are atherosclerosis, thrombosis, anaemia, cardio-respiratory insufficiency and increased demand of the tissue for oxygen. Depending on the cell type, nutritional and hormonal status of the cell, hypoxia may produce reversible or irreversible cellular injury. For instance, neurons are highly susceptible to irreversible injury in 3-5 min; tissues like heart, liver and kidney take 30 min to 2 hours to produce irreversible injury, whereas fibroblasts, skeletal muscle, skin take very long to cause permanent damage of cells.

In reversible cell injury the following sequential changes follow ischemia: decreased generation of ATP, reduction of the intracellular pH, clumping of nuclear chromatin, cellular swelling, formation of blebs at the cell surface, swelling of endoplasmic reticulum and mitochondria.

If ischemia persists, the following changes lead to irreversible injury: mitochondrial dysfunction, cell membrane damage, liberation of hydrolytic enzymes from ruptured lysosome, nuclear changes (pyknosis, karyolysis, karyorrhexis), death of cell.

2. Physical cell injury-is caused by mechanical trauma, heat (burn), cold (frostbite), electricity, radiation, rapid changes in atmospheric pressure, etc. Injuries caused by mechanical force may lead to the state of shock.

The radiant energy (ultraviolet, radioactive, X-rays) more easily affects the cells which rapidly proliferate. As a result of radiation often the genetic apparatus of cells is damaged and mutations come into being. Radiation injury to human by accidental or therapeutic exposure is of importance in treatment of persons with malignant tumors as well as may have carcinogenic influences.

3. Chemical cell injury-is caused by numerous chemical agents (drugs, strong acids, alcalies, poisons, environmental pollutants, insecticides, industrial processes, occupational hazards, etc.). Some chemicals (cyanide) cause death instantaneously by inactivation of cytochrome oxidase, and others cause prolonged effects or local injury.

Bacterial toxins (tuberculosis, syphilis, leprosy, abdominal typhoid, dysentery, etc.) and some toxic substances of endogenic origin (for instance, surplus of phenylalanine, phenylpyruvic acid, phenyllactic acid, phenylacetic acid in phenylketonuria) also cause cell injury.

Chemicals cause cell injury by one of the following two mechanisms:

a) direct cytotoxic effects(for instance, in mercuric chloride poisoning the greatest damage occurs to cells of the alimentary tract and kidney);

b) conversion to reactive toxic metabolites(which then cause cell injury by direct cytotoxic effect or by formation of free radicals).

Both physical (mechanical, thermal, electrical, etc.) and chemical (concentrated solutions of acids and alkalies) factors may cause traumatic cell injury. This may be caused also by physiologically active substances(especially enzymes) that are formed in the organism (damage of stomachal mucous membrane as a result of gastric juice hypersecretion, pancreatonecrosis as a result of activation of trypsin in internal pancreatic ducts, etc.).

4. Cell injury of vascular origin-occurs as a result of disturbance of blood flow in arteries.

5. Trophoneurotic cell injuries - are caused by disturbance of neural trophism in tissues (necrotic and necrobiotic processes in cells as a result of damage of the central and peripheral nervous systems, bedsore in chronic patients that are in bed rest for a long time).

6. Microbial cell injury. Bacteria usually produce harmful effect by toxins. Viruses may cause direct cytopathic effect or may be oncogenic.

7. Allergic cell injury-originates as a result of hypersensitivity of the organism to heterologous substances. For example, the changes connected with skin tuberculin test, necrotic processes in tissues as a result of Arthus phenomenon, etc.

8. Psychological cell injury-is caused by mental stress and strains, anxiety, overwork, and frustration which account for some acquired mental diseases (depression, etc.).

9. Cell injuries connected with hereditary enzymopathies-are observed in different types of hereditary glycogenoses (Gierke’s disease, Pompe’s disease, etc.) and systemic lipidoses (Tay-Sachs disease, Gaucher’s disease, Niemann-Pick disease, etc.).

**Pathogenetic mechanisms of the cell injury are the following:**

1. Damage to membrane apparatus of the cell.

2. Disturbance of energy supply of processes taking place in the cell.

3. Disturbance in the ferment systems of the cell.

4. Disbalance of ions and fluid in the cell.

5. Disorder in the genetic program of the cell or in the mechanisms of its realization.

6. Disturbance of intracellular mechanisms of regulation of cell functions.

According to the rate of development, cell injuries may be divided into two groups: acute and chronical. Mechanical flow, high and low temperature, intoxications (with the compounds of phosphorus, arsenic, mercury, etc.), acute infectious diseases (diphtheria, dysentery, pneumonia, etc.) cause acute cell injury. Chronical cell injuries are caused, in the first place, by some diseases resulting in hypoxia (chronical diseases of cardiovascular system and lungs, etc.), chronic alcoholism, avitominoses, etc.

 In multicellular organisms cell injuries are manifested in the form of dystrophy and necrosis. Dystrophy is the structural changes occurring as a result of metabolic disorders in cells and tissues. It may be caused by intracellular and extracellular factors. In many cases dystrophy is the initial stage of development of necrosis.

Necrosis is the pathological process resulting in death of cells and tissues. The following successive stages are distinguished in the process of necrosis:

a) paranecrosis-in favourable conditions the life of cell in this stage may be restored;

b) necrobiosis-consists of irreversible dystrophic cellular changes; catabolism prevails over anabolism, but the cells can fulfill some of their functions;

c) necrosis-is characterized by complete cessation of cell’s vital activity;

d) autolysis-disintegration of dead cells(by hydrolytic enzymes that are released from lysosomas; their remains are phagocytized by macrophages.

One of the significant indices of cell injury is disturbance of structure and functions of cell organoids-nuclei, endoplasmic reticulum, mitochondria, lysosomes, ribosomes.

In damaged cells dissolving (karyolysis), induration (karyopyknosis) and destruction (karyorrhexis) of nuclei are observed.

The changes of cytoplasm include coagulation plasmorrhexis (destruction of cytoplasm), plasmolysis (dissolving of cytoplasm).

The main and initial sign of damage of mitochondria is swelling. In severe forms of cell injury their crests and membranes swell.

Damage to lysosomas causes destructions of their membrane; about 40 enzymes that are in lysosomas, are released. They damage the cytoplasm. So, enzymes of lysosoma closely participate in autolysis of necrotic cells.

The main signs of damage of endoplasmic reticulum are changes of its configuration, swelling, degranulation. Number of ribosomes in membrane of the damaged endoplasmic reticulum is decreased, loops are deformed.

The substances inhibiting synthesis of proteins increase number of ribosomes in cells, whereas the substances accelerating growth and reproduction of cells decrease their number. Number and configuration of ribosomes may be changed.

**The pathophysiological signs of cell injuries divided into two groups:non-specific and specific.** Non-specific signs of cell injury are changes of the same character caused by different damaging factors. The morphological and functional changes of cells which depend on the character of some damaging factors are specific signs of cell injury.

Frequently specific signs of cell injury appear earlier than non-specific signs, but sometimes non-specific signs may appear first. Non-specific disturbances are found in all types of cell injury regardless of the type of pathegenic agent.

*Non-specific signs of cell injury are the following:*

1. Disturbance of the cell membrane permeability. All of the damaging factors (especially the free radicals, salts of heavy metals) cause changes in the structure and functions of the cell membrane. Usually permeability of injured cell membrane is increased both for macromolecules (proteins, colloidal dyestuffs) and substances with the low molecular mass (amino acids, membranes of cell organoids).

Amount of free radicals which affect cell membrane powerfully, s sharply increased under the influence of ionizing and ultraviolet rays. Carcinogenic substances and some tissue poisons (for instance, alcoholic intoxication) also increase their quantity. The main sources of free radicals are water (H +, OH-, O2H-) and oxygen ( O O ).

Cell membrane injury may be conditioned by the damage of its lipide components as well as protein (enzyme) components. Increase of membrane permeabilty is connected by disturbance of the activity of cell pumps.

2. Denaturation of proteins-may be caused by the high temperature, sharp changes in pH of medium, action of heavy metal salts, etc. As a result of denaturation physicochemical properties of proteins are changed (for instance, their solubility is increased), enzymatic activity is disturbed, some functional groups (SH-group of cystein, OH-group of tyrosine, etc.) that are in protein molecule in the form of complex compounds, are released.

3. Disturbance of water metabolism. In damaged cell water is released from its protoplasm and goes out into the medium surrounding the cell. Accourdingly the quantity

of extracellular water is increased in damaged tissue. This causes traumatic edema (for instance, brain edema in concussion of the brain).

4. Disturbance of intracellular metabolism. One of the main indices of this process is

release of potassium ions from the cells into the blood. This is connected with the damage of potassium and sodium pumps.

5. Change of intracellular enzymes activity-occurs as a result of damage of mitochondria, destruction of lysosomas, endoplasmic reticulum, ribosomes and other intracellular organelles. Enzymes of the organoids go out into protoplasm and surrounding medium. At the same time in the damaged cells activity of natural inhibitors of proteases is decreased. This leads to activation of intracellular proteases which rapidly decompose protein-lipoid components of protoplasm. The products of proteolysis, as low-molecular substances, change colloido-osmotic pressure and pH of plasma. As a result of accumulation of acid products of proteolysis (polypeptides, amino acids) pH of protoplasm in injured cells becomes lower. These processes underlie autolysis of damaged cells.

In the mitochondria of the damaged cells also activity of intracellular oxidative enzymes is disturbed, and absorption of oxygen is reduced. Simultaneously anaerobic glycolysis is increased. Because activity of enzymes which inhibit this process in the presence of oxygen (Pasteur’s effect) is suppressed.

6. Reduction of oxidative phosphorylation. In the conditions of hypoxia during 3 hours the coefficient P/O2 for the isolated kidney tissues is decreased twice. This coefficient is important not only for appreciation of the degree of damage of the organ, but also when the problem of viability and usefulness of the organ for transplantation is solved.

 In hypoxia as a result of decrease of macroergic phosphoric compounds (ATP) the activity of Ca pump, Na-K pump and other pumps is disturbed. Prolonged hypoxia causes irreversible changes and damage of cell membranes.

7. Acidosis of injury. All types of the damage cause acidosis in protoplasm. The primary acidosis of cell injury must be differed from the secondary acidosis in inflamed tissue which occurs considerably later after the damage is caused. The primary acidosis of cell injury is resulted from activation of proteolysis, lipolysis, glycogenolysis and glycolysis in the damaged cell. Great is significance of damage of lysosomas which release about 40 hydrolytic enzymes.

8. Mediators of injury – are physiologically active substances which come into being under the influence of pathogenic factors which injure the cell: histamine, adenosine, different polypeptides, kinines, serotonin, norepinephrine, acetylcholine, some metabolic products, etc.

 These substances are absorbed from the injured areas into the blood, spread in the organism and cause local reactions in different tissues and organs. Their general influence on the organism causes a number of complications.

9. Decrease of membrane potential (damage potential) – may be conditioned by breach of structure of cytoplasmic membrane or disturbance of activity of ionic pumps which maintain transmembrane difference of potentials.

10. Decrease of resistance of tissues to the electric current. The total value of resistance of living cells to the alternating current (impedance) consists of ohmic and capacity resistance. Different damages cause mainly decrease of ohmic resistance.

11. Increase of sorptional properties of cells - is determined according to absorption of dyes and other substances by damaged cells.

12. Intensification of ultraweak luminescence. Ultraweak luminescence is discharge of comparatively small amounts of light energy by tissues. It is used for appreciation of state of vitality (or degree of damage) of preserved tissues.

13. Calcification, that is, accumulation of phosphoric compounds of calcium and then magnesium and sodium carbonate in damaged cells. It is observed in tuberculosis, arteriosclerosis, infarction, etc., and may be caused by chronical hypoxia.

Although each of these signs is common for all or most of pathogenic factors causing cell injury, some of them are specific for one of these factors. That is, each damaging agent is able to cause in cells the changes that are characteristic of only this agent.

*The specific signs of cell injury are the following:*

1. in the mechanical injury – breach of integrity of tissue, cells, subcellular and intercellular structures;
2. in the thermal injury (as well as in injuries caused by strong acids and alcalies) – coagulation and denaturation of protein – lipoid structures of cells;
3. in cell injuries caused by ionizing radiation – formation of free radicals;
4. in specific chemiccal (toxic) injury – inhibition of activity of different enzymes (for instance, activity of cytochrome oxidase is inhibited by cyanides, of succinate dehydrogenase – by the salts of malonic acid, etc.)

In a number of specific injuries caused by inhibition of different enzymes metabolism in cells is considerably changed. For instance, inhibition of processes of phosrylation of glucose in epithelium of renal tubules by phloridzin (which inhibits activity of hexokinase).

Damaging action of many poisons (snake venom, bacterial toxin of gas gangrene) is connected with their ability to dissolve in membrane lipides and selectively change the activity of a number of hydrolytic enzymes.

**In the process of evolution cells of organism have acquired a number of defence-recovery mechanisms which protect them from the injury:**

1. antimutation system;
2. antioxidant system;
3. detoxication system;
4. buffer system.

In human cells special enzymatic system promotes recovery of normal structure of DNA (deoxyribonucleic acid). This antimutation system serves chiefly protection of skin’s cells from ultraviolet rays. Destruction of DNA molecules caused by ionizing radiation, ultrasound and other mutagenous agents, and disturbance of DNA’s matrix activity may be eliminated by the help of this system.

The following stages are distinguished in the process of elimination of injuries in DNA molecules, that is, in the process of reparation:

1. The special enzyme of ring – shaped molecular structure “inspects” DNA molecules in longitudinal direction and reveals the local foci of damage (defect).
2. By the participation of enzyme endonuclease the nucleotides situated between the normal part of DNA molecule and its damaged part are separated by the hydrolytic way.
3. By the participation of enzyme exonuclease the damaged area of DNA spiral (with some of its normal part) is separated from the molecule.
4. By the action of exonuclease the polynucleotide chain which has been separated from the DNA, is decomposed into its constituent parts (nucleotides).
5. By the participation of enzyne DNA - polymerase the new healthy spiral is synthesized instead of polynucleotide which was separated from the DNA molecule.
6. By the participation of enzyme ligase the new synthesized polynucleotide chain is joined up with the DNA molecule.

When the antimutation system is weakened, sensitivity of the organism to mutagenous factors is increased. One of the diseases which are connected with the pathology of this system is xeroderma pigmentosum (Kaposi’s disease). This is the hereditary disease characterized by hypersensitivity of the skin to ultraviolet rays. In this disease deficiency of enzyme DNA – endonuclease in skin was revealed.

Antioxidant system of cells protects lipides (which are the main components of cell membrane) from oxidative reactions, especially from the peroxide oxidation. This system includes vitamin E, ubichinon, some enzymes (superoxiddysmutase, catalase, glutathione peroxidase, etc.)

The enzymatic detoxication system of cells takes part in decontamination and removal from the organism of exogenous and endogenous toxic substances. The main principle of the intracellular detoxication is based on the conversion of hydrophobic (insoluble) substances into polar (dissoluble) compounds whose toxic action on the biological membranes is weaker. This system includes cytochrome P450, glutathione – S – transferase and other enzymes.

The buffer systems take part in protection of cells from damaging substances of acid and alkaline character.

The injury caused by different pathogenic factors, besides local changes, leads also to development of general reactions of the organism. They include stress, shock, coma, fever, “acute phase” reaction, etc.

The basis of “acute phase” reaction is formation and releasing of peptide – interleukine – 1 in the acute period of injury especially in the cases with development of infectious process, activation of mononuclear, phagocytic and immune systems and inflammation. This leads to intensification of synthesis of proteins of acute period (c – reactive protein, haptoglobin, components of complement, ceruplasmin, fibrinogen) in liver, stimulation of development of neutrophils in bone marrow, activation of thermoregulation center in hypothalamus, stimulation of protein catabolism in muscles, activation of T and B lymphocytes.

**Disturbances of Microcirculation. Lymph Circulation Insufficiency. Arterial Hyperemia. Venous Hyperemia. Ischemia. Stasis. Infarct. Thrombosis. Embolism**

**Disturbances in the microcirculatory system are divided into 4 groups:**

1. Changes in the vessels (vascular walls ) of the microcirculatory system – inflammation, avitaminosis, trauma, injuries of autoimmune character, atherosclerosis, metabolic disorders result in disturbances in the vascular wall permeability which leads to disorders in transcapillary metabolism.

2. Intravascular disturbances - include mainly changes in the rheologic properties of the blood –disturbances in the blood coagulability, aggregation and adhesion of blood cells. Unlike agglutination, aggregation is reversible process. However, large aggregates may cause obstruction not only in capillaries, but also in arterioles and venules - the blood cells do not pass into capillaries and the plasmatic capillaries are formed. Formation of a large number of aggregates in the vessels of the microcirculatory system causes the phenomenon of sludge: blood cells are stuck together and plasma is separated; as a result of microembolism blood flow is completely stopped. Burns, severe traumata, thrombosis and embolism are accompanied by sludge phenomenon.

3. Disturbances connected with the extravascular changes – tumors, scars, growth of pregnant uterus, edema round the vessels press them and cause disorders in the microcirculation.

4. Disturbances of mixed character.

Pathological changes in the vessels of the microcirculatory system cause changes in the tissues that are supplied by these vessels, and vice versa, changes in tissues cause disorders in the microcirculation. Especially when mast cells of the connective tissue are damaged, the physiologically active substances (histamine, heparin, serotonin, etc.) are released which lead to different changes in the microcirculatory system.

Lymphatic system fulfils the drainage function, that is, participates in the transport from the interstitial spaces of non- reabsorbed part of water, electrolytes, high- molecular substances (proteins, lipides, etc.). Two litres of lymph is formed daily.

 Different etiologic factors may cause disorders in lymph circulation. Growing tumors, scars that are formed after traumata and operation, edema may press lymph vessels from the outside and disturb the movement of the fluid. Congenital and acquired defects of vascular valves, filariasis (the disease that is found in tropical countries) also result in lymph circulation insufficiency.

**According to the mechanism of development the following types of lymph circulation insufficiency are distinguished:**

1. Mechanical insufficiency – may be of two types:

a) connected with the organic changes- squeezing of lymph vessels by growing tumor, scar, ligature; lymphangitis, thrombophlebitis, etc.;

b) of functional character- develops as a result of spasm of lymph vessels and increase of venous pressure.

2. Dynamic insufficiency – is result from increase of filtration in blood capillaries (for instance, edema as a result of hypoproteinuria) when a large amount of fluid passes into interstitial space, and lymph vessels are unable to transport them.

3. Resoptional insufficiency – develops as result of changes in biochemical properties of tissue proteins or decrease of permeability of lymph vessels. Intercellular fluid is delayed in tissues.

4. Mixed type.

The main symptoms of lymph circulation insufficiency are congestion and dilatation of lymph vessels. Congestion is eliminated thanks to activity of compensatory – adaptative reactions (reserve collaterals, formation of new lymphatic capillaries in tissues, etc.). But when they are insufficient, lymphatic capillaries and vessels are filled to overflowing, some of their parts swell and resemble thin walled sacs. This is called lymphangiectasia.

One of the main signs of decompensation of the lymph circulation is lymphatic edema. Acute and chronic, local and general types of the lymphatic edema are distinguished.

The chronic lymphatic congestion is accompanied by the chronic hypoxia in tissues which results in sclerosis of tissues. Because in hypoxia fibroblasts are proliferated and their collagen synthesizing activity is increased. Volume of tissues (especially those of the skin and subcutaneous layers) is increased, their form and structure is changed. Elephantiasis develops by this mechanism. This disease is characterized by the deformity, roughness and extraordinary increase of the skin of extremities (especially that of lower extremities) which become like elephant’s skin.

The severe lymphostasis may cause rupture of lymph capillaries and loss of lymph, that is, lymphorrhea (lymphorrhagia). External and internal lymphorrhea are distinguished. As a result of the internal lymphorrhea lymph is accumulated in the pleural cavity (chylothorax) and peritoneal cavity (chylous ascites).

Local circulatory disorders mean typical disturbances in blood supply of tissues and organs. These disturbances are called local somewhat conditionally, since they are closely connected with general circulatory disorders.

For example, elevated general blood pressure in hypertensive disease frequently leads to circulatory disturbances in the brain and kidneys. On the other hand, occlusion or protracted spasm of cerebral or cardiac vessels gives rise to disturbances in general blood circulation.

The following types of the local circulatory disorders are distinguished: arterial hyperemia, venous hyperemia, ischemia (local anaemia ), stasis, infarct, thrombosis, embolism.

**Arterial hyperemia** (Gr. Hyper - excessive increase, haima- blood) is an increased content of blood in organ or tissue as a result of more blood flowing through its dilated arteries and capillaries. Sometimes hypervolemia and erythremia may cause general arterial hyperemia .

Biological, physical and chemical factors of the external environment, increase of activity of organs and tissues , physical stimuli may cause physiological and pathological arterial hyperemia.

The following types of the physiological arterial hyperemia are distinguished:

1) working hyperemia – is a result of increased activity of organs and tissues;

2) reflex hyperemia – is resulted from increase of blood supply of skin under the influence of physical and chemical stimuli (cold, warmth, ultraviolet rays, massage);

3) conditional reflex hyperemia- for instance, reddening of the face in anger or shame.

The main types of the pathological arterial hyperemia are the following:

1) angioneurotic hyperemia – occurs as a result of increased tonicity of vasodilative nerves or decreased tonicity of vasoconstrictive nerves;

2) postanemic hyperemia – occurs when the factor causing squeezing of arteries is suddenly eliminated; for instance, when ligature is removed from the ligated artery or the fluid accumulated in the cavities of the body (in ascites, hydrothorax) is rapidly pumped out;

3) collateral hyperemia- as a result of occlusion or squeezing of artery its proximal branches are dilated by the reflex way and are filled by the blood more than usually;

4) vacate (Lat. vacatum – to be empty ) hyperemia – is resulted from decreased pressure on the body surface ( for example, when caisson workers or divers are rapidly lifted ); accumulation of blood under the wet cups is connected with local vacate hyperemia;

5) inflammatory hyperemia – is one of the main stages in the pathogenesis of inflammation;

6) hyperemia connected with arteriovenous anastomoses- occurs when arteries and veins are wounded at the same time, and the arterial blood passes into veins through anstomoses.

Pathogenesis of the arterial hyperemia is based on the dilatation of arterioles (mainly by the reflex way ) which results in increase of blood amount entering them.

According to its pathogenic mechanisms, 3 types of the arterial hyperemia are distinguished:

1) neurotonic hyperemia- develops as a result of increased tone of vasodilative nerves caused by different mechanical, thermal, chemical, biological, psychical factors (for instance, arterial hyperemia in the skin caused by the action of xylol);

2) neuroparalytic hyperemia – is due to diminished tone of vasoconstrictive nerves (transection of the peripheral sympathetic nerves in Walter’s or Claude Bernard’s experiments, injury to the vasoconstrivtive centers, action of ganglioblockators, etc.);

3) myoparalytic hyperemia- is resulted from dysfunction of the muscular coat of the vessels caused by some physiologically active substances and metabolic products (bradykinin, histamine, serotonin, carbon dioxide, lactic acid, etc.).

The main signs of the arterial hyperemia are: redness of the tissues (due to increased content of oxyhemoglobin), elevated temperature (due to increased inflow of arterial blood), swelling of the tissues and enlargement of the hyperemic part (due to increased lymph formation and greater filtration of fluid through the capillary walls), elevated blood pressure in the vessels of the hyperemic part (due to the greater mass of circulating blood), acceleration of blood flow, increase of the number of functioning capillaries, etc.

Arterial hyperemia is one of the important compensatory- adaptative reactions of the organism. Mostly it leads to intensification of metabolism in tissues and increased activity of organs. The increased blood supply favourably affects tissue nutrition.

But arterial hyperemia may also cause some undesirable changes in the organism. It is the most dangerous in the central nervous system which is more sensitive than any other organ to changes in the blood supply and local elevation of blood pressure. An intense rush of blood to the brain is usually accompanied by unpleasant sensations (vertigo, tinnitus, excitement). Hemorrhages from cerebral vessels (in cases of pathological changes in their elasticity and permeability ) are particularly dangerous (development of insult).

**Venous hyperemia** is an excess of blood and diminished blood circulation in organ or tissue as a result of impeded outflow of the blood. The main etiologic factors causing venous hyperemia are:

1) cardiac insufficiency – causes general venous hyperemia (congestive hyperemia ) in the organism (right ventricular failure causes venous hyperemia in the greater circulation, and left ventricualr failure – in the lesser circulation);

2) occlusion of veins by thrombus;

3) squeezing of veins (without injury to arteries) by tumor, scar, gravid uterus;

4) increase of capillary permeability and acceleration of filtration (change of arterial hyperemia into venous in inflammation);

5) constitutional weakness of the muscular coat of veins (especially if the patient's profession forces him to long standing) causes chronic venous congestion which leads to varicosis.

The main link in pathogenesis of the venous hyperemia is difficulty in transport of the blood from tissues by veins. This causes decrease of circulation rate in veins, increase of pressure, their dilatation, decrease of difference in pressure between arteries and veins and decrease of circulation rate in capillaries, increase of vascular permeability, etc.

The characteristic signs of venous hyperemia are:

1) cyanosis (Gr.kyanos- dark-blue), that is, redness of the tissue with a bluish tint (due to hemostasis and the excess of reduced hemoglobin);

2) lowered temperature of the affected part of the body (due to diminished outflow of blood and continued heat loss);

3) decelerated blood flow (due to obstruction on the way to the heart);

4) elevated blood pressure in the veins peripherally from the obstruction;

5) enlargement (swelling)of the hyperemic organ or tissue;

6) inactivation of respiratory enzymes (influence of metabolic products that are accumulated in tissues);

7) mixed (circulatory and histotoxic) hypoxia;

8) hypercapnia;

9) disturbed tissue nutrition.

Venous hyperemia causes a number of local and general changes in the organism. It may lead to varicosis, phlebosclerosis, obstruction of the large veins, disturbances in hemodynamics. Protracted venous congestion, hypoxia, nutritional disturbances, dysfunction of the hyperemic organs cause induration, atrophy of parenchymal elements and reactive growth of connective tissue (for instance, stasis, hepatocirrhosis, nutmeg liver). Obstruction of the portal vein is especially dangerous: a large amount of blood is accumulated in the organs of the abdominal cavity, circulating blood volume and arterial pressure are decreased, and blood supply of different parts of the organism is disturbed. Protracted cerebral anemia in such cases may lead to syncope, respiratory paralysis and death.

But venous hyperemia may be beneficial in some cases. Venous congestion in the focus of inflammation alters metabolism and fosters accumulation in the tissues of biologically active products which create unfavourable conditions for the development of microorganisms in the focus of affection. This suppresses the infectious process in the given part of the body. Chronic venous congestion may hasten the healing of wounds by stimulating the growth of connective tissue.

**Ischemia** (Gr. ischo- to impede, haima –blood ) or local anemia is diminution of blood supply of organ or tissue as a result of diminution or cessation of inflow of arterial blood. Several forms of ischemia are distinguished according to the causes of their development:

1. Angiospastic (or neurotic) ischemia- is local anemia connected with the spasm of arteries (as a result of emotional strain, physical factors, chemical substances, biological stimuli, etc.). The action mechanism of vasoconstrictive preparations (adrenalin, norepinephrine, etc.) is connected with the angiospastic ischemia that they cause in the organism.

2. Obstructive ischemia – is resulted from obstruction of the supplying artery (thrombus, embolus) or obliteration, that is, occlusive changes in the wall (inflammatory, atheroscleretic changes in the intima, etc.).

3. Compressional ischemia- is due to compression of the supplying artery or the given part of the body by a growing tumor, cicatrix, foreign body, ligature of the artery, application of tourniquet, etc.

4. Collateral (redistribution) ischemia – develops as a result of increased blood flow to other part of the organism (for instance, cerebral ischemia due to sharp dilatation of the vessels in the abdominal cavity and increased blood flow to the abdominal organs).

Ischemia causes disorders in the microcirculatory system. At the first stage of this process inflow of blood into microcirculatory system is weakened, and circulation rate is decreased. Since the functioning capillaries are constricted, blood cells cannot enter them, and number of plasmatic capillaries is increased. Then activity of these capillaries is completely ceased.

As a result of decreased intravascular pressure filtration becomes difficult, and resorption is increased. This results in decrease of intercellular fluid and weakening of lymph circulation.

Ischemia causes metabolic changes connected with hypoxia. Accumulation of acid products of intermediate metabolism leads to acidosis which results in inactivation of some enzymes. Since a large amount of amino acids is consumed to satisfy the power needs of the cells, the protein synthesis is decreased. Metabolic disturbances in their turn may cause dystrophy to the extent of necrosis.

Ischemia is characterized by pallor, cooling of the tissue or organ, dysfunction and decrease of its volume, pain, numbness, pricking, itching and creeping sensations in the skin, and a number of other phenomena, depending on the site and extent of development of ischemia.

Outcome of the ischemia depends on the rate of its development, duration, localization, state of collateral blood circulation, functional state of tissue and organ, etc. The angiospastic ischemia takes an easier course. Because soonly the vessels are dilated by the reflex way.

Ischemia causes ultrastructural (swelling of mitochondria) or deep destructive changes in tissues. Acute and long ischemia causes at first dystrophia, then necrobiosis and necrosis (infarct) in cells and tissues. Even the slight ischemia of long duration results in atrophy of the parenchymal elements and sclerotic changes in organs.

Since the rate of metabolism is low in connective tissue, ischemia of bones and cartilages takes an easier course. Then come kidneys, lungs and spleen. Ischemia of the brain and heart is the most dangerous.

Ischemia in the central nervous system causes irreversible changes in nerve cells in several minutes, in cardiac muscle- in 20-40 minutes, whereas the viability of skeletal muscles and connective tissue is continued several hours.

Frequently ischemia terminates in restoration of the functions of the affected tissue (even if the obstruction to the arterial circulation has not been removed). Favourable results depend on the extent of development of compensatory collateral circulation. The sooner collateral circulation develops, the less danger there is for the tissue. Collateral circulation is established because the blood pressure drops below the obstruction in the vessel and blood rushes through capillaries from the higher parts of the vascular bed to the lower parts.

Ischemia is particularly dangerous in cases of occlusion or spasm of vessels which do not have sufficiently well- developed collateral branches (the coronary, renal, splenic arteries).

**Stasis** (Gr. stasis-standing) is complete cessation of the blood flow in the vessels of the microcirculatory system with the vessels dilated and filled with a mass of closely adhering erythrocytes.

According to the mechanism of development 3 types of the stasis are distinguished:

1) ischemic stasis- is resulted from cessation of inflow of blood from arteries into the capillary network;

2) venous (congestive) stasis – is a result of impeded outflow of blood from capillary network through a draining vein;

3) capillary (true ) stasis –is independent circulatory disturbance in the microcirculatory system.

Capillary stasis may appear irrespective of any obstacles to the outflow of blood. It occurs as a result of various excessively strong influences, for instance, tissue desiccation (exposed peritoneum), effect of heat or cold, acids, alkalines, mustard or croton oil. There are also infectious and toxic forms of capillary stasis (stasis in the limbs, pinnas of the ears and other peripheral parts of the body in typhus, inflammatory stasis in acute and rapidly developing inflammatory processes, as in hyperergic inflammation).

Vasomotor disturbances (reflex constriction of arteries and arterioles, diminished blood flow into corresponding capillaries, etc.), changes in the rheologic properties of the blood (pachyemia, increase of viscosity , hyperproteinemia, aggregation of erythrocytes, phenomenon of sludge), hypoxia (changes in the vascular wall) play a part in the mechanism of the stasis.

Increased capillary permeability, changes in surface potentials of erythrocytes, increased blood content of large – molecular proteins, disturbances of vascular walls innervation in the microcirculatory system, dyscirculatory disturbances promote aggregation of erythrocytes.

Stasis is reversible process. In cases where no major disturbances in the vascular walls and the blood have occurred, the blood flow may be restored after elimination of the cause of stasis. But in cases of damage to the vascular walls and adhesion of erythrocytes in the blood, stasis is irreversible and necrosis of the corresponding part of the body develops.

The stasis may cause especially severe complications in brain, heart, kidneys.

**Infarct** (Lat. infarcire- to stuff) is necrosis of tissues as a result of sharp disturbance of blood circulation.

Etiologically infarct may be regarded as a result of ischemia with severe course. Frequently it results from protracted spasm, thrombosis and embolism of arteries. Besides, infarct may occur if in the period of functional strain the blood flow into organ does not increase properly. Damage to arterial wall, decrease of circulation rate, weak development of anastomoses and collaterals in arterial metabolism promote formation of infarct.

Usually infarct develops on the background of the diseases which are connected with damage to arterial wall and disturbance in blood circulation (atherosclerosis, hypertension, lingering septic endocarditis, rheumatism, heart disease, etc.).

Two successive stages are distinguished in the development of the infarct:

1) the stage of ischemia – is characterized by dystrophic and necrobiotic changes;

2) the stage of necrosis- is characterized by necrosis and autolysis.

According to the changes in the necrotic area 3 types of infarct are distinguished:

1. White (ischemic) infarct- frequently occurs where developed collateral vessels are absent (in brain, heart, kidneys, spleen). Blood does not enter the necrotic area and it is tinged yellowish- white. In experiment white infarct can be produced in the rabbit’s kidney by ligature of a branch of the renal artery.

2. Red (hemorrhagic) infarct – is frequently observed in the lungs, and rarely – in intestine, kidneys and spleen. Its colour is connected with hemorrhage into necrotic tissues.

3. White infarct surrounded by the red border ( hemorrhagic zone )- is connected with dilatation of vessels in the peripheral part of the infarction area and diapedesis of erythrocytes ( in cardiac muscle, kidneys).

Outcome of infarct depends on the state of the organism and organ where it is developed, complications of the disease, size of the necrotic area, etc. Both white and, especially, red infarcts are usually resorbed, and the resorption is accompanied by organization (formation of scar). In cardiac muscle, kidneys and spleen the infarct develops as coagulation necrosis (necrotic area becomes hard); in brain and intestine – as colliquative necrosis (necrotic area becomes soft and is dissolved). In its place cyst may be formed (often in brain).

The small infarct zone after the autolysis may be completely regenerated. Organization of infarct area may be accompanied by petrifaction (settlement of calcium salts) or hemosiderosis (settlement of iron compounds).

Infection of the infarct accompanied by its purulent dissolution is a dangerous complication- often the infection spreads from the infarct throughout the organism.

**Thrombosis** (Gr. thrombos- lump – clot ) is formation of blood clots (thrombi) in blood vessels or cavities of the heart with the result that they impede the circulation.

According to the structure of thrombi their four types are distinguished:

1. White thrombosis (including thrombocytes, fibrinous fibers, leukocytes ) is gradually formed in the vessels where blood flow is rapid (in arteries).

2. Red thrombus (including also a large number of erythrocytes ) is rapidly formed in the vessels where blood flow is slow (especially in veins).

3. Mixed thrombus is more frequent (in veins, aortic aneurysm, cavites of the heart ). Its head resembles the white thrombus, tail- the red thrombus, and in the body the elements forming the thrombus are mixed.

4. Hyaline thrombus (including decomposed erythrocytes, thrombocytes, precipitated plasma proteins and rarely – fibrinous fibers) occurs in the microcirculatory system in infectious and septic diseases.

In the pathogenesis of thrombosis general and local factors take part which are interconnected.

The main cause of formation of thrombus is increased blood coagulability and decreased activity of anticoagulative system. General factors include also changes in thre physicochemical properties of the blood (increase of high- molecular proteins, lipides in plasma,number of thrombocytes, viscosity and other rheologic properties of the blood ).

The local factors include changes in the vascular wall (atherosclerosis, arteritis phlebitis, etc.) and slowing of the blood flow (thrombi are formed 4-5 times oftener in veins than in arteries).

In the mechanism of thrombosis 3 phases are distinguished:

1) agglutination of thrombocytes;

2) coagulation of fibrinogen and formation of fibrin;

3) agglutination of erythrocytes and precipitation of plasma proteins.

Outcome of thrombosis depends on the size of thrombi, their location, rapidity of formation, etc. The small thrombi are mostly autolysed. The large thrombi are replaced by the connective tissue (organization). Cavities may form in the middle of the thrombus and between the thrombus and the walls of the vessel, the cavities subsequently being encapsulated by endothelium and filled with blood (canalization), as a result the blood flow through the vessel is resumed (vascularization). Accumulation of calcium compounds on the area of the canalized thrombus causes petrifaction, in these cases in the venous walls calculi may be formed (phlebolith ).

Obstructive thrombi in the arteries of the brain, kidneys, mesentary cause infarcts in these organs. Thrombosis in the portal vein causes portal hypertension and ascites, in splenic vein – splenomegalia, in renal veins- venous infarct of the kidney, in lower extremities- phlebitis.

Complication of the inflammatory processes in arteries (endarteritis) by thrombosis results in thromboarteritis.

One of the dangerous complications of thrombosis is thromboembolism. Under the influence of pyogenic bacteria septic autolysis and thrombobacterial embolism occur.

**Embolism** (Gr. embolos- wedge, plug) is occlusion of blood vessels with bits of matter (emboli) carried by the blood or lymph and usually foreign to the blood stream.

All types of emboli are divided into two groups:

1)endogenous emboli (thrombi, fat, tissue, cell, amniotic water);

2)exogenous emboli ( air, gas, solid foreign bodies, bacteria, parasites ).

Thromboembolism is the most frequent type of the embolism. It occurs as a result of rejection of thrombus or its part from the vascular wall. Particularly easily abrupted are parts of thrombi formed on heart valves where the conditions for transfer of these parts to the systemic and pulmonary circulation are the most favourable. Very dangerous is embolism of cerebral vessels.

Usually the new masses of thrombi are accumulated on the thromboemboli, that is, thromboembolism is replaced by the embolothrombosis. In some persons with the short intervals several times thromboembolism occurs which damages different tissues and organs. This is called thromboembolic syndrome (in cardiac insufficiency, malignant tumors, in severe surgical operations, etc.).

Usually fat embolism results from traumata of subcutaneous fat fractures of bones and rarely - exogenous fats, (the drugs prepared in oils, injection of the radiopaque substances into the vessels by mistake) may cause it.

Tissue (cell) embolism is caused by the cells of the malignant tumors (in the period of disintegration of tumor), particles of cardiac valves (in ulcerous endocarditis), cerebral cells (in craniocerebral or birth injuries), etc.

The gaseous embolism is caused by gaseous bubbles in caisson disease.

Bacteria, yeast fungi, parasites, solid foreign bodies may penetrate the vessels and cause embolism. In the areas where bacterial embolism obstructs the vessel abscesses occur.

Usually emboli move in three main directions:

1. Emboli of the greater circulation are carried from the left heart, aorta, the arteries of the greater circulation (sometimes from the pulmonary veins) into heart, brain, kidneys, spleen, intestine, extremities and other organs. They may cause ischemia, infarct, gangrene in these organs.

2. Emboli of the lesser circulation are brought in from the veins of the greater circulation and the right heart. The larger particles lodge in the branches of the pulmonary arteries, the smaller particles- in the capillaries. Some particles may pass through capillaries into the pulmonary veins, left heart and thence into the greater circulation. An embolism of the pulmonary artery is characterized by pallor of the face as a result of a reflex spasm of the vessels, reflex spasm of bronchi and sometimes sudden coronary insufficiency also of reflex origin. Usually emboli in the small branches of the pulmonary artery cause hemorrhagic infarct in lung, whereas

obstruction of the large branches may lead to sudden death.

3.Emboli in the branches of the portal vein are brought from numerous abdominal veins. Obstruction of the portal vein or one of its large branches causes congestion in the organs of the abdominal cavity (up to 90% of the circulating blood may be accumulated in these organs). Ascites develops, spleen is increased, the veins in the anterior wall of the abdomen are dilated. At the same time inflow of blood into the heart, stroke volume and cardiac output, arterial pressure are decreased. Dyspnea, infrequent respiration, apnea, loss of consciousness, paralysis of the respiratory center may occur.

In some developmental defects emboli from the right heart get directly into the left atrium (through a patent foramen ovale) and further into the left ventricle and greater circulation without passing through the lesser circulation. These are called paradoxical embolisms.

Rarely the embolus moves not in the direction of the blood flow, but against it (depending on the specific gravity of the embolus, the character of the blood flow, etc.). This is called retrograde embolism. Its origin is connected with increased intrathoracic pressure in sudden exhalations (intense coughing), elevated blood pressure in the right heart, etc. In such cases embolus from the vein is carried not to the right heart, but against the blood current, for instance, from the inferior vena cava into the hepatic or renal veins or those of the lower limbs.

The outcome of the embolism depends on the site of its occurrence, the particular vessel to which the embolus has been delivered, the possibility of reflex influences and the collateral communications of the vessel with other ones, the quality of the embolus, etc. When the collateral circulation is inadequate, embolism is usually accompanied by necrosis of tissue or formation of infarct. Coronary and cerebral embolisms are especially dangerous.