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«UZHHOROD NATIONAL UNIVERSITY»
MEDICAL FACULTY N 2
Department of the Physiology and Pathophysiology

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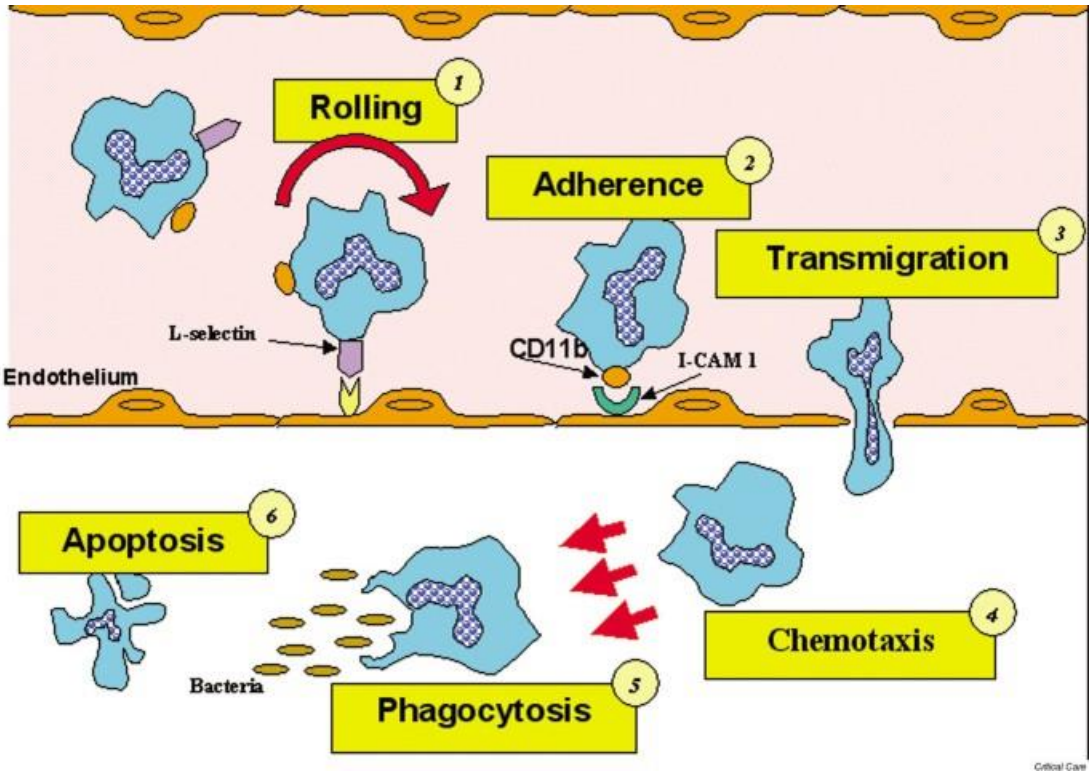
TYPICAL PATHOLOGICAL PROCESSES

METHODICAL INSTRUCTIONS

for practical classes and self-study on Pathophysiology
for 3rd year students
of medical faculty №2, specialty 222 “Medicine”



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Methodological instructions for practical classes on Pathophysiology for students of the Medical faculty № 2 from the section “Typical Pathological Processes" have been prepared in accordance with the requirements of the Syllabus on Pathophysiology for students of the medical faculty of higher medical educational institutions of the III-IV levels of accreditation.

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Submodule 2	5	5	-	10

Methodological instruction to practical lesson №6
Module 1. General pathology

Theme: CELL DAMAGE. DISORDERS OF THE PERIPHERAL CIRCULATION AND MICROCIRCULATION

Student should know:

- Determination of concept of damage of cell, local disorders of blood circulation and microcirculation.
- Basic forms of disorders of peripheral circulation of blood.

Student should be able to:

- Analyze changes of structure, function and metabolism of cells in pathogenesis of cellular damage.
- Explain the mechanisms of damage of cells in pathogenesis of typical pathological processes.

LIST OF CONTROL QUESTIONS

1. Characteristic of concept of "damage". Principles of classification of cell damage. Structural, functional, physical-chemical, biochemical and thermodynamical signs of cell damage. Exo- and endogenous reasons of damage of cells: hypoxia, action of physical, chemical, pathogens, immunoreactions, genetic defects
2. Characteristic of universal mechanisms of cell damage:
   - O2-dependent (action of oxygen and his derivates - free radicals);
   - calcium-dependent;
   - caused by deficit of ATP or by primary disorders of membrane permeability;
   - as a result of development of intracellular acidosis;
   - caused by activation of proteolysis;
   - conditioned by disorders of genetic apparatus of cell.
3. Mechanisms and signs of subcellular structures damage. Consequences of damage of cells. Necrosis and apoptosis, their characteristic signs.
4. Exo- and endogenous inductors of apoptosis. Mechanisms of apoptosis.
5. Mechanisms of defence and adaptation of cells to the action of harmful agents. Cellular stress proteins. Heat shock proteins (HSP).
6. Basic forms of disorders of peripheral circulation of blood: arterial and venous hyperemia, ischemia, stasis, their types, reasons and mechanisms of development, external signs.
7. A role of endothelial factors is in pathogenesis of local disorders of circulation of blood. Changes in tissues, caused by disorders of local circulation of blood, their role and consequences.
8. A concept about repefusion syndrome, ischemic toxicosis.
9. Thrombosis and embolism as reasons of local disorders of circulation of blood. Reasons and terms of thrombosis. Types of emboli, mechanisms of embolism. A role of reflex mechanisms in development of general disorders,

caused by emboli. Features of course of emboli in large and small circles of circulation of blood, portal vein.

10. Typical disorders of microcirculation, intavessel disorders. Sludge-syndrome. Syndrome of disseminated intracellular blood coagulation. Capillary (real) stasis. Disorder of tone, mechanical integrity and permeability of microvessels. Extravessel disorders of microcirculation. Capillary trophic insufficiency.
11. Typical disorders of lymphokinesis. Mechanical, dynamic and resorbtive insufficiency of lymphokinesis.

A cell is the smallest structural and functional unit of the multicellular organism which possesses all main mechanisms sustaining its viability. That is why any pathological process develops involving cells, and any pathological changes in the organs and systems may develop secondarily after pathological changes in the cells, their distortion or loss of functions and cells themselves.

Cells constantly customize their function and structure to accommodate demands and environmental influences (physiological or pathological). This process of maintaining of physiologic parameter in small range of variability (homeostasis) names ***adaptation***. This process can lead to new steady state of vital activity which allows saving cell function and structure under new conditions. The basic adaptive responses are hypertrophy, hyperplasia, atrophy, and metaplasia.

Hypertrophy is increase in the size of cells. Increased workload leads to increased
protein synthesis & increased size & number of intracellular organelles which, in turn,
leads to increased cell size. The increased cell size leads to increased size of the organ.

Examples: the enlargement of the left ventricle in hypertensive heart disease & the increase in skeletal muscle during sternous exercise.

Hyperplasia is an increase in the number of cells. It can lead to an increase in the size of the organ. It is usually caused by hormonal stimulation. It can be physiological as in enlargement of the breast during pregnancy or it can pathological as in endometrial hyperplasia.

Atrophy is a decrease in the size of a cell. This can lead to decreased size of the organ. The atrophic cell shows autophagic vacuoles which contain cellular debris from degraded organelles.

Atrophy can be caused by:

- Disuse
- Undernutrition
- Decreased endocrine stimulation
- Denervation
- Old age

Metaplasia is the replacement of one differentiated tissue by another differentiated tissue. There are different types of metaplasia. Examples include:

1. Squamous metaplasia (This is replacement of another type of epithelium by squamous epithelium. For example, the columnar epithelium of the bronchus can be replaced by squamous epithelium in cigarette smokers)
2. Osseous metaplasia (This replacement of a connective tissue by bone, for example at sites of injury).

Reversible cellular changes & accumulations

1. Fatty change

This is accumulation of triglycerides inside parenchymal cells. It is caused by an imbalance between the uptake, utilization, & secretion of fat. Fatty change is usually seen in the liver, heart, or kidney. Fatty liver may be caused by alcohol, diabetes mellitus, malnutrition, obesity, & poisonings. These etiologies cause accumulation of fat in the hepatocytes by the following mechanisms:

a. Increased uptake of triglycerides into the parenchymal cells.
b. Decreased use of fat by cells.
c. Overproduction of fat in cells.
d. Decreased secretion of fat from the cells.

2. The accumulations of pigments

Pigments can be exogenous or endogenous. Endogenous pigments include melanin, bilirubin, hemosiderin, & lipofuscin. Exogenous pigments include carbon. These pigments can accumulate inside cells in different situations.

a. Melanin

Melanin is a brownish-black pigment produced by the melanocytes found in the skin. Increased melanin pigmentation is caused by suntanning & certain diseases e.g.
nevus, or malignant melanoma. Decreased melanin pigmentation is seen in albinism & vitiligo.

b. Bilirubin

Bilirubin is a yellowish pigment, mainly produced during the degradation of hemoglobin. Excess accumulation of bilirubin causes yellowish discoloration of the
sclerae, mucosae, & internal organs. Such a yellowish discoloration is called jaundice. Jaundice is most often caused by

1. Hemolytic anemia (Hemolytic anemia is characterized by increased destruction of red blood cells).
2. Biliary obstruction (This is obstruction of intrahepatic or extrahepatic bile ducts. It can be caused by gallstones).
3. Hepatocellular disease (This is associated with failure of conjugation of bilirubin).

c. Hemosiderin

Hemosiderin is an iron-containing pigment derived from ferritin. It appears in tissues as golden brown amorphous aggregates & is identified by its staining reaction (blue color) with the Prussian blue dye. Hemosiderin exists normally in small amounts within tissue macrophages of the bone marrow, liver, & spleen as physiologic iron stores. It accumulates in tissues in excess amounts in certain diseases. This excess accumulation is divided into 2 types:

1. Hemosiderosis (When accumulation of hemosiderin is primarily within tissue macrophages & is not associated with tissue damage, it is called hemosiderosis).
2. Hemochromatosis (When there is more extensive accumulation of hemosiderin, often within parenchymal cells, which leads to tissue damage, scarring & organ dysfunction, it is called hemochromatosis).

If the ability for adaptation is insufficient or if the external stress is essentially harmful, *cell injury* develops.

Injury is the change of cell functioning which is saved after removing of disturbing factor. We can distinguish direct action of disturbing factor and indirect action which is provided by action on other cells, tissues, organs and the whole body.

Basic **causes of cell injury** are:

• oxygen deficiency (hypoxia),

•chemical agents (osmotic disturbances, acids, alkali, toxins, drugs)

•infectious agents (prions, viruses, bacteria, fungi, protozoa, worms)

•immunologic reactions (antibodies, complement, cytotoxic cells)

•genetic defects (chromosomal and genomic mutation)

•nutritional imbalance

•physical agents (trauma, cold, heat, radiation, electric current, extremes in atmospheric pressure)

• aging

Mechanisms of cell injury

1) Impaired energy production
2) Impaired membrane function
3) Severe damage of DNA
4) Metabolic derangement
5) Mitochondrial alterations
6) Damage of lysosomes

Direct action includes action of infections, immune reactions, poisons and toxins which act straight to the cell. For example: cyanide inhibits respiratory chain enzyme (cytochrome oxidase). When we say about indirect action it means that disturbing stress acts on cell- targets and changes of their function or structure leads to injury (*secondary*) of other cells. For example abnormality of heart rhythm due to digitalis poisoning leads to disturbance of brain blood supply and cerebral ischemia.

Cell injury can be *reversible (paranecrosis)*, and cells can return their normal level of function and structure after cessation of damaging stress. During this stage increase of membrane permeability and activation of some intracellular systems (proteinkinases, phospholipases, synthesis of proteins, cyclic nucleotids) occurs. The aim of these events is compensation of changes of physiological parameters.

Nonlethal injury to a cell may produce *cell degeneration***,** which is manifested as some abnormality of biochemical function, a recognizable structural change, or a combined biochemical and structural abnormality. Degeneration is reversible but may progress to necrosis if injury persists.

Irreversible injury occurs if damage action is strong enough or acts for a long time and process of it names *necrobiosis*. It's time "between life and death". Severe cell injury can be accompanied by processes which lead to its death.

Two types of cell death are distinguished: ***1) Necrosis*****,** which appears as a result cell damage under impact of physical, chemical or biological factors, the intensity of which exceeds cell defense capacity; 2) Programmed death of cell like ***apoptosis*** or autophagia when cell dies after receiving a specific signal and switching on of the programmed mechanisms.

Necrotic cell death occurs under influence of external damaging factors which can specifically interact with certain organelles or be involved in different processes in the cell. Thus, membranes are damaged under impact of the lipotropic factors, toxins of the microorganism, snake venom, activated complement and oxidative stress. Damage of the membrane induces the loss of selective permeability, lack of intracellular potassium, excess uptake of sodium, calcium and chlorides by cells. This is accompanied by disturbances in metabolism, water retention in cells (edema), increase of its volume, rupture of cell membrane and cytolysis. The gene function is disturbed under impact of ionizing radiation, some antibiotics, analogs of nucleic acids and viruses. Other organelles (lyso-somes and mitochondria) can also undergo specific injuries, about which we mentioned earlier. Noteworthy is an increased intensity of the lipid peroxidation as a result of hyperproduction of active oxygen forms or due to the disturbance of antioxidant systems and activation of membrane phospholipases. Energy production by the mitochondria is disturbed and the glycolysis is activated, leading to the increase of the concentration of hydrogen ions in the cytoplasm and to the development of intracellular acidosis. Destruction of the lysosome membrane and release of activated proteolytic enzymes leads to cell autolysis. Under such forced cell death lots of bioactive compounds (eicosanoids, cytokines and kinins) are released into extracellular environment signaling organism about danger and activating its defense mechanism (for example, phagocytes), thereby initiating inflammation.

Such activation of the phagocytes and immune system cells, inducing inflammation or immune response, does not occur during apoptosis in contrast to necrosis. The apoptosis plays a crucial role in normal functioning of the organism. It is involved in its growth, by regulating quantitative and qualitative composition of cells, eliminating non-viable or potentially dangerous cells. The process of apoptosis can be triggered by means of several external signals such as tumor

necrosis factor (TNF) and some other cytokines which bind with specific receptors on cell surface. The specialized lymphocytes like natural killers or cytotoxic T-lymphocytes can also induce cell to self-destruction. They insert into target cell the granules with enzymes, which trigger apoptosis. On the contrast, high levels of the glucocorticoids during stress cause apoptosis of the T-lymphocytes.

Apoptosis inside the cell is initiated by the factors localized between the outer and inner mitochondrial membranes, in particular, the cytochrome C and other factors, which induce apoptosis and are released into the cytoplasm after damage of the mitochondria. Also these factors distort the cell cycle that can be observed during damage of DNA molecule and switching-on of a system that controls cell cycle. This induces activation of the complex enzyme system called caspase cascade that ultimately activates the nuclear endonucleases, rapid DNA fragmentation, denaturation of many essential enzymes of the synthesis, activation of the proteolytic enzymes, migration of phosphatidylserine into the plasma membrane outer layer leading not only to an immediate terminationof all life processes in the cell but also to its quick phagocytosis by the macrophages and further lysis inside these cells.

One of the variants of the programmed cell death is the autophagy, a controllable degradation of the cytoplasmic proteins, organelles and cells via activation of the lysosomal system. Autophagy occurs under conditions of starvation (food deprivation) as the form of compensation aimed at the survival of a cell and whole organism, as well as a i result of impacts of various negative factors (rapamycin, herpes viruses, intracellular parasites) and at reperfusion after myocardial ischemia.

Thus, the cell destined to die is quickly and effectively eliminated from the organism. This plays an important role during malignant transformation of cells or their virus infections that frequently prevent its replication. The programmed cell death is an adjusted process including pro-apoptotic signals and a powerful anti-apoptotic system. Therefore, the final fate of a cell depends on the combined effect of many factors.

Apoptosis activation is observed after ionizing radiation, hypoxia, under effects of the microbes' waste products (e.g., superantigens of the staphylococcus or human immunodeficiency virus, which induce apoptosis in the immune-competent cells and thereby disarm the organism). The higher rate of apoptotic neuronal death in some areas of the central nervous system can lead to the Alzheimer's disease or amyotrophic lateral sclerosis. It is noteworthy that long-term resting of any group of cells induces a decrease in their number via apoptosis (death by neglect) and, on the contrary, the functional loading promotes their life. The rule 'use-or-lose' is applied to many systems, including immune and brain cells.

However, sometimes the apoptosis can be inhibited. For instance, some viruses can block apoptosis in the infected cells and provide conditions for their replication. Inactivation of the pro-apoptotic signal as a result of somatic mutation of protein p53 gene or non-regulated activation of the antiapoptotic signal {Bel-2 gene) is observed in the majority malignant cells.

Pathophysiology of peripheral blood circulation

Arterial hyperemia is an active increase of organ or tissue blood filling due to excessive blood inflow by arterial vessels.Active hyperemia occurs when artery dilatation results in increased inflow of the blood into capillary beds with opening inactive capillaries. It is caused by neurogenic mechanisms or vasoactive substances.

Arterial hyperemia is divided into ***physiological*** (working) and ***pathological.*** In its turn, pathological arterial hyperemia is subdivided into ***neurogenic*** and ***metabolic.*** In its turn, neurogenic arterial hyperemia is subdivided into ***neurotonic*** and ***neuroparalytic.***

Etiological factors are *physical* (mechanical, heat, ultraviolet radiation), *chemical* and *biological* (infectious, immune, emotional), which lead to arterial vessel dilatation.

Neurotonic arterial hyperemia develops due to neurotonic mechanism activation. Claude Bernard was the first to reproduce it by stimulation of the chorda tympani (a branch of the facial nerve), containing parasympathetic vasodilating fibers. In the vessels, which have no parasympathetic stimulation, hyperemia is caused by the sympathetic system (cholinergic, histaminergic and p-adrenergic mechanisms). Sympathetic cholinergic nerves dilate the small arteries and arterioles of the skeletal muscles, facial muscles, mucosa of the cheeks and intestine. Acetylcholine is a mediator. A clinical example of neurotonic hyperemia is reddening and sensation of heat in the skin in the region of neuralgia.

Neuroparalytic arterial hyperemia may be modeled in experimental animals by cutting of the vasoconstrictive fibers and nerves (sympathetic a-adrenergic ones). Norepinephrine is a mediator. Claude Bernard observed hyperemia and hyperthermia of the skin on a rabbit's head (ear) on the side of the removed cervical node of the sympathetic trunk (ganglionary sympathectomy). Their mediator is norepinephrine.

Metabolic arterial hyperemia is caused by BAS of different origin (cellular and plasmatic). ATP, ADP, adenosine, nonorganic ions, p0 2 reduction and pC02 increase in the blood and tissues have the same effect. In some cases prostaglandins
E and A, which have a vasodilative effect on arterioles, metarterioles, precapillaries
and venules, cause hyperemia.

Venous hyperemia is an increase of organ or tissue blood filling due to limitation
of blood outflow by venous vessels.Contrary to arterial hyperemia, which is active, venous hyperemia (congestion or passive hyperemia) results from impaired venous drainage.

Etiological factors of venous hyperemia are those, which narrow the lumen or decrease the tonus of veins. They may be exogenous and endogenous. They are:

• obstruction of veins with a thrombus or an embolus;

• compression of veins by a tumor, enlarged internal organ (for example, uterus),

exudate in the region of inflammation;

• compression of veins by exudative pleuritis, hemothorax, pneumosclerosis, emphysema;

• cardiac left- or right-ventricular failure;

• professional overloading (maintaining vertical position for a long time);

• genetic predisposition to venous congestion (weakness of the venous elastic apparatus, low tonus of the smooth muscle elements of the vascular wall).

The disorders are caused by a local lack of oxygen (hemoglobin deoxygenation, tissue hypoxia) and substrates. It leads to tissue disbolism. As a result, atrophic and dystrophic changes develop.

Blood viscosity increases as well as permeability of capillaries. Transudate is formed due to high hydrostatic blood pressure. Congestion in the capillary bed is closely related to edema development. Therefore, congestion and edema commonly

occur together (***venous edema).*** Congestion leads to intravascular thrombosis. Prolonged venous congestion results in the excessive growth of the connective tissue, which substitutes the parenchyma (so-called cirrhosis).

Ischemia is a decrease of organ or tissue blood filling due to limitation or complete stop of arterial blood inflow.

Ischemia is divided into compressive, obstructive and angiospastic. Every type of ischemia has its own etiology and pathogenesis.

Compressive ischemia is a result of mechanical influence on arteries (tumor, foreign body, ligature, etc.).

Obstructive ischemia is a result of vessel lumen narrowing by a thrombus, an embolus or atherosclerotic process.

Angiospastic ischemia is a functional disorder, which consists in derangement of the motor (vasoconstrictive) apparatus of the vessels.

Various agents can cause ischemia. Angiospastic ischemia develops as a result of stimulation of the vasoconstrictor apparatus of vessels or their reflex spasm caused by: a) *physical* factors (cold, mechanical and other injuries); b) *chemical* agents; c) *biological* factors (bacterial toxins); d) *emotional* factors (fear, pain, rage)

and pathologic reflexes.

The duration and consequences of ischemia depend on such conditions, which can modify the effect of etiological factors: a) time of harmful effect; b) type of ischemia; c) localization; d) condition of collateral circulation; e) functional state of the organ or tissue.

The mechanism of angiospastic ischemia depends on the permeability of smooth muscle cell membranes for Na+, Ca2+, K+ and CI" ions. Neurogenous a-adrenergic,

histaminergic, serotoninergic, dopaminergic mechanisms also matter. Angiotensin II is one of the most potent vasoconstrictors. It effects smooth muscle cells directly causing depolarization as a result of increased Na+ permeability. When Na+ ions accumulate in the muscle fibers of vessels, their sensitivity to vasoconstrictors (catecholamines, vasopressin and angiotensin) increases.

Endothelium injury results in its inability to produce relaxing factors (NO). This leads to spastic reactions. Angiospastic ischemia may have a conditioned reflex nature. Ischemia leads to oxygen deficiency (hypoxia).

Stasis is deceleration or complete stop of blood flow in capillaries, small arteries
and veins.

The following types of stasis are distinguished: *true* (capillary), *ischemic* (complete stop of blood inflow), and *venous.*

True Stasis

True stasis develops as a result of pathological changes in capillaries or abnormality of rheological properties of the blood. In capillaries and small veins the
blood becomes stagnant and homogenized. Erythrocytes swell and lose most of their pigment. Together with the released hemoglobin, the plasma escapes from the vessel. In the focus of stasis the tissues show signs of dystrophy.

Etiological factors of true stasis are *physical* (cold, burn), *chemical* (poisons, turpentine, mustard oil), and *biological* (microbial toxins).

The mechanism of true stasis development is based on the intravascular aggregation of erythrocytes (adherence) and formation of conglomerates, which hamper blood flow. It also causes an increase of peripheral resistance. Erythrocytes aggregate as a result of alteration of the physical properties of erythrocyte plasmolemma under the direct effect of the factors entering the capillary. The surface of erythrocytes, which is smooth under normal conditions, becomes furry. Erythrocytes aggregate as a result.

A significant role in true stasis pathogenesis belongs to hemoconcentration and increased permeability of the capillary walls. The etiological factor itself and metabolites, produced in tissues, promote it. An important role in stasis genesis belongs to BAS (serotonin, bradykinin, histamine), local acidosis and changes in the
colloidal state of the blood. It results in increased vessel permeability and dilatation leading to hemocoagulation, blood flow deceleration, erythrocyte aggregation and, consequently, to stasis. It should be noted that stasis alone does not induce thrombosis. Stasis of poorly oxygenated blood causes chronic local tissue hypoxia.

Ischemic and venous stasis is a consequence of blood flow deceleration and arrest. These conditions are caused by the same factors as venous hyperemia and ischemia. Ischemic stasis is a consequence of artery spasm, compression or occlusion. Venous stasis is a result of vein compression or occlusion with a thrombus

or an embolus. Elimination of the cause leads to restoration of normal circulation. However, the progress of ischemic and venous stasis promotes the development of true stasis.

Thrombosis is lifetime formation of a mass containing blood elements (cells and
coagulated proteins) on the internal surface of vessels.

The final mass is termed *thrombus.* Depending on the components, thrombi can be *white* (formed of platelets, leukocytes and a small amount of plasma proteins), *red* (contain erythrocytes), and *mixed* (have alternating white and red layers).

The conditions, which predispose to thrombosis, are known as Virchow's triad:

1. Injury of the vessel wall (endothelium).
2. Imbalance between coagulative, anticoagulative and fibrinolytic blood systems (hypercoagulability).
3. Blood flow deceleration.

It explains why thrombosis of veins occurs more often than that of arteries. All the factors creating these conditions are etiological factors of thrombosis. They are exogenous and endogenous. The exogenous ones are *physical* (trauma, electric current), *chemical* (tobacco smoking, side effects of some drugs) and *biological* (infectious, immune) agents, which damage the blood vessels or change the rheological properties of the blood. Atherosclerosis, arterial hypertension and allergy may cause an injury of the vessel wall and predispose to thrombosis. Diabetes
mellitus and obesity change coagulation and predispose to thrombosis.

The course of thrombosis can be divided into two stages:

A. cellular (reaction of platelets);
B. plasmatic (coagulative).

Cellular Stage. This stage of thrombogenesis begins after 2—3 minutes from the moment of vessel injury and consists in platelet adherence (adhesion) on the endothelium. It results from the changes of both the vascular wall (its potential, decrease of prostacycline production) and platelets (which release thromboxane (PG). Platelet adhesion is followed by their aggregation. Then platelet destruction follows.

There are various platelet-aggregating stimulators (thrombin, serotonin, epinephrine, norepinephrine, PGD2, PGH2, PGI2-prostacyclin). A shift of the ATP/ADP ratio to the ADP content provides platelet adherence and aggregation. Aggregated platelets lose their internal structure and release granules rich in a variety of products.

Plasmatic Stage. Substances, derived from activated platelets, promote coagulation. Formation of BAS and various coagulation factors triggers the coagulative
system of the blood and begins the second stage of thrombosis. Fibrin is formed, constituting the stroma of thrombi, which contain (besides thrombocytes) a small amount of erythrocytes.

A thrombus makes blood circulation difficult. It diminishes or obstructs vascular flow, causing an ischemic injury of tissue, and may give rise to embolism. In the course of time a thrombus may be changed by: a) aseptic (enzymatic, fibrinolytic) lysis; b) organization and substitution by the connective tissue; c) recanalization; d) septic (purulent) disintegration.

The septic outcome is especially dangerous because it may cause septicopyemia and numerous abscesses in various organs. Necrosis development (infarction, gangrene) is possible at the terminal stage of thrombosis.

A thrombus must be differentiated from a blood clot. The latter is formed by coagulation of extravasal blood. Thrombi, on the contrary, are formed intravascularly in the circulation (on the internal surface of vessels).Those thrombi, which are formed in the rapidly moving arterial circulation, are composed predominantly of fibrin and platelets with only a few trapped red cells.Thus, a thrombus bears a little resemblance to a blood clot. However, in a very sluggish venous flow thrombi may closely resemble blood clots.

Embolism is formation and carrying along the blood flow of a mass, which is not typical of normal blood composition.This mass is called *embolus.* The blood carries it to a site distant from its point of origin. An embolus may be solid, liquid or gaseous. About 99 % of all emboli originate from thrombi. Indeed, thrombosis and embolism are closely interrelated (thromboembolism).

Rare forms of emboli are: a) foreign bodies such as bullets; b) droplets of fat (in case of bone fracture); c) bits of tumor; d) fragments of bones or bone marrow; e) bubbles of air, nitrogen or another gas. Inevitably, emboli get stuck in vessels too small to permit their further passage. It results in complete vessel occlusion. Emboli may slow down and stop anywhere within the cardiovascular system producing different clinical effects.

KROK 1_mcqs (A is correct answer):

1.During the intravenous transfusion of the saline the patient's condition deteriorated dramatically, and the patient died from asphyxiation. Autopsy revealed acute venous congestion of internal organs with the dramatic right heart dilatation. When the right ventricle was punctured underwater, the bubbles escaped. What pathological process occurred in the patient?

A. Air embolism
B. Gaseous embolism
C. Adipose embolism
D. Tissue embolism
E. Thromboembolism

2.Decreased blood supply to the organs causes hypoxia that activates fibroblasts function. Volume of what elements is increased in this case?

A. Intercellular substance
B. Vessels of microcircular stream
C. Nerve elements
D. Parenchymatous elements of the organ

E. Lymphatic vessels

3.Oval and round organelles with double wall are seen at the electron micrograph. The outer membrane is smooth, the inner membrane folded into cristae contain enzyme ATP-ase synthetase. These are:

A. Mitochondria
B. Golgi complex
C. Lysosomes
D. Centrioles
E. Ribosomes

4.A tissue sample of benign tumor was studied under the electron microscope. A lot of small (15-20 nm) spherical bodies, consisting of 2 unequal subunits were detected. These are:

A. Ribosomes
B. Golgi complex
C. Smooth endoplasmic reticulum
D. Microtubules
E. Mitochondria

5.In course of metabolic process active forms of oxygen including superoxide anion radical are formed in the human body. By means of what enzyme is this anion inactivated?

A. Superoxide dismutase
B. Catalase
C. Peroxidase
D. Glutathioneperoxidase
E. Glutathionereductase

6.A patient who was previously ill with mastectomy as a result of breast cancer was prescribed radiation therapy. What vitamin preparation has marked radioprotective action caused by antioxidant activity?

A. Tocopherol acetate
B. Ergocalciferol
C. Thiamine chloride
D. Riboflavin
E. Folic acid

7.Low level of albumins and fibrinogen was detected in the patient's blood. Decreased activity of what organelle of the liver hepatocytes can most probably cause it?

A. Granular endoplasmatic reticulum
B. Agranular endoplasmatic reticulum
C. Mitochondrions
D. Golgi complex
E. Lysosomes

8.Labeled amino acids alanine and tryptophane were introducted to a mouse in order to study localization of protein biosynthesis in its cells. Around what organellas will the accumulation of labeled amino acids be observed?

A. Ribosomes
B. Agranular endoplasmic reticulum
C. Cell centre
D. Lysosomes
E. Golgi apparatus

9.Utilization of arachidonic acid via cyclooxigenase pathway results information of some bioactive substances. Name them:

A. Prostaglandins
B. Thyroxine

C. Biogenic amins
D. Somatomedins
E. Insulin-like growth factors

10. In course of practical training students studied a stained blood smear of a mouse with bacteria phagocyted by leukocytes. What cell organella completes digestion of these bacteria?

A. Lisosomes
B. Mytochondrions
C. Granular endoplasmic reticulum
D. Golgi apparatus
E. Ribosomes

11. In order to speed up healing of a wound of oral mucosa a patient was prescribed a drug that is a thermostable protein occuring in tears, saliva, mother's milk as well as in a new-laid hen's egg. It is known that this protein is a factor of natural resistance of an organism. What is it called?

A. Lysozyme
B. Complement
C. Interferon
D. Interleukin
E. Imanine

12. There are several groups of molecular mechanisms playing important part in pathogenesis of insult to cells which contributes to the pathology development. What processes are stimulated by proteinic damage mechanisms?

A. Enzyme inhibition
B. Lipid peroxidation
C. Phospholipase activation
D. Osmotic membrane distension
E. Acidosis

13. While playing volleyball a sportsman jumped and then landed across the external edge of his foot. This caused acute pain in the talo-crural articulation, active movements became limited, passive movements remained unlimited but painful. In the region of the external ankle a swelling appeared, the skin turned red and became warmer to the touch. What type of peripheral circulation disorder has developed in this case?

A. Arterial hyperaemia
B. Venous hyperaemia
C. Embolism
D. Thrombosis
E. Stasis

14. A student failed to answer all the questions of examination paper correctly. As a result he blushed, felt hot and lost confidence. What type of arterial hyperemia has developed in this case?

A. Neurotonic hyperemia
B. Neuroparalytic hyperemia
C. Metabolic hyperemia
D. Pathologic hyperemia
E. Postishemic hyperemia

15. A patient suffering from thrombophlebitis of deep veins suddenly died. The autopsy has shown freely lying red friable masses with dim crimped surface in the trunk and bifurcation of the pulmonary artery. What pathologic process was revealed by the morbid anatomist?

A. Tromboembolism
B. Thrombosis
C. Tissue embolism
D. Embolism with foreign body
E. Fat embolism

16. The pulmonalis embolism has suddenly developed in a 40 year-old patient with opened fracture of the hip. Choose the possible kind of embolism.

A. Fat
B. Thrombus-embolus
C. Air
D. Tissue
E. Foreign body

17. Upper neck node of sympathetic trunk was removed from the rabbit on experiment. Reddening and increased temperature of the skin of head is observed. What disorder of peripheral circulation of the blood has developed?

A. Neuroparalytic arterial hyperemia
B. Neurotonic arterial hyperemia
C. Metabolic arterial hyperemia
D. Venous hyperemia
E. Stasis

18. A patient with thrombophlebitis of lower extremities had got chest pains, blood spitting, growing respiratory failure that caused his death. Autopsy revealed multiple pulmonary infarctions. What is the most probable reason of their development?

A. Pulmonary artery embolism
B. Pulmonary artery thrombosis
C. Bronchial artery thrombosis
D. Bronchial artery embolism
E. Pulmonary venous thrombosis

19. A rabbit's nerve that innervates the right ear was cut and its right superior cervical ganglion was removed. Immediately after operation the temperature of ear skin was measured. It was revealed that the temperature of the rabbit's ear skin on the side of denervation was by 1, 50*C* higher than on the opposite intact side. What of the following is the most probable explanation of the above mentioned effects?

A. Arterial neuroparalytic hyperemia
B. Arterial neurotopical hyperemia
C. Atrerial hyperemia induced bymetabolic factors
D. Reactive arterial hyperemia
E. Physiological arterial hyperemia

20.While playing volleyball a sports manmade a jump and landed on the outside edge of his foot. He felt acute pain in the talo-crural joint, active movements are limited, passive movements are unlimited but painful. A bit later there appeared a swelling in the area of external ankle, the skin became red and warm. What type of peripheral circulation disturbance is the case?

A. Arterial hyperemia
B. Stasis
C. Embolism
D. Venous hyperemia
E. Thrombosis

21.A patient with arthritis and varicose veins has been taking a non-

steroidal antiinflammatory drug for a long time, which caused thrombosis of skin veins. Which of the following drugs might have caused this complication?

A. Celecoxib
B. Indomethacin
C. Aspirin
D. Phenylbutazone
E. Ibuprofen

22. A 54-year-old female was brought to the casualty department after a car accident. A traumatologist diagnosed her with multiple fractures of the lower extremities. What kind of embolism is most likely to develop in this case?

A. Adipose
B. Tissue
C. Thromboembolism
D. Gaseous
E. Air

23.A 54-year-old female was brought to the casualty department after a car accident. A traumatologist diagnosed her with multiple fractures of the lower extremities. What kind of embolism is most likely to develop in this case?

A. Fat
B. Tissue
C. Thromboembolism
D. Gaseous
E. Air

24. Oval and round organelles with double wall are seen at the electron micrograph. The outer membrane is smooth, the inner membrane folded into cristae contain enzyme ATPase synthetase. These are:

A. Mitochondria
B. Golgi complex
C. Lysosomes
D. Centrioles
E. Ribosomes

25. While playing volleyball a sportsman made a jump and landed on the outside edge of his foot. He felt acute pain in the talo-crural joint, active movements are limited, passive movements are unlimited but painful. A bit later there appeared a swelling in the area of external ankle, the skin became red and warm. What type of peripheral circulation disturbance is the case?

A. Arterial hyperemia
B. Stasis
C. Embolism
D. Venous hyperemia
E. Thrombosis

26. Inflammation of a patient's eye was accompanied by accumulation of turbid liquid with high protein at the bottom of anterior chamber that was called hypopyon. What process underlies the changes under observation?

A. Disturbance of microcirculation
B. Primary alteration
C. Secondary alteration
D. Proliferation
E. -

27. A 42 year old woman with neuralgia of trifacial nerve complains about periodical reddening of the right part of her face and neck, sense

of warmth gush, increased skin sensitivity. These effects can be explained by the following type of arterial hyperemia:

A. Neurotonic
B. Neuroparalytic
C. Metabolic
D. Functional
E. Reactive

28. A rabbit's nerve that innervates the right ear was cut and its right superior cervical ganglion was removed. Immediately after operation the temperature of ear skin was measured. It was revealed that the temperature of the rabbit's ear skin on the side of denervation was by $1,5^{o}C$ higher than on the opposite intact side. What of the following is the most probable explanation of the above-mentioned effects?

A. Arterial neuroparalytic hyperemia
B. Arterial neurotopical hyperemia
C. Atrerial hyperemia induced by metabolic factors
D. Reactive arterial hyperemia
E. Physiological arterial hyperemia

29. There are several groups of molecular mechanisms playing important part in pathogenesis of insult to cells which contributes to the pathology development. What processes are stimulated by proteinic damage mechanisms?

A. Enzyme inhibition
B. Lipid peroxidation
C. Phospholipase activation
D. Osmotic membrane distension
E. Acidosis

30. A 45 year old woman is ill with breast cancer. Her left arm has symptoms of lymphatic system insufficiency - limb edema, lymph node enlargement. What form of lymphatic circulation insufficiency is it?

A. Mechanic insufficiency
B. Dynamic insufficiency
C. Resorption insufficiency
D. Combined insufficiency
E. -

31. A patient is diagnosed with hereditary coagulopathy that is characterised by factor VIII deficiency. Specify the phase of blood clotting during which coagulation will be disrupted in the given case:
A. Thromboplastin formation
B. Thrombin formation
C. Fibrin formation
D. Clot retraction
E. –

32. During intravenous saline transfusion a patient’s condition deteriorated drastically, and the patient died from asphyxiation. Autopsy revealed acute venous congestion of internal organs with sharp right heart dilatation. When the right ventricle was punctured underwater, the bubbles escaped. What pathological process occurred in the patient?
A. Air embolism
B. Gaseous embolism
C. Adipose embolism
D. Tissue embolism
E. Thromboembolism

33. A 54-year-old woman was brought to a casualty department after

a car accident. A traumatologist diagnosed her with multiple fractures of the lower extremities. What kind of embolism is most likely to develop in this case?
A. Adipose
B. Tissue
C. Thromboembolism
D. Gaseous
E. Air

34. A 25-year-old patient complains of increasing pain in his leg muscles occurring during walking and forcing him to make frequent stops. Objectively: skin of legs is pale, no hair-covering, toenails are with trophic changes, no pulsation of pedal arteries. The most probable cause of these changes is:
A. Ischemia
B. Venous hyperemia
C. Arterial hyperemia
D. -
E. Embolism

35. A man has suffered multiple bone fractures of his lower extremities during a traffic accident. During transportation to a hospital his condition was further aggravated: blood pressure decreased, there were signs of pulmonary artery embolism. What kind of embolism is the most likely in the given case?
A. Fat embolism
B. Air embolism
C. Gas embolism
D. Tissue embolism
E. Thromboembolism

36. A 63-year-old man suffers from esophageal carcinoma, presents with metastases into the mediastinal lymph Capillaroscopy detected damage to the vessel walls of the microcirculation system. What disorder is possible in the given case?
A. Blood ”sludge” phenomenon
B. Thrombosis
C. Embolism
D. Arterial hyperemia
E. Venous hyperemia

37.Ionizing radiation or vitamin E deficiency affect the cell by increasing lysosome membrane permeability.What are the possible consequences of this pathology?
A. Partial or complete cell destruction
B. Intensive protein synthesis
C. Intensive energy production
D. Restoration of cytoplasmic membrane
E. Formation of maturation spindle

38.A 45-year-old man diagnosed with hepatic cirrhosis and ascites underwent drainage of 5 liters of fluid from his abdominal cavity, which resulted in development of syncopal state due to insufficient blood supply to the brain. What circulatory disorder occurred in the abdominal cavity in this case?
A. Arterial hyperemia
B. Ischemia
C. Venous hyperemia
D. Thrombosis
E. Embolism

39.Coronary artery thrombosis resulted in development of myocardial infarction. What mechanisms of cell damage are leading in this disease?
A. Calcium
B. Lipid
C. Acidotic
D. Electroosmotic
E. Protein

40.A 65-year-old woman, who had been suffering from deep vein thrombophlebitis of the lower leg, suddenly died when awaiting her appointment with the doctor. Autopsy revealed loose friable red masses with corrugated dull surface in the main pulmonary artery and its bifurcation. What pathologic process was discovered by the pathologist in the pulmonary artery?
A. Thromboembolism
B. Thrombosis
C. Tissue embolism
D. Foreign body embolism
E. Fat embolism

Tests for Self-Control

1. A 38-year-old man complains of pain in the heart, which arises after negative emotions. A doctor diagnosed ischemic illness (stenocardia). What mechanism of ischemia is the most probable?
A. Angiospastic.
B. Obturative.
C. Compressive.
D. Mechanical.
E. Occlusive.

2. A patient with a closed fracture of the humeral bone had a plaster bandage applied. The next day the hand swelled, became cyanotic and cold. What kind of pathology of peripheral circulation took place?
A. Gas embolism.
B. Air embolism.
C. Ischemia.
D. Venous hyperemia.
E. Arterial hyperemia.

3. After exercising a patient with thrombophlebitis of the lower extremities has dyspnea, acute pain in the chest, cyanosis, swelling of the cervical veins. What kind of circulation pathology took place?
A. Thromboembolism of the mesenteric vessels.
B. Thromboembolism of the coronary vessels.
C. Thromboembolism of the brain vessels.
D. Thromboembolism of the pulmonary artery.
E. Thromboembolism of the v. porta.

4. A patient with obliterating endarteritis had ganglionary sympathectomy performed. The positive medical effect of this operation is connected with arterial hyperemia development. What type of hyperemia is it?
A. Reactive.
B. Neurotonic.
C. Metabolic
D. Working.
E. Neuroparalytic.

5. A small NaCl crystal was placed near the mesenteric vein of a frog during an experiment. This operation leaded to the formation of a blood clot. What is the initial point in thrombogenesis?
A. Blood flow deceleration.
B. Activation of coagulation.
C. Activation of thrombocyte adhesion.
D. Damage of the vascular wall.
E. Decreased activity of anticoagulants.

6. Embolism of the small circle of circulation occurred after a femur fracture.What kind of embolism took place?
A. Fat.
B. Thromboembolism.
C. Cellular.
D. Gas.
E. Air.
7. A 27-year-old woman with neuralgia complains of reddening in the right part of the face and neck, dermal hypersensitivity and pain in the region of n. trigemini. What kind of arterial hyperemia explains these symptoms?
A. Metabolic.
B. Neuroparalytic.
C. Neurotonic.
D. Working.
E. Reactive

Recommended literature:

Basic

1. Simeonova N.K. Pathophysiology/ N.Simeonova.// Kyiv, Ukraine. – 2010. – 105-113pp.
2. Krishtal N.V. Pathophysiology: textbook/ N.Krishtal et al.// Kyiv: AUS Medicine Publishing, 2017. – 86-94, 194-209 pp.
3. Victor N. Jelski, Svetlana V. Kolesnikova. Handbook Of Pathophysiology Part 1: General Pathophysiology. - Donetsk, Ukraine. – 2009. – 22-32 pp.
4. Lecture Notes For Health Science Students. General Pathology// Mesele Bezabeh, Abiye Tesfaye, Bahiru Ergicho, Mengistu Erke, Seyoum Mengistu, Alemayehu Bedane, Abiyot Desta/ Jimma University, Gondar University Haramaya University, Dedub University. – 2004. – 14-22,61-96pp.

Additional

5. Porth, Carol. Essentials of pathophysiology: concepts of altered health states /Carol Mattson Porth ; consultants, Kathryn J. Gaspard, Kim A. Noble. — 3rd ed. 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins. – 2011. – 1282 p.
6. Robbins Pathology basis of disease / Cotran R.S., Kumar V., Robbins S.L. - 2000.

Methodological instruction to practical lesson №7
Module 1. General pathology

Theme: INFLAMMATION

Student should know:

- Determination of concept of inflammation. Pathogenesis of acute inflammation.
- Classification of mediators of inflammation.
- Mechanisms of exudation in the focus of acute inflammation.
- Disorders of phagocytosis.

Student should be able to:

- Explain the stages of emigration of leucocytes and mechanisms of neutralizing of microbes in the focus of inflammation.

LIST OF CONTROL QUESTIONS

1. Determination of concept of inflammation. Classifications of inflammation (immune, nonimmune; infectious, noninfectious; acute, chronic; normo-, hypo-, hyperergic, etc). Etiology of inflammation: classification and characteristic of phlogogenic factors. General and local signs of inflammation.
2. Pathogenesis of acute inflammation. Stages of inflammation. Alteration (primary and secondary), reasons and mechanisms of secondary alteration.
3. Biochemical, physical-chemical disorders in the core of inflammation.
4. Mediators of inflammation, their classification. Plasma mediators (proteins of acute phase, proteins of the complement system, pro- and anticoagulants, fibrinolysis, kinins). Mediators of cellular origin, specific and nonspecific. Cytokins: types, characteristic of action. Mediators from tissue basophilies. Eicosanoids.
5. Disorder of local circulation of blood in the focus of acute inflammation. Pathogenesis of ischemia and arterial hyperemia. Reasons of transition of arterial hyperemiainto venous. Changes of rheologic properties of blood in the focus of acute inflammation.
6. Exudation in the focus of acute inflammation, reasons and mechanisms. Characteristic of exudates.
7. Emigration of leucocytes in the focus of inflammation. Stages, reasons and mechanisms of emigration of leucocytes. Adhesive molecules of leucocytes and endotheliocytes. Reasons and mechanisms of chemotaxis of leucocytes. Mechanisms of neutralizing of microbes by leucocytes: stages, mechanisms of elimination of objects of phagocytosis.
8. Proliferation in the place of inflammation - regeneration and/or fibroplasia. Reasons and mechanisms of proliferation. Mitogenic signals (factors of growth, cytokins, hormones, absence of the contact slowing down of proliferation). Transmission of mitogenic signal by intracellular alarm ways.

Role of mithogen activated proteinkinases in stimulation of cellular division. Mechanisms of sclerosis, organization of scar.

9. Chronic inflammation. General characteristic, features of system and local signs (comparing with acute inflammation). Features of pathogenesis (infiltration, reparation/fibrosis, formation of granuloma).
10. Role of the reactivity of organism, pathological immune answer in the development of inflammation (normo-, hypo-, hyperergic inflammation).
11. Principles of anti-inflammatory therapy.

The inflammation is a typical pathological process that develops in vascularizing organs and tissues in response to damage and serves for isolation, decontamination, and removal of both the pathological factor and necrotic cells and tissues with subsequent substitution of the formed defect by the connective tissue.

The five cardinal signs of acute inflammation are:

1) **Redness** (rubor) which is due to dilation of small blood vessels within damaged tissue as it occurs in cellulitis.
2) **Heat** (calor) which results from increased blood flow (hyperemia) due to regional vascular dilation
3) **Swelling** (tumor) which is due to accumulation of fluid in the extravascular space which, in turn, is due to increased vascular permeability.
4) **Pain** (dolor), which partly results from the stretching & destruction of tissues due to inflammatory edema and in part from pus under pressure in as abscess cavity. Some chemicals of acute inflammation, including bradykinins, prostaglandins and serotonin are also known to induce pain.
5) **Loss of function**: The inflammed area is inhibited by pain while severe swelling may also physically immobilize the tissue.

Etiological factors of inflammation are called *flogogens.* They are exogenous and endogenous.

- **physical agents** - mechanical injuries, alteration in temperatures and pressure,
  radiation injuries.
- **chemical agents**- including the ever increasing lists of drugs and toxins.
- **biologic agents (infectious)**- bacteria, viruses, fungi, parasites
- **immunologic disorders**- hypersensitivity reactions, autoimmunity, immunodeficiency states etc
- **genetic/metabolic disorders**- examples gout, diabetes mellitus etc…

Inflammatory Mediators

- ✓ TNF-a and IL-1 are responsible for fever and the release of stress hormones (norepinephrine, vasopressin, activation of the renin-angiotensin-aldosterone system).
- ✓ TNF-a and IL-1 are responsible for the synthesis of IL-6, IL-8, and interferon gamma.

- ✓ Cytokines, especially IL-6, stimulate the release of acute-phase reactants such as C-reactive protein (CRP).
- ✓ The proinflammatory interleukins either function directly on tissue or work via secondary mediators to activate the coagulation cascade, complement cascade, and the release of nitric oxide, platelet-activating factor, prostaglandins, and leukotrienes.

Complement fragments and cytokines

- ✓ It stimulates chemotaxis of neutrophils, eosinophils and monocytes;
- ✓ C3a, C5a increase vascular permeability;

Cytokines

- ✓ Interleukins (IL-1, IL-6, IL-8)
  - ◦ Stimulates the chemotaxis, degranulation of neutrophils and their phagocytic activity
  - ◦ Induce extravascularization of granulocytes
  - ◦ Fever
- ✓ Tumor necrosis factor (TNF) and IL-8
  - ◦ Leukocytosis
  - ◦ Fever
  - ◦ Stimulates prostaglandins production

Prostaglandins

The prostaglandins are ubiquitous, lipid soluble molecules derived fro arachidonic acid, a fatty acid liberated from cell membrane phospholipids, through the cyclooxygenase pathway.

Prostaglandins contribute to vasodilation, capillary permeability, and the pain and fever that accompany inflammation.

The stable prostaglandins (PGE1 and PGE2) induce inflammation and potentiate the effects of histamine and other inflammatory mediators:

They cause the dilation of precapillary arterioles (edema), lower the blood pressure, modulates receptors activity and affect the phagocytic activity of leukocytes.

The prostaglandin thromboxane A2 promotes platelet aggregation and vasoconstriction.

Leukotrienes

The leukotrienes are formed from arachidonic acid, but through the lipoxygenase pathway.

Histamine and leukotrienes are complementary in action in that they have similar functions.

Histamine is produced rapidly and transiently while the more potent leukotrienes are being synthesized.

Leukotrienes C4 and D4 are recognized as the primary components of the *slow reacting substance of anaphylaxis* (SRS-A) that causes slow and sustained constriction of the bronchioles.

The leukotrienes also have been reported to affect the permeability of the postcapillary venules, the adhesion properties of endothelial cells, and stimulates

the chemotaxis and extravascularization of neutrophils, eosinophils, and monocytes.

Histamine

It is found in high concentration in platelets, basophils, and mast cells.

Causes dilation and increased permeability of capillaries (it causes dilatation of precapillary arterioles, contraction of endothelial cells and dilation of postcapillary venules).

It acts through H1 receptors.

Platelet-activating factor (PAF)

It is generated from a lipid complex stored in cell membranes;
It affects a variety of cell types and induces platelet aggregation;
It activates neutrophils and is a potent eosinophil chemoattractant;
It contributes to extravascularization of plasma proteins and so, to edema.

Plasma Proteases consist of:

Kinins

Bradykinin - causes increased capillary permeability (implicated in hyperthermia and redness) and pain;

Clotting factors

The clotting system contributes to the vascular phase of inflammation, mainly through fibrin peptides that are formed during the final steps of the clotting process.

The classic stages of the inflammation. There are such stages of the inflammation:

I. The alteration:
a) Primary — is due to the lesion factors;
b) Secondary — is caused by mediators of the inflammation;
II. The exudation and emigration;
III. The proliferation and regeneration.

Major actions during the inflammation:

- The primary alteration, i.e. the tissue damage, primarily of the cell membrane during the action of the flogogenic agent on them, with the simultaneous release of mediators of inflammation (metabolites and BAS) by the damaged cells, macrophages, and mast cells;
- The intermittent spasm of the arterioles, activation of glycolysis, the development of intra- and extracellular local acidosis, activation of lysosomal enzymes and beginning of the secondary alteration; formation of new inflammatory mediators, and arterial hyperemia;
- The further development of disturbances of microcirculation (the venous hyperemia, stasis), increased vascular permeability, exudation and emigration of neutrophils;
- The strengthening of the secondary alteration due to the destruction of cells and macromolecules by the active oxygen radicals, lysosomal enzymes, cationic proteins, lactoferrin and lysocyme released by the neutrophils;

- The development of hyperoncia in the inflammatory focus with the increased exudation and normalization of pH;
- The emigration of monocytes-macrophages and then lymphocytes; the cleansing of the inflammatory focus, neutralization of the BAS stimulating the inflammatory process; the enhance production of the anti-inflammatory mediators;
- The proliferation of fibroblasts, endothelial, non-striated muscular, epidermal cells as a result of reducing the number of keylongs, elimination of contact inhibition, increased production of growth factors by the macrophages;
- The substitution of the defect tissue by (repairing) using the regeneration and fibroplasia.

The term *alteration* means damage. Two types of alteration are distinguished in the focus of inflammation — primary and secondary. ***Primary alteration*** is tissue damage by the etiological factor itself. This effect may be very short-term, but the local damage of tissue is not finished.

Secondary alteration is an additional tissue damage by numerous factors of endogenous origin. These factors are the following:

- inflammatory cells;
- BAS (mediators of inflammation);
- microcirculatory disorders;
- hypoxia;
- local increase of osmotic and oncotic pressure;
- local acidosis;
- products of tissue decay.

Acute inflammation is categorized into an early vascular and a late cellular responses.

1) The **Vascular response** has the following steps:
   a) Immediate (momentary) vasoconstriction in seconds due to neurogenic or chemical stimuli.
   b) Vasodilatation of arterioles and venules resulting in increased blood flow.
   c) After the phase of increased blood flow there is a slowing of blood flow & stasis due to increased vascular permeability that is most remarkably seen in the post-capillary venules. The increased vascular permeability cauzes protein-rich fluid into extravascular tissues. Due to this, the already dilated blood vessels are now packed with red blood cells resulting in stasis. The protein-rich fluid which is now found in the extravascular space is called exudate. The presence of the exudates clinically appears as swelling. Chemical mediators mediate the vascular events of acute inflammation.

2) Cellular response:

The cellular response has the following stages:

I. Migration, rolling, pavementing, & adhesion of leukocytes
II. Transmigration of leukocytes
III. Chemotaxis
IV. Phagocytosis

Normally blood cells particularly erythrocytes in venules are confined to the central
(axial) zone and plasma assumes the peripheral zone. As a result of increased vascular permeability (See vascular events above), more and more neutrophils accumulate along the endothelial surfaces (peripheral zone).

A) **Migration, rolling, pavementing, and adhesion of leukocytes:**

- Margination is a peripheral positioning of white cells along the endothelial cells.
- Subsequently, rows of leukocytes tumble slowly along the endothelium in a process known as rolling
- In time, the endothelium can be virtually lined by white cells. This appearance is called pavementing
- Thereafter, the binding of leukocytes with endothelial cells is facilitated by cell adhesion molecules such as selectins, immunoglobulins, integrins, etc which result in adhesion of leukocytes with the endothelium.

B). **Transmigration of leukocytes:**

- Leukocytes escape from venules and small veins but only occasionally from capillaries. The movement of leukocytes by extending pseudopodia through the vascular wall occurs by a process called diapedesis.
- The most important mechanism of leukocyte emigration is via widening of interendothelial junctions after endothelial cells contractions. The basement membrane is disrupted and resealed thereafter immediately.

C) **Chemotaxis:**

- A unidirectional attraction of leukocytes from vascular channels towards the site of inflammation within the tissue space guided by chemical gradients (including bacteria and cellular debris) is called chemotaxis.
- The most important chemotactic factors for neutrophils are components of the complement system (C5a), bacterial and mitochondrial products of arachidonic acid metabolism such as leukotriene B4 and cytokines (IL-8). All granulocytes, monocytes and to lesser extent lymphocytes respond to chemotactic stimuli.
- How do leukocytes "see" or "smell" the chemotactic agent? This is because

receptors on cell membrane of the leukocytes react with the chemoattractants resulting in the activation of phospholipase C that ultimately leads to release of cytosolic calcium ions and these ions trigger cell movement towards the stimulus.

D) **Phagocytosis**

- Phagocytosis is the process of engulfment and internalization by specialized cells of particulate material, which includes invading microorganisms, damaged cells, and tissue debris.
- These phagocytic cells include polymorphonuclear leukocytes (particularly neutrophils), monocytes and tissue macrophages.

Phagocytosis involves three distinct but interrelated steps.

1). **Recognition and attachment** of the particle to be ingested by the leukocytes:

Phagocytosis is enhanced if the material to be phagocytosed is coated with certain plasma proteins called **opsonins**. These opsonins promote the adhesion between the particulate material and the phagocyte's cell membrane. The three major opsonins are: the Fc fragment of the immunoglobulin, components of the complement system C3b and C3bi, and the carbohydrate-binding proteins – lectins. Thus, IgG binds to receptors for the Fc piece of the immunoglobulin (FcR) whereas 3cb and 3bi are ligands for complement receptors CR1 and CR2 respectively.

2). **Engulfment:** During engulfment, extension of the cytoplasm (pseudopods) flow around the object to be engulfed, eventually resulting in complete enclosure of the particle within the phagosome created by the cytoplasmic membrane of the phagocytic cell. As a result of fusion between the phagosome and lysosome, a phagolysosome is formed and the engulfed particle is exposed to the degradative lysosomal enzymes.

3) **Killing or degradation**

The ultimate step in phagocytosis of bacteria is killing and degradation. There are two forms of bacterial killing

a) **Oxygen-independent mechanism:**

- ✓ This is mediate by some of the constituents of the primary and secondary granules of polymorphonuclear leukocytes. These include:
  - Bactericidal permeability increasing protein (BPI)
  - Lysozymes
  - Lactoferrin
  - Major basic protein
  - Defenses
- ✓ It is probable that bacterial killing by lysosomal enzymes is inefficient and relatively unimportant compared with the oxygen

dependent mechanisms. The lysosomal enzymes are, however, essential for the degradation of dead organisms within phagosomes.

b) **Oxygen-dependent mechanism**:

There are two types of oxygen- dependent killing mechanisms:

1. **Non-myeloperoxidase dependent**
   - ✓ The oxygen - dependent killing of microorganisms is due to formation of reactive oxygen species such as hydrogen peroxide (H2O2), super oxide (**O2)** and hydroxyl ion (HO-) and possibly single oxygen (1O2). These species have single unpaired electrons in their outer orbits that react with molecules in cell membrane or nucleus to cause damages. The destructive effects of **H2O2** in the body are gauged by the action of the glutathione peroxidase and catalase.
2. **Myloperoxidase–dependent**
   - ✓ The bactericidal activity of **H2O2** involves the lysosomal enzyme myeloperoxidase, which in the presence of halide ions converts H2O2 to hypochlorous acid (HOCI). This **H2O2** – halide - myecloperoxidease system is the most efficient bactericidal system in neutrophils. A similar mechanism is also effective against fungi, viruses, protozoa and helminths. Like the vascular events, the cellular events (i.e. the adhesion, the transmigration, the chemotaxis, & the phagocytosis) are initiated or activated by chemical mediators.

Termination of acute response

Inflammation declines spontaneously

- ◦ Mediators of inflammation are produced in rapid bursts only while the stimulus persists
- ◦ Mediators have short half-lives and are degraded after their release.
- ◦ Neutrophils also have short half-lives in tissues and die by apoptosis within a few hours after leaving the blood

Active termination mechanisms include

- ◦ Switch from pro-inflammatory leukotrienes to anti-inflammatory lipoxins
- ◦ Release of anti-inflammatory cytokines, including transforming growth factor-β (TGF-β) and IL-10, from macrophages production of anti-inflammatory lipid mediators, called resolvins and protectins, derived from polyunsaturated fatty acids neural impulses (cholinergic discharge) that inhibit the production of TNF in macrophages

Outcomes

1) Resolution

The complete restoration of the inflamed tissue back to a normal status. Inflammatory measures such as vasodilation, chemical production, and leukocyte

infiltration cease, and damaged parenchymal cells regenerate. In situations where limited or short lived inflammation has occurred this is usually the outcome.

2) Fibrosis

Large amounts of tissue destruction, or damage in tissues unable to regenerate, can not be regenerated completely by the body. Fibrous scarring occurs in these areas of damage, forming a scar composed primarily of collagen. The scar will not contain any specialized structures, such as parenchymal cells, hence functional impairment may occur.

3) Abscess formation

A cavity is formed containing pus, an opaque liquid containing dead white blood cells and bacteria with general debris from destroyed cells.

4) Chronic inflammation

A prolonged inflammatory process (weeks or months) where an active inflammation, tissue destruction and attempts at repair are proceeding simultaneously.

Chronic inflammation = long duration

• Components:

– Lymphocyte, plasma cell, macrophage (mononuclearcell) infiltration

– Tissue destruction by inflammatory cells

– Repair with fibrosis and angiogenesis (new vessel formation)

Causes of chronic inflammation

• Persistent injury or infection

– Ulcer, tuberculosis

• Prolonged exposure to a toxic agent

– Pulmonary silicosis (silica in the lung)

• Autoimmune disease—self-perpetuating immune reaction that results in tissue damage and inflammation

– Rheumatoid arthritis

– Systemic lupus erythematosus

– Multiple sclerosis

KROK 1_mcqs (A is correct answer):

1.A patient has been administered an anti-inflammatory drug that blocks the action of cyclooxygenase. Specify this anti-inflammatory agent:

A. Aspirin
B. Analgene
C. Allopurinol
D. Thiamin
E. Creatine

2. Deficiency of linoleic and linolenic acids in the body leads to the skin damage, hair loss, delayed wound healing, thrombocytopenia, low resistance to infections. These changes are most likely to be caused

by the impaired synthesis of the following substances:

A. Eicosanoids
B. Interleukins
C. Interferons
D. Catecholamines
E. Corticosteroids

3.A patient who had been taking diclofenac sodium for arthritis of mandibular joint developed an acute condition of gastric ulcer. Such side effect of this medicine is caused by inhibition of the following enzyme:

A. Cyclooxygenase-1 (COX-1)
B. Cyclooxygenase-2 (COX-2)
C. Lipoxygenase
D. Phosphodiesterase
E. Monoamine oxidase

4. A 7-year-old boy got ill with diphtheria. On the third day he died of asphyxiation. At autopsy the mucosa of the larynx, trachea and bronchi had thickened, edematous, lustreless appearance and was covered with gray films which could be easily removed. Specify the type of laryngeal inflammation:

A. Croupous
B. Diphtheritic
C. Purulent
D. Catarrhal
E. Intermediate

5. An 8-year-old child was admitted to the infectious department with fever (up to 38°C) and punctuate bright-red skin rash. The child was diagnosed as having scarlet fever. Objectively: mucous membrane of pharynx is apparently hyperaemic and edematic, the tonsils are enlarged and have dull yellowish-grey foci with some black areas. What inflammation is the reason for the pharynx alterations?

A. Purulent necrotic
B. Haemorrhagic
C. Fibrinous
D. Catarrhal
E. Serous

6. Colonoscopy of a patient with dysentery revealed that the mucous membrane of the large intestine was hyperemic, edematic, and its surface was covered with grey-and-green layerings. What morphological form of dysenteric colitis is it?

A. Fibrinous
B. Catarrhal
C. Necrotic
D. Purulent
E. Ulcerous

7. A 17 year old boy fell seriously ill, the body temperature rose up to 38, 5oC, there appeared cough, rhinitis, lacrimation, nasal discharges. What inflammation is it?

A. Catarrhal
B. Serous
C. Fibrinous
D. Purulent
E. Hemorrhagic

8. Inflammatory processes cause synthesis of protein of acute phase in an organism. What substances stimulate their synthesis?

A. Interleukin-1
B. Immunoglobulins
C. Interferons

D. Biogenic amins
E. Angiotensin

9. A 4 year old child complained of pain during deglutition, indisposition. Objectively: palatine arches and tonsils are moderately edematic and hyperemic, there are greyish-white films up to 1 mm thick closely adhering to the subjacent tissues. What pathological process are these changes typical for?

A. Inflammation
B. Dystrophy
C. Necrosis
D. Metaplasia
E. Organization

10. Necrosis focus appeared in the area of hyperemia and skin edema in few hours after burn.What mechanism strengthens destructive events in the inflammation area?

A. Secondary alteration
B. Primary alteration
C. Emigration of lymphocytes
D. Diapedesis of erythrocytes
E. Proliferation of fibroblasts

11. A diseased child has a high fever, sore throat, swelling of submandibular lymph nodes. Objectively: pharyngeal mucosa is edematous, moderately hyperemic, the tonsils are enlarged, covered with grayish membrane tightly adhering to the tissues above. Attempts to remove the membrane produce the bleeding defects. What disease are these presentations typical for?

A. Diphtheria
B. Catarrhal tonsillitis
C. Scarlet fever
D. Meningococcal disease
E. Measles

12. The cellular composition of exudate largely depends on the etiological factor of inflammation. What leukocytes are the first to get into the focus of inflammation caused by pyogenic bacteria?

A. Neutrophil granulocytes
B. Monocytes
C. Myelocytes
D. Eosinophilic granulocytes
E. Basophils

13. Microscopy of the bronchial wall revealed atrophy of the mucosa, metaplastic change from columnar to squamous epithelium, an increase in the number of goblet cells, diffuse infiltration of the bronchial wall with lymphoplasmacytic elements with a large number of neutrophilic granulocytes, pronounced sclerosis. Spesify the morphological form of bronchitis:

A. Chronic purulent bronchitis
B. Acute bronchitis
C. Polypoid chronic bronchitis
D. Acute purulent bronchitis
E. Chronic bronchitis

14. During autopsy approximately 2,0 liters of pus have been found in the abdominal cavity of the corpse. Peritoneum is lustreless and has grayish shade, serous tunic of intestines has grayish-colored coating that is easily removable. Specify the most likely type of peritonitis in the patient:

A. Fibrinopurulent peritonitis
B. Hemorrhagic peritonitis
C. Serous peritonitis
D. Tuberculous peritonitis
E. ----

15. As a result of careless handling of an iron, a 34-year-old female patient has got acute pain, redness, swelling of her right index finger. A few minutes later, there appeared a blister filled with a transparent liquid of straw yellow color. The described changes are a manifestation of the following pathological process:

A. Exudative inflammation
B. Traumatic edema
C. Alternative inflammation
D. Proliferative inflammation
E. Vacuolar degeneration

16. A 37-year-old male patient developed pseudoarthrosis after a closed fracture of the femur.Specify the type of regeneration in the patient:

A. Pathological hypo-regeneration
B. Pathological hyper-regeneration
C. Reparative
D. Physiological
E. –

17. A patient underwent surgical removal of a cavitary liver lesion 2 cm in diameter. It was revealed that the cavity wall was formed by dense fibrous connective tissue; the cavity contained muddy, thick, yellowish greenish fluid with an unpleasant odor. Microscopically, the fluid consisted mainly of polymorphonuclear leukocytes. What pathological process are these morphological changes typical for?

A. Chronic abscess
B. Acute abscess
C. Phlegmon
D. Empyema
E. –

18. A 16-year-old boy was performed an appendectomy. He has been hospitalized for right lower quadrant abdominal pain within 18 hours. The surgical specimen is edematous and erythematous. Infiltration by what of the following cells is the most typical for the process occuring here?

A. Neutrophils
B. Eosinophils
C. Basophils
D. Limphocytes
E. Monocytes

19. Inflammation of a patient’s eye was accompanied by accumulation of turbid liquid with high protein at the bottom of anterior chamber that was called hypopyon. What process underlies the changes under observation?

A. Disturbance of microcirculation
B. Primary alteration
C. Secondary alteration
D. Proliferation
E. -

20. In course of histidine catabolism a biogenic amin is formed that has powerful vasodilatating effect. Name it:

A. Histamine
B. Serotonin
C. Dioxyphenylalanine
D. Noradrenalin
E. Dopamine

21. Utilization of arachidonic acid via cyclooxigenase pathway results information of some bioactive substances. Name them:

A. Prostaglandins
B. Thyroxin
C. Biogenic amins
D. Somatomedins
E. Insulin-like growth factors

22. Colonoscopy of a patient ill with dysentery revealed that mucous membrane of his large intestine is hyperemic, edematic, its surface was covered with grey-and-green coats. Name the morphological form of dysenteric collitis:

A. Fibrinous
B. Catarrhal
C. Ulcerous
D. Purulent
E. Necrotic

23. 24 hours after appendectomy blood of a patient presents neutrophilic leukocytosis with regenerative shift. What is the most probable mechanism of leukocytosis development?

A. Amplification of leukopoiesis
B. Redistribution of leukocytes in theorganism
C. Decelerated leukocyte destruction
D. Deceleratied emigration of leukocytesto the tissues
E. Amplification of leukopoiesis and decelerated emigration of leukocytes to the tissues

24. On simulation of inflammation of the lower extremity the animal exrerienced raise of the temperature, increase of amount of antibodies and leucocytes in the blood. What substances caused this general reaction of the organism on inflammation?

A. Interleukin
B. Glucocorticoid
C. Mineralcorticoid
D. Leucotriens
E. Somatomedins

25. A 7-year-old child has acute onset of disease: temperature rise up to 38*oC*, rhinitis, cough, lacrimation, and large-spot rash on the skin. Pharyngeal mucosa is edematous, hyperemic, with whitish spots in the buccal area. What kind of inflammation causes the changes in the buccal mucosa?

A. Catarrhal inflammation
B. Suppurative inflammation
C. Fibrinous inflammation
D. Hemorrhagic inflammation
E. Serous inflammation

26.A 30-year-old man complains of suffocation, heaviness in the chest on the right, general weakness. Body temperature is 38,9oC. Objectively the right side of the chest lags behind the left side during respiration. Pleurocentesis rewiled exudate. What is the leading factor of exudation in the patient?

A. Increased permeability of the vessel wall B. Increased blood pressure
C. Hypoproteinemia
D. Erythrocyte aggregation
E. Decreased resorption of pleural fluid

27.Microscopy of the puncture sample obtained from the inflammation focus

of the patient with cutaneous abscess revealed numerous blood cells of different types. What cells are the first to transfer from vessels to tissues during inflammation?
A. Neutrophils
B. Monocytes
C. Basocytes
D. Eosinophils
E. Lymphocytes

28.A 30-year-old person has been stung by a bee. The stung area exhibits edema, hyperemia, and elevated temperature. What is the initial pathogenetic factor of inflammatory edema in this case?
A. Increase of microvascular permeability
B. Increase of osmotic pressure in the inflammation focus
C. Decrease of oncotic blood pressure
D. Increase of capillary blood pressure
E. Disturbed lymphatic efflux

Tests for Self-Control
(give correct answers)

1. An intradermal tuberculin injection was given to an animal sensibilized by tuberculin. In 24 hours in the place of injection venous hyperemia and edema formed. A histological analysis of the skin showed a lot of lymphocytes and monocytes. What kind of inflammation took place?
A. Purulent.
B. Serous.
C. Allergic.
D. Fibrinous.
E. Aseptic.
2. A patient had a skin abscess. A microscopic examination of the punctate from the focus of inflammation showed plenty of different blood cells. What type of leukocytes are first to get from vessels into tissues?
A. Lymphocytes.
B. Monocytes.
C. Basophiles.
D. Eosinophils.
E. Neutrophils.
3. A 4-year-old child had a hyperergic inflammation of the upper respiratory tract. Later the beginning of a serious respiratory pathology forced to apply an anti-inflammatory hormone. What hormone has anti-inflammatory action?
A. Epinephrine.
B. Hydrocortisone.
C. Somatotropin.
D. Testosterone.
E. Insulin.
4. Reproduction of inflammation of the frog's mesentery demonstrates peripheral orientation of leukocytes inside the vessels and their migration through the vascular wall. What factors predetermine this process?
A. Decrease of oncotic pressure in vessels.
B. Increase of oncotic pressure in the focus of inflammation.
C Local acidosis.
D. Influence of chemotactic substances.
E. Decrease of hydrostatic pressure in vessels.
5. A patient suffers from pleuritis. Pleural cavity puncture showed

exudate. What is the initial mechanism of exudation?
A. Increase of vessel permeability.
B. Increase of blood pressure.
C. Hypoproteinemia.
D. Aggregation of erythrocytes.
E. Decrease of oncotic pressure in tissues.
6. Reproduction of inflammation of the inferior extremity of an animal is associated with a high body temperature, increased quantity of antibodies, leukocytes. What substances provoked the development of these systemicl reactions of the organism?
A. Histamin.
B. Glucocorticoids.
C. Mineralocorticoids.
D. Interleukins.
E. Somatomedins.
7. A lot of leukocytes are accumulated in the focus of inflammation. What is the order of emigration of different types of leukocytes into the inflammation zone according to Mechnikov?
A. Neutrophils, lymphocytes, monocytes.
B. Lymphocytes, neutrophils, monocytes.
C. Monocytes, neutrophils, lymphocytes.
D. Monocytes, lymphocytes, neutrophils.
E. Neutrophils, monocytes, lymphocytes.
8. An experimental model of inflammation was reproduced with turpentine. A lethal dose of tetanine was injected into the abscess cavity, but the animal stayed alive. What is the probable cause of such a result of the experiment?
A. Activation of antibody synthesis.
B. Formation of a barrier around the focus of inflammation.
C. Stimulation of leukopoiesis.
D. Intensification of vascularization of the focus of inflammation.
E. Activation of desintoxicating functions of phagocytes.
9. In some hours after burn in the site of hyperemia and edema a focus of necrosis appeared. What is the main mechanism, which intensified destructive processes in the focus of inflammation?
A. Emigration of lymphocytes.
B. Primary alteration.
C. Secondary alteration.
D. Emigration of erythrocytes.
E. Proliferation of fibroblasts.

Recommended literature:

Basic

1. Simeonova N.K. Pathophysiology/ N.Simeonova.// Kyiv, Ukraine. – 2010. – 120-128pp.
2. Krishtal N.V. Pathophysiology: textbook/ N.Krishtal et al.// Kyiv: AUS Medicine Publishing, 2017. – 218-250pp.
3. Victor N. Jelski, Svetlana V. Kolesnikova. Handbook Of Pathophysiology Part 1: General Pathophysiology. - Donetsk, Ukraine. – 2009. – 60-81 pp.
4. Lecture Notes For Health Science Students. General Pathology// Mesele Bezabeh, Abiye Tesfaye, Bahiru Ergicho, Mengistu Erke, Seyoum Mengistu, Alemayehu Bedane, Abiyot Desta/ Jimma University, Gondar University Haramaya University, Dedub University. – 2004. – 24-39pp.

Additional

5. Porth, Carol. Essentials of pathophysiology: concepts of altered health states /Carol Mattson Porth ; consultants, Kathryn J. Gaspard, Kim A. Noble. — 3rd ed. 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins. – 2011. – 1282 p.
6. Robbins Pathology basis of disease / Cotran R.S., Kumar V., Robbins S.L. - 2000.

Methodological instruction to practical lesson №8
Module 1. General pathology

Theme: FEVER. NEOPLASIA. TUMORS

Student should know:

- The etiology, pathogenesis, the dynamics of fever development and evaluate its significance in pathology.
- Definition of notion "tumor", "tumor growth".
- Etiology of tumors, main classes of carcinogens .
- Difference of benign and malignant tumor.
- Methods of experimental study of tumor.

Student should be able to:

- Formulate conception of oncogene essence.
- Explain the mechanisms ofcancerogenesis.
- Explain mechanisms of metastasing.

LIST OF CONTROL QUESTIONS

1. Determination of concept «fever».
2. General characteristic of fever, its development in ontogenesis and phylogenesis.
3. Etiology of fever, characteristic of pyrogens, primary and secondary pyrogens.
4. Stages of fever.
5. Protective value and pathological signs of fever.
6. Pathophysiological principles of antipyretic therapy.
7. Basic differences between the fever, exogenous overheat and other types of hyperthermia.
8. General characteristic of basic types of disorders of tissue growth (hypoplasia, hyperplasia).
9. Determination of "tumor" and "tumor process". General laws of tumor growth. Molecular genetic bases of unlimited growth and potential immortality of tumorous cells. Anaplasia: signs of structural, functional, physical and chemical, biochemical, antigen anaplasia. Characteristic of expansive and infiltrative (invasive) growth of tumors. Principles of classification of tumors.
10. Experimental study of etiology and pathogenesis of tumors: methods of induction, transplantation, explantation.
11. Etiology of tumors. Physical, chemical and biological carcinogenic factors. Properties of carcinogenic factors which determine their carcinogenic action.
12. Factors of risk (genetic/chromosome defects and anomalies of constitution) and condition of appearing and the development of tumors.
13. Physical carcinogenic factors. Main laws of blasthomogen action of ionizing radiation and ultraviolet rays.

14. Chemical carcinogens, their classification. Exo- and endogenous carcinogens. Chemical carcinogens action. Features of chemical structure of substances which determine their cancerogenicity.
15. Biological carcinogenic factors: mycotic (aphlatoxin), viruses. Classification of oncogenic viruses. Viral cancerogenesis. Experimental proofs of viral origin of tumors.
16. Pathogenesis of tumor growth. Stages of pathogenesis: initiator, procourse and progression.
17. Stage of transformation (initiator). Immortalization and damage of cellular mechanisms of division as basic events of tumor transformation. Mutational and epigenome mechanisms of malignant transformation. Disorder of the system of genes which provide a cellular division. Concept of protooncogenes, oncogenes (cellular, viral), genes-suppressors of cellular division. Methods of transformation of protooncogene into oncogene. Types of oncoproteins.
18. A role of apoptosis in pathogenesis of tumor growth. A concept about inductors and suppressors of apoptosis. Mechanisms of deviation of the transformed cells from an apoptosis. Characteristic of promotors of tumor growth (influences are hormonal, chemical matters, chronic irritation and other).
19. Stage of progression. Mechanisms of tumor progression.
20. Co-existance of tumor and organism. Influence of tumor on an organism. Mechanisms of cancer cachexia.
21. Mechanisms of natural antioncological defence, immune and nonimmune mechanisms of resistancy. Mechanisms of tumors escape from immune supervision.
22. Pathophysiological bases of prophylaxis and treatment of tumors.

The fever is the typical pathological process, which is manifested by increased body temperature due to the restructuring of thermoregulation in response to the action of pyrogenic factors.

The fever arose as a reaction to infection, so in addition to high temperature they also observe other signs of the infectious process. Intoxication and self-heating of the body make a complicated presentation, in which the manifestation of damage and protection are combined. However, the development of the fever may be a result of damage by agents of non-infectious origin (the aseptic fever).

The normal thermoregulation is carried out with the participation of a complex system of neurohumoral influences. On the periphery of the body (the skin, internal organs) there are the cold and heat receptors that perceive temperature fluctuations of the external and internal environments, the information from which comes to the thermoregulation center located in the hypothalamus. The located there neurons are sensitive both to heat and cold. Integration of temperature signals from the periphery and the temperature of the hypothalamus form the so-called fixed point, which in normal conditions is 37.2 °C, equal to the nucleus temperature (the internal organs), and the effector mechanisms determine the level

of heat supply due to changes of metabolism and muscle activity, and regulate the intensity of heat emission by changing the intensity of the peripheral circulation, sweating (perspiration) and loss of water from the surface of the lungs and mucous membranes. Thus, the fever starts with the restructuring of thermoregulation to a higher level, that is, the increase of the body temperature is achieved by the heat imbalance in the direction to accumulation of additional quantity of heat.

They distinguish between the infectious and non-infectious causes of the fever. In the process of evolutionary development the febrile reaction was formed primarily as a response of the organism to the penetration of microorganisms and their toxins. However, it is known that it may occur in the case of entering the body or formation of substances not related to infection, e.g. in the blood transfusions, use of proteins for parenteral nutrition, or in aseptic damage, etc.

Pyrogenic are substances, which penetrating into the body or being formed in it, determine the heat. By origin they are divided into exogenous (bacterial, abacterial) and endogenous (from the cells of macrophage-monocytic series, neutrophils, etc.); as for the mechanism of action they may be primary (inductive) and secondary (true). The primary pyrogens only initiate the process encouraging own leukocytic cells to the formation of proteins (secondary pyrogens), which, in turn, affect the mechanisms of thermoregulation and cause the fever. Thus, the primary pyrogens are etiological factors, the secondary pyrogens are pathogenetic.

The primary pyrogens enter the body together with infectious agents. Almost all bacteria (both gram-positive and gram-negative) as well as some viri, spirochetes, Rickettsiae, and fungi have the pyrogenic activity. The role of bacterial toxins (exotoxins, endotoxins) as the primary sources of pyrogens has been studied the best. It was installed, in particular, that the endotoxins of gram-negative bacteria are polysaccharides — the complex biopolymers. The ability to cause the fever has the lipid portion of lipopolysaccha-rides (lipoid A).

The primary pyrogens can be produced in the body regardless of infectious pathogens (the fever after a fracture, during the myocardial infarction, hemolytic crisis, etc.). These substances are formed as a result of damage or destruction of own tissues and affect the body as the primary exogenous, i.e., bacterial pyrogens.

PATHOGENESIS: The formation of endogenous pyrogens follows the penetration of the microbial ones. They are not damaged tissue products, but the products of endogenous protein synthesis. Endogenous pyrogen production is called *pyrogenesis.* It is realized by healthy leukocytes - macrophages (fixed and free monocytes), lymphocytes and neutrophils after their activation. Pyrogenesis is not realized in damaged leukocytes. If energy formation in leukocytes is damaged (under experimental conditions), as well as after protein synthesis blockade (by puromycin), pyrogenesis does not occur. Among different endogenous pyrogens *interleukin-1* is the most potent. It is a hormone-like protein, which is produced in macrophages and causes fever together with various other effects IL-1 plays an important role in inflammationAll the systems, which are responsible for immunity and inflammation, are sensitive to IL-1. Fever, immunity and inflammation are a triad, which determines organism reaction to infection. The connection between

them is so close that they do not exist without each other. It has been shown experimentally that IL-1 does not pass through the hematoencephalic barrier and does not reach the hypothalamus. At the level of the cerebral arteries and capillaries prostaglandins E, and E2 are formed, reach the hypothalamus and influence its function.

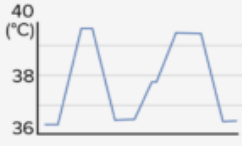
Thermal homeostatic control is one of hypothalamus functions. The organism
works as a biological thermostat, and the regulator (thermoregulatory center) is located in the hypothalamus. The function of the thermoregulatory center consists I in the maintenance of temperature homeostasis, balancing the processes of heat production and heat emission. This is based on the mechanism of establishing in the
hypothalamus of the so-called fixed point, according to which body temperature is regulated. The normal fixed point in man is about 36—37°C. Due to endogenous pyrogens the fixed point rises, and the hypothalamus regulates body temperature on another, more useful (for a new situation) level. Different types of infection have developed their fixed points in the process of evolution. It is very important to understand that a change of the fixed point is not a disorder of thermostatic control but its regulation on another level. After the fixed point reaches an adequate level, the hypothalamus sends regulatory impulses to proper organs, and additional heat is formed for body warming.

There are three mechanisms of heat accumulation during fever. *1. Limitation of heat emission* is the main mechanism. Spasms of the peripheral vessels, pale skin, decreased sweating and evaporation are noted.
2. Activation of heat production (thermogenesis) is an additional mechanism. Intensification of metabolism actually takes place, but to a less degree — about 35—
45 %. Contractile and noncontractile thermogenesis is actually intensified in fever, but insignificantly. Muscular tremor takes place. Glycogen is split off in the muscles and liver. *3. Disconnection (uncoupling) of oxidation* and *phosphorylation* allows to receive additional quantity of heat calories without additional consumption of oxygen.

Stages of Fever

Fever develops in three stages:

(1) body temperature increase (*stadium incrementi);*
(2) maintenance of high body temperature (*stadium fascigii*) with some fluctuations in the morning and evening;
(3) body temperature reduction (normalization) (*stadium decrementi).* The relationship between heat production and heat emission is different at these stages. At the first stage heat emission is less than heat production. At the second stage heat emission and heat production are equal. At the third stage heat emission considerably rises; vasodilatation, intense sweating and loss of water are noted.

Pattern type	Description	Associated diseases
Continuous fever	 Temperature continuously remains above normal, with daily fluctuations < 1°C.	• Typhus • Viral pneumonia
Remittent fever	 Temperature continuously remains above normal, with daily fluctuations ≥ 1°C.	• Typhus • Sepsis • Tuberculosis • Rheumatic fever
Intermittent fever	 Temperature remains above normal only for a certain period, later returning back to normal.	• Pleuritis • Sepsis
Biphasic fever	 Fever that breaks and returns twice a day	• Yellow fever • Dengue • Malaria • Typhoid • Leptospirosis
Undulant fever	 Temperature continuously remains above normal, with daily fluctuations ≥ 1°C.	• Brucellosis
Recurrent fever	 **Relapsing fever:** Days of fever followed by an afebrile period of several days and then a relapse into additional days of fever, usually after 14–21 days. **Pel-Ebstein fever:** Fever lasting 1–2 weeks followed by 1–2 weeks of an afebrile period **Periodic fever:** Fever that recurs over months or years; associated with the absence of infection of malignancy	• Pleuritis • Sepsis

Types of fewer patterns

DIFFERENCE BETWEEN FEVER AND HYPERTHERMIA

The fever should be distinguished from the overheating, or hyperthermia. Both processes are similar only in the final result — the increase of the body temperature, but their mechanisms are different. The overheating is not connected with the action of the pyrogenic substance. The body temperature rises due to the external impact, which limits the heat emission, or due to the primary dysfunction of the thermoregulatory center. The overheating of the body due to the detention of warmth in it is observed on the enterprises with high temperature of manufacturing environments or in the regions with the hot climate. The increased heat production because of the muscle activity and high humidity contribute to the overheating in such cases.

Compensation in the overheating process is aimed at eliminating of heat emission and maintaining of the thermal homeostasis. Since the ambient temperature is above 33 °C, the heat emission with convection is practically stopped, the process is carried out only by evaporation of the sweat and moisture during respiration. However, at high humidity the specified path is also closed, and all compensatory mechanisms become ineffective. The body temperature rises, but this is not the fever, because in the hyperthermia there is no restruction of the thermo-regulation, and its disorder or damage is observed.

EFFECT OF FEVER ON BODY ORGANS AND SYSTEMS

In addition to disorders of the thermoregulation in the fever there are also other manifestations, especially of the metabolism, functions of the cardiovascular, digestive and respiratory systems.

The most pronounced are changes of the ***circulatory system***. Under the rule of Von Liebermeister if the body temperature rises on 1 °C, it is accompanied by an increase of the pulse on 8—10 beats per minute. Because the local heating of the pacemaker of the heart rhythm causes the acceleration of the heart rate, the tachycardia on the background of the fever explains the same. In addition, the increased tone of the sympathetic nerves is of great importance. Rates of the heart beating and minute volume of the heart are also increased. In the first stage of the fever the blood pressure may increase with narrowing of the blood vessels of the skin and enlargement of the blood vessels of the internal organs. In the third stage in the case of the critical decrease of the body temperature the collapse may occur.

However, the tachycardia is not always observed. In some infectious diseases the temperature increases on the background of the bradycardia. An example is the typhoid and recurrent fever. These diseases are accompanied by the severe intoxication, when the heart responds not so much to the high body temperature, but to effects of the toxins of exogenous and endogenous etiology.

The ***external respiration*** in the first stage of the fever is somewhat slow. After reaching the maximum temperature of the body the breathing becomes faster, sometimes in 2—3 times. Because the depth of respiration decreases, the pulmonary ventilation has no major changes. The faster breathing (tachypnea) is the result of the increased brain temperature.

The ***digestive system*** in the fever is undergone significant changes, such as: the loss of appetite; inhibition of secretion of the salivary glands (the tongue is dry and coated); the volume and acidity of the gastric juice are reduced; there are disorders of the parietal digestion and peristalsis of the intestines. However, the extent of these changes is different and depends mainly on the nature of the disease and non-thermogenic effect of bacterial toxins. For example, during the influenza they are less pronounced than in the typhoid.

The fever is accompanied by dysfunctions of the ***endocrine system***: the pituitary-adrenal system is activated; there are signs of the stress. In the infectious fever there is hypersecretion of thyroid hormones; it leads to the increased basal metabolism.

In ***the central nervous*** system the processes of excitation and inhibition are broken. After the introduction of pyrogens the patients may have the insomnia, fatigue, and headache. These manifestations are higher in the infectious diseases. The hallucinations, loss of consciousness, and dizziness are possible. Because these symptoms occur with the moderate increase in the body temperature, then obviously, they are caused not so much by the increased body temperature, but by the intoxication.

The fever is characterized by changes of the ***water-electrolyte metabolism***. In the first stage there is the increased urine output due to increasing of the blood pressure and blood flow to internal organs, particularly to the kidneys. In the second stage of the fever as a result of intense synthesis of aldosterone and vasopressin in the tissues sodium and water are accumulated. So, the diuresis decreases. In the third stage the excretion of sodium chloride increases, there is the tissue dehydration, the diuresis and sweating increase.

Neoplasia is a typical pathological process, which is characterized by an unlimited (uncontrolled, independent and endless) increase of tissue growth, which does not correspond to the normal structure and function of the organism.

Cardinal sings for neoplasia are:

- ***endless growth*** (absence of the so-called limit of division, immortality);
- ***independence of growth,*** autocrine (own) regulation (tumor grows from itself, from one single transformed cell) infiltrating healthy tissues;
- ***anaplasia,*** reversion to a simpler, less differentiated form (like embryonic state);
- ***metastatic expansion.***

Classification

According to the clinical course and outcome, it is accustomed to divide tumors into ***benign*** (usually do not substantially impair the vital activity of the organism) and ***malignant*** (very often lethal). The former are characterized by expansive growth, when surrounding tissues are moved apart. The latter have an infiltrative growth pattern. Malignant tumors may be ***primary*** and ***metastatic.***

Etiology of tumors:

Cancer is not a single disease; hence it is reasonable to assume that it does not have a single cause. More likely cancer occurs because of integrations between multiple risk factors or repeated exposure to a single carcinogenic agent. Among the risk factors that have been linked to cancer are the following:

- chemical and environmental carcinogens
- cancer- causing viruses
- immunologic defects
- hereditary

Factors which are able to cause tumor growth are called *carcinogens.* Carcinogens are divided into *exogenous* and *endogenous* ones. *Exogenous carcinogens* in turn are subdivided into chemical physical and biological ones.

Chemical carcinogens

In humans, 80% of cancers are caused by chemical carcinogens. The main groups of chemical carcinogens include:

1.Polycyclic aromatic hydrocarbons (PAH) including benzpyrene and dimethylbenzantracene.

2. *Aromatic amines* including aniline and its derivatives such as beta-naphthylamine and dimetylaminoazobenzol.

3. *Nitrosamines* including dimethylnitrozamine and diphenylnitrosamine. Nitrosamines can cause cancer of the stomach or esophagus.

4. *Ackylating agents* including some drugs used in cancer chemotherapy as cytostatics (prokarlazene, melphalane).

5. *Aflotoxin B* that is the most potent carcinogen. It is synthesized by the fungus Aspergillus flavum and affects nuts, rice, and corn. It may cause cancer of the liver.

The mechanism of action of chemical carcinogens: Chemical carcinogens form highly reactive species, i. e. free radicals. The action of these reactive species tends to cause cell mutation (or alteration in synthesis of cell enzymes and structural proteins) in a manner that alters cell replication and interferes with cell regulatory controls.

Physical carcinogens

Ionizing radiation and *ultraviolet radiation* are physical carcinogens. The mechanism of action of physical carcinogenesis is damage to DNA causing transformation of a normal cell into a tumor one.

Biological carcinogens

A large number of DNA and RNA viruses (i.e. retroviruses) have been shown to be oncogenic in animals. However, only a few viruses have been linked to cancer in humans.

Among the recognized oncogenic viruses in humans are the following:

- human papilloma virus (HPV)
- Epstein- Barr virus (EBV)
- Hepatitis B (HBV)
- Human T- cell leukemia virus- 1 (HTLV- 1)

Three DNA containing viruses have been implicated in human cancers: HPV, EBV, and HBV.

HPV have been shown to cause:

• benign squamous papillomas (warts)

• squamous cell carcinoma of the cervix

EBV, a member of the herpesvirus family, has been implicated in the pathogenesis of four human cancers:

• Burkitt's lymphoma

• nasopharyngeal cancer

• B- cell lymphomas in immunosuppressed individuals such as those with acquired immunodeficiency syndrome (AIDS)

• some cases of Hodgkin's lymphoma

HTLV- 1, a retrovirus, is associated with a form of T- cell leukemia that is endemic in certain parts of Japan and some areas of the Caribbean and Africa and is found sporadically elsewhere, including the United States and Europe. Similar to the AIDS virus HTLV- 1 is attracted to the CD4+ T- cells and this subset of T- cells is therefore the major target for cancerous transformation.

The mechanism of action of biological carcinogens: A development of a tumor caused by an oncogenic virus includes the following stages:

• reception of a virus by a plasmatic membrane of a host cell;

• entering of a virus into the host cell;

• integration of a viral genome with cell genome; It is a central and obligatory stage of viral carcinogenesis. In a case if a virus is DNA- containing, integration of its DNA into cell DNA occurs. In a case if a virus is RNA- containing integration of DNA- provirus with cell DNA occurs.

• persistention of a virus into a cell genome (continuous presence)

• transformation of a host cell

• promotion

• progression

Endogenous carcinogens

Endogenous carcinogens can be formed inside the organism due to abnormalities in metabolism or hormonal dysfunction. The sources of endogenous carcinogens include cholesterol, bile acids, steroid hormones, and amino acid tryptophan. Some hormones, e.g., gonadotropin, the hormone which stimulates proliferation of ovarian cells may cause development of cancer if their production is excessive.

Pathogenesis of tumor growth or cancerogenesis includes three stages:

• initiation

• promotion

• progression

Initiation involves the exposure of cells to appropriate doses of a carcinogenic agent that makes it susceptible to malignant transformation. The carcinogenic agent produces irreversible changes in the genome of a previously normal cell. There are two classes of normal regulatory genes that control cell growth and replication:

• growth- promoting proto-oncogenes
• growth- inhibiting antioncogens

Both protooncogenes and antioncogenes have been implicated as the principal *targets of genetic damage* occurring during the development of cancer cells.

Protooncogens may transform into cancer- causing *oncogens* by retroviral transduction (v- oncs) or by influences that alter their ehavior in situ, thereby converting them into cellular oncogens(c- oncs).

Antioncogens, p53 and Rb tumor suppressor genes, encode nuclear proteins that suppress cell proliferation. Loss or inactivation of these proteins- by gene deletion or mutation or by binding to the oncoproteins of DNA tumor viruses- releases growth restraints and favors malignant transformation. Thus, activation of growth- promoting protooncogens or inhibition of cancer suppressor antioncogens causes expression of altered gene products (oncoproteins) and loss of regulatory gene products.

Promotion Cells that have been initiated may remain in inactive state for a long (latency) period. *Promotion* is stimulation of tumor induction, following initiation, by a promoting agent that may of itself be noncarcinogenic. For instance, estrogens can cause cells which have been previously transformed to proliferate with resultant monoclonal tumor.

Progression Over a period of time many tumors become more aggressive and acquire malignant phenotypic attributes, such as excessive growth, local invasiveness, and the ability to form distant metastases. This phenomenon is referred to as tumor *progression.* Despite the fact that most malignant tumors are monoclonal in origin, by the time they become clinically evident their constituent cells are extremely heterogenous. At the molecular level tumor progression and associated heterogeneity most likely result from accumulation of additional genetic lesions.

Tumor influence on organism, clinical manifestations of neoplasia. Neoplasia is a disease of the entire organism. As to its clinical manifestations, they depend on the form of the tumor and its localization (details are studied at clinical departments). Independently from localization, malignant tumor leads to extreme exhaustion, which is called *cancer cachexia.* It is caused by retention of glucose, carbon, nitrogen, amino acids by a tumor. All reserves are depleted. Neoplasm development is accompanied with intoxication by tissue decay products. Malignant cells produce substances (peptides), which activate apoptosis of healthy cells (for example, erythropoietic, resulting in *diserythropoietic anemia).*Anemia develops irrespective of the localization of malignant tumors. This anemia together with leukopenia appears to be the *hematological syndrome,* which accompanies neoplasia. *Immunological depression* provokes infectious diseases. In neoplasia pathogenesis, the state of the endocrine system matters. At old age the risk of neoplasia development rises. Uncontrolled synthesis of hormones sometimes occurs. Hormones themselves may become cancerogens. Patients lose weight. Lethal outcome is frequent.

KROK 1_mcqs (A is correct answer

1.A 25 year old man has spent a long time in the sun under high air humidity. As a result of it his body temperature rose up to 39oC. What pathological process is it?

A. Hyperthermia
B. Infectious fever
C. Hypothermia
D. Noninfectious fever
E. Burn disease

2.A patient has been diagnosed with influenza. His condition became drastically worse after taking antipyretic drugs. His consciousness is confused, AP is 80/50 mm Hg, Ps is 140/m, body temperature dropped down to 35, 8oC.What complication developed in this patient?

A. Collapse
B. Hyperthermia
C. Hypovolemia
D. Acidosis
E. Alkalosis

3. Chronic inflammation and transformation of the one-layer ciliated epithelium into multiple-layers flat epithelium was revealed in the thickened mucous membrane of the bronchus bioptate of the patient with smoke abuse. Which of the processes is the most likely?

A. Metaplasia
B. Hyperplasia of the epithelium
C. Squamous cancer
D. Leucoplacia
E. Epithelium hypertrophy

4. A patient who suffers from pneumonia has high body temperature. What biologically active substance plays the leading part in origin of this phenomenon?

A. Interleukin-I
B. Histamine
C. Bradykinin
D. Serotonin
E. Leukotrienes

5. A 52 year-old patient with bronchial asthma was treated with glucocorticoids. Fever reaction appeared as a result of postinjective abscess. The patient had subfebrile temperature, which didn't correspond to latitude and severity of inflammatory process. Why did patient have low fever reaction?

A. Inhibited endogen pyrogens production
B. Violation of heat loss through lungs
C. Inflammatory barrier formation in injection place
D. Violation of heat-producing mechanisms
E. Thermoregulation center inhibition

6. A 50-year-old patient with typhoid fever was treated with Levomycetin, the next day his condition became worse, temperature rose to 39, 60_. What caused the complication?

A. The effect of endotoxin agent
B. Allergic reaction
C. Irresponsiveness of an agent to the levomycetin
D. Secondary infection addition
E. Reinfection

7. A patient experienced a sudden temperature rise up to 390_. After 6 hours the temperature normalized. On the 2-ndday the attack recurred: in the period of paroxysm the temperature reached 41˚C,apyrexial period began after 8 hours. What type of temperature profile is it?

A. Intermitting
B. Recurrent
C. Hectic
D. Septic

E. Continued

8. A lightly dressed man is standing in a room, air temperature is +14˚*C*, windows and doors are closed. In what way does he emit heat the most actively?

A. Heat radiation
B. Heat conduction
C. Convection
D. Evaporation
E. Perspiration

9. A patient who suffers from pneumonia has high body temperature. What biologically active substance plays the leading part in origin of this phenomenon?

A. Interleukin-I
B. Histamine
C. Bradykinin
D. Serotonin
E. Leukotrienes

10.Workers of a hothouse farm work under conditions of unfavourable microclimate: air temperature is +37*oC*,relative humidity is 90%, air speed is 0,2m/s. The way of heat emission under these conditions will be:

A. Evaporation
B. Heat conduction
C. Convection
D. Radiation
E. All the ways

11. A 50-year-old patient has been administered laevomycetin for the treatment of typhoid fever, but on the next day the patient's condition worsened, the temperature rose to 39, 60C. The deterioration of the patient's condition can be explained by:

A. Effects of endotoxins of the causative agent
B. Allergic reaction
C. Insensitivity of the pathogen to laevomycetin
D. Secondary infection
E. Re-infection

12. A patient with lobar pneumonia has had body temperature of 39oC with daily temperature fluctuation of no more than 1oC for 9 days. This fever can be characterized by the following temperature curve:

A. Persistent
B. Hectic
C. Remittent
D. Hyperpyretic
E. Recurrent

13. The temperature in a production room is 36oC. Relative air humidity is 80%. Under these conditions the human body transfers heat mainly through:

A. Sweat evaporation
B. Heat conduction
C. Radiation
D. Convection
E. –

14. Thermometry revealed that the temperature of the exposed skin is by 11,5o lower than the temperature of the adjacent areas covered with clothing from natural fabrics. The reason for this is that the clothes reduce the heat loss through:

A. Convection
B. Radiation
C. Conduction
D. Evaporation
E. –

15. The processes of heat transfer in a naked person at room temperature have been studied. It was revealed that under these conditions the greatest amount of heat is transferred by:

A. Heat radiation
B. Heat conduction

C. Convection
D. Evaporation
E. ---

16. In a patient elevation of body temperature takes turns with drops down to normal levels during the day. The rise in temperature is observed periodically once in four days. Specify the type of temperature curve:
A. Febris intermittens
B. Febris continua
C. Febris reccurens
D. Febris hectica
E. Febris remitens

17. A patient has acute bronchitis. The fever up to 38, 5oC had lasted for a week, presently there is a decrease in temperature down to 37,0˚C. Specify the leading mechanism in the 3rd stage of fever:
A. Peripheral vasodilation
B. Increased heat production
C. Development of chill
D. Increased diuresis
E. Increased respiratory rate

18. Measurements of the arterial pCO2 and pO2 during an attack of bronchial asthma revealed hypercapnia and hypoxemia respectively. What kind of hypoxia occurred in this case?
A. Respiratory
B. Hemic
C. Circulatory
D. Tissue
E. Histotoxic

19. If strong oxidizers get into the bloodstream, a methemoglobin is formed. It is a compound, where iron (II) be comesiron (III).What has to be done to save the patient?
A. Interchangeable hemotransfusion has to be done
B. Patient has to be exposed to the fresh air
C. He has to be calmed down and put to bed
D. He has to be given pure oxygen
E. Respiratory centers have to be stimulated

20. Cyanide is a poison that causes instant death of the organism. What enzymes found in mitochondria are affected by cyanide?
A. Cytochrome oxidase (aa3)
B. Flavin enzymes
C. Cytochrome
D. NAD+-dependent dehydrogenase
E. Cytochrome P-450

21. The resuscitation unit has admitted a patient in grave condition. It is known that he had mistakenly taken sodium fluoride which blocks cytochrome oxidase. What type of hypoxia developed in the patient?
A. Tissue
B. Hemic
C. Cardiovascular
D. Hypoxic
E. Respiratory

22. A public utility specialist went down into a sewer well without protection and after a while lost consciousness. Ambulance doctors diagnosed him with hydrogen sulfide intoxication. What type of hypoxia developed?
A. Hemic
B. Overload
C. Tissue
D. Circulatory
E. Respiratory

23. A patient has the oxyhemoglobin dissociation curve shifted to the left. What blood changes induce this condition?

A. Alkalosis, hypocapnia, temperature drop
B. Acidosis, hypercapnia, temperature rise
C. Acidosis, hypercapnia, temperature drop
D. Acidosis, hypocapnia, temperature rise
E. –

24. After transfusion of 200 ml of blood a patient presented with body temperature rise up to 37,9^{o}C. Which of the following substances is the most likely cause of temperature rise?
A. Interleukin-1
B. Interleukin-2
C. Tumor necrosis factor
D. Interleukin-3
E. Interleukin-4

25. A patient who has been abusing tobacco smoking for a long time has got cough accompanied by excretion of viscous mucus; weakness after minor physical stress, pale skin. The patient has also lost 12,0 kg of body weight. Endoscopic examination of biosy material his illness was diagnosed as squamous cell carcinoma. Name a pathological process that preceded formation of the tumor:
A. Metaplasia
B. Hypoplasia
C. Hyperplasia
D. Necrosis
E. Sclerosis

26. A patient who abuses smoking has chronic bronchitis. Biopsy of his primary bronchus revealed multilayer pavement epithelium. What pathological process was revealed in the bronchus?
A. Metaplasia
B. Physiological regeneration
C. Reparative regeneration
D. Hyperplasia
E. Dysplasia

27. A female patient has been diagnosed with cervical erosion, which is a precancerous pathology. What defense mechanism can prevent the development of a tumor?
A. Increase in natural killer level (NK cells)
B. High-dose immunological tolerance
C. Increase in the activity of lysosomal enzymes
D. Simplification of the antigenic structure of tissues
E. Low-dose immunological tolerance

28. A 35-year-old female patient underwent biopsy of the breast nodules. Histological examination revealed enhanced proliferation of the small duct epithelial cells and acini, accompanied by the formation of glandular structures of various shapes and sizes, which were located in the fibrous stroma. What is the most likely diagnosis?
A. Fibroadenoma
B. Adenocarcinoma
C. Cystic breast
D. Invasive ductal carcinoma
E. Mastitis

29. Histological examination of the biopsy material obtained from the lower third of the esophagus of a 57-year-old male with the symptoms of continuous reflux revealed the change of the stratified squamous epithelium to the single layer columnar glandular epithelium with signs of mucus production. Specify the pathological process in the mucous membrane:
A. Metaplasia

B. Hyperplasia
C. Hypertrophy
D. Organization
E. Regeneration

30. A patient complains of pain in the right lateral abdomen. Palpation revealed a dense, immobile, tumor like formation. A tumor is likely to be found in the following part of the digestive tube:
A. Colon ascendens
B. Colon transversum
C. Colon descendens
D. Colon sigmoideum
E. Caecum

31. In cancer patients who have been continuously receiving methotrexate, the target cells of tumor with time become insensitive to this drug. In this case, gene amplification of the following enzyme is observed:
A. Dihydrofolate reductase
B. Thiaminase
C. Deaminase
D. Thioredoxin reductase
E. –

32. A 62 y.o. woman complains of frequent pains in the area of her chest and backbone, rib fractures .A doctor assumed myelomatosis (plasmocytoma). What of the following laboratory characteristics will be of the greatest diagnostical importance?
A. Paraproteinemia
B. Hyperalbuminemia
C. Proteinuria
D. Hypoglobulinemia
E. Hypoproteinemia

33. A 62 year old patient who previously worked as stoker was admitted to a hospital with complaints about general weakness, abrupt weight loss, hoarse voice, dyspnea, dry cough. Laryngoscopy revealed a tumor in the pharynx that invaded vocal cords and epiglottis. What is the most probable cause of tumor development?
A. Polycyclic aromatic carbohydrates
B. Nitrosamines
C. Aromatic amines and amides
D. Retroviruses
E. Ionizing radiation

34. This year influenza epidemic is characterised by patients' body temperature varying from 36, 9*oC* to 37, 9*oC*. Such fever is called:
A. Subfebrile
B. High
C. Hyperpyretic
D. Apyretic
E. Moderate

35. A person is in a room with air temperature of 38oC and relative air humidity of 50%. What type of heat transfer ensures maintenance of constant body core temperature under these conditions?
A. Evaporation
B. Radiation
C. Conduction and convection
D. Convection
E. –

36. In hot weather ventilators are often used to normalize the microclimate in the heated rooms. It leads to intensified heat transfer from the human body by means of:
A. Convection
B. Conduction and convection
C. Conduction
D. Radiation
E. Evaporation

37. A patient with pneumonia has body temperature of 39,2oC. What cells are the main producers of endogenous pyrogen that had caused such temperature rise?

A. Monocytes
B. Eosinophils
C. Neutrophils
D. Endotheliocytes
E. Fibroblasts

Tests for Self-Control
(give correct answers)

1. A woman fell ill with acute pneumonia. There is fever up to 39°C, general
weakness, dry cough appeared. What inflammation mediator has the properties
of an endogenous pyrogen?
A. Thromboxane A2.
B. Interleukin-1.
C. Histamine.
D. Serotonin.
E. Bradykinin.

2. A patient has a fever. Body temperature rises and keeps high from 1 till 3 a.m.
and then decreases to the normal level. Such fever is observed every fourth day.
What type of temperature curve is it?
A. Febris intermittens.
B. Febris continua.
C. Febris reccurens.
D. Febris hectica.
E. Febris remittens.

3. After overcooling the patient's body temperature increased to 39.7°C and rose
from 39°C to 39.8°C in 3 days. What type of temperature curve is it?
A. Febris hectica.
B. Febris reccurens.
C. Febris continua.
D. Febris intermittens.
E. Febris remittens.

4. A clinical examination of a patient allowed giving a preliminary diagnosis: liver
cancer. The presence of what type of protein in the blood will confirm the diagnosis?
A. y-Globulin.
B. Properdin.
C. Paraprotein.
D. C-reactive protein.
E. a-Fetoprotein.

5. Experimental animals received sodium nitrite with food. In 80 % of cases
tumors developed. What type of cancerogens does this substance belong to?
A. Nitrosamines.
B. Aminonitrocompounds.
C. Polycyclic aromatic hydrocarbons.
D. Simple chemicals.
E. Hormones.

6. A man has been working for a long time in the petroleum-refining industry.
What classes of carcinogenic agents did he contact?
A. Nitrosamines.
B. Aminonitrocompounds.
C. Polycyclic aromatic hydrocarbons.
D. Carcinogenic agents of biological nature.
E. Simple chemicals.

Recommended literature:

Basic

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Methodological instruction to practical lesson № 9
Module 1. General pathology

Theme: STARVATION. HYPOXIA

Student should know:

- Types of starvation.

Student should be able to:

- Differentiate the types of hypoxia and learn mechanisms of basic compensate reactions.

LIST OF CONTROL QUESTIONS

1. Definition of "Starvation". Types of starvation. External and internal causes.
2. Characteristics of metabolic disorders in certain periods of complete starvation with water. The pathophysiological features of partial starvation. Etiology and pathogenesis of partial starvation.
3. Protein-energy deficiency. Alimentary marasmus, kwashiorkor, alimentary dystrophy.
4. Factors affecting the resistance to starvation.
5. Definition "hypoxia". Classification of hypoxia.
6. Hypoxic hypoxia.
7. Hemic hypoxia.
8. Hemodynamic (circulative) hypoxia.
9. Hystotoxic (tissue) hypoxia.
10. Respiratory indexes of blood for hypoxias.
11. Immediate and long-term mechanisms of adaptation to hypoxia. Resistance to hypoxia. Mechanisms of hypoxic cell damage.
12. Modern principles of oxygen therapy. Toxic effects of oxygen.

Starvation is a typical pathological process, which is characterized by reorganization of metabolism and functions as a result of a decreased intake of food by the organism or a disorder of food utilization.

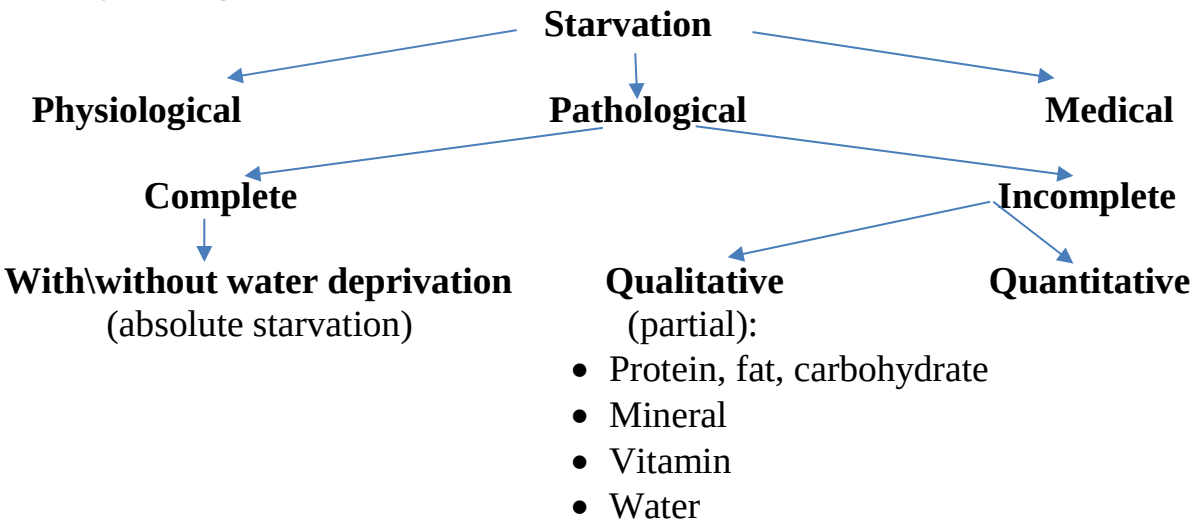

Fig.2 Classification of starvation

COMPLETE STARVATION WITHOUT WATER DEPRIVATION

This type of starvation is characterized by complete absence of food. Causes can be exogenous and endogenous.

The conditions**,** which determine the course and duration of starvation, are the
following:

• Environmental factors, which increase heat loss (decreased ambient temperature).

• Age (low resistance of newborns to starvation is explained by a high level of basal metabolism; small body size and less perfect regulation of metabolism and heat balance; longer duration of starvation in elderly people is determined by a decreased level of basal metabolism).

• Sex (women starve more easily).

• General state of the organism.

• Quantity and quality of lipid and protein reserves.

• Initial level of basal metabolism.

•Individual peculiarities of the organism connected with the character of the neurohumoral regulation and organism reactivity.

• Individual constitution.

• Animal species.

•Relationship between body surface and body weight

Clinical Periods. The four clinical periods of complete starvation are the following:

1. ***Indifference*** (4—6 hours in man, more in some experimental animals).
2. ***Excitation*** (connected with sensation of hunger and active hunting for food).
3. S***uppression*** (the most prolonged period).
4. ***Terminal,*** or the period of *paralysis and death* (3—4 days).
5. ***Restoration*** comes if starvation is stopped before the terminal period and nourishment is restored. In people fasting deliberately with a serious motivation, excitation and suppression may not take place.

Pathophysiological Periods. Three pathophysiological periods of complete starvation are distinguished on the basis of changes of metabolism and energy consumption. The respiratory quotient is used as an index. They are:

1. ***Uneconomical use of energy*** (2—4 days in man, respiratory quotient increases
   to 1).

2. Maximal adaptation (40—50 days in man, respiratory quotient decrease to 0.7).

3. Tissue decay, intoxication and death (3—5 days, respiratory quotient equals 0.8).

Starvation proceeds in two stages — compensation and decompensation.

The stage of compensation is such a stage when adaptive reactions prevail and homeostasis is maintained.

The stage of decompensation is such a stage, when defense reactions are exhausted and homeostasis fails. Pathological changes prevail.

Adaptive reactions are created in the process of evolution of adaptation to the absence of food and serve to maintain homeostasis and physiological functions under unusual life circumstances. They maintain: a) body temperature; b) blood glucose level; c) blood pH; d) ATP formation; e) function of the organs that work permanently — heart, organs of respiration, renal filtration, hormone production, etc.

The *first period* is a realization of the hunger instinct. It is an active stage, which provides an active search for food and preserves life. The duration of this period is 3—4 days.

Metabolism is activated. It is a period of uneconomical energy and substance expenditure. Basal metabolism increases as well as oxygen consumption. The respiratory quotient increases to 1. It means that oxidation and energy formation are provided by increased carbohydrate expenditure. It is carbohydrates that are utilized predominantly.

The blood glucose level is normal or temporarily increased. The reserve of glycogen (in the liver), which is used for energy formation, decreases quickly, during 6 hours of starvation. However, it does not disappear because it is formed as a result of glyconeogenesis. The glucocorticoidal function of the adrenal cortex is stimulated. Insulin secretion decreases, the activity of pancreatic a-cells increases with glucagon secretion. The excretion of nitrogen in the urine decreases (from 12—14 g to lOg daily) on the 2nd—3rd day of starvation. The negative nitrogen balance establishes.

The second period is the most prolonged one. Together with the first period, it is a ***stage of compensation*** but regulated by other mechanisms. The second stage is a stage of maximal adaptation. It is a period of economical utilization of substances and energy. The second period determines practically the whole course of starvation. Its duration depends on many factors mentioned above. In men it is 30-40 days and more. Metabolism demonstrates maximal adaptation and deep reorganization directed at economical expenditure of energy resources. *Basal metabolism* decreases by 10—20 % and remains at this level. Reserves of carbohydrates in the form of glycogen are exhausted after 5—6 days and metabolism is switching over to fat metabolism. Lipids are utilized predominantly. It is demonstrated by respiratory quotient decrease to 0.7. The organism receives about 80 % of energy as a result of fat oxidation, 3 % — from glucose oxidation, 13 % — from protein oxidation. Lipolysis is activated in the liver while lipogenesis is inhibited. *Transport lipemia* is observed. Free fatty acids come into the blood and other organs. In the liver and muscles fatty acids are transported through the mitochondrial membranes to the places of oxygenation. In glycogen exhaustion, ketone bodies production begins. Intensification of (3-oxygenation is marked in increased *ketone body concentration* in the blood. In 48—72 h of starvation the level of ketone bodies is 3 mmol/1.

As to the blood *glucose level,* it is nevertheless maintained normal in spite of the absence of food for many days and carbohydrate reserve exhaustion. It is provided by glyconeogenesis activation, which is registered in the kidneys and liver. 80 g of glucose is produced every day and half of this quantity is formed from glycerin (fat catabolism) and amino acids (protein catabolism). The level of insulin decreases resulting in the inhibition of hexokinase and Krebs cycle efficiency. A decrease of glucose entering the cells occurs in those tissues, in which the transport of glucose through the cellular membranes depends on insulin (myocardium, skeletal muscles and adipose tissue). It is these organs where lipid utilization increases. The brain gets a normal quantity of glucose. Catabolism is directed at provision of metabolism and function of the vitally important organs, especially of the brain, which needs 1.600—1.800 kcal/day provided by splitting of 100—150 g of glucose. It is very important to note that blood pH is maintained normal in spite of increased ketogenesis. Regulatory mechanisms join this process for ketoacidosis compensation. Ammonia, which is released by desamination, binds ketone bodies. Other mechanisms of acid-base regulation (acidogenesis and ammoniogenesis in the kidneys) are activated. *Non-respiratory (metabolic) acidosis* develops as a result of this, but it is compensated up to the terminal period of starvation. The amount of blood bicarbonates is decreased. The excretion of ammoniacal salts in the urine increases. The amount of oxidative water increases. As to proteins, they are generally preserved at this stage of complete starvation without water deprivation. Nitrogen excretion in he urine decreases to 7— 4 g reflecting the economical expenditure of proteins. Nevertheless, the *nitrous balance* is negative as a result of increased deamination and use of amino acids for glyconeogenesis and maintenance of the blood sugar level. At the same time, the possibility of protein synthesis for vitally important organs is preserved at the expense of protein splitting in other organs. It is provided by the so-called endogenous nourishment as an exclusive mechanism of adaptation in complete starvation.

The third period is a period of ***decompensation,*** the terminal one. Its duration is some days (about 3—5 days). It is a period of tissue decay, intoxication and death. The respiratory quotient increases in comparison with the previous period and equals 0.8. It means that proteins are used as a source of energy. There is an increased lysis not only of the proteins that are easily mobilized (blood proteins) but also of the stable proteins of the muscles. The decrease of body mass is accelerated again reflecting the destructive processes. There appear destructive changes in the mitochondria. The level of oxidative phosphorylation decreases in cells. A disorder of the enzymal systems, which are destructed in the process of starvation, provokes deep disbolism. The blood glucose level is less than 3 mmol/1.

Excretion of nitrogen, potassium and phosphorus in the urine increases. Their ratio in the urine is the same as in the protoplasm. Metabolic acidosis becomes decompensated

COMPLETE STARVATION AND WATER DEPRIVATION (ABSOLUTE)

Complete starvation with water deprivation has the same periods as complete
starvation without water deprivation, but it is severer and shorter (3—6 days). If water does not come from the outside, it is taken from the tissues. It is oxidative water. The largest quantity of water is produced by fat oxidation - 100 g lipids give 112 g of water, protein and carbohydrate oxidation provides half that quantity. The metabolic products, which are formed, require more water for their excretion and thus a vicious circle is formed, which approximates death. Catabolic processes are excessively activated, tissue decay products are accumulated, and intoxication develops.

QUALITATIVE (PARTIAL) INCOMPLETE STARVATION

Qualitative starvation develops when the content of one or some nutrient components (proteins, lipids, carbohydrates, minerals, vitamins, and electrolytes) in food is insufficient. The energy value of food is normal. Qualitative starvation is often combined with the quantitative one. Clinical manifestations are specific and depend on insufficient intake of certain substances.

In *carbohydrate* deficiency the liver becomes poor in glycogen resulting in ketogenesis due to lipid transport into the liver. Deficiency of *fats* in food is easily compensated by carohydrates and proteins used as a source of energy. However, to provide the plastic function of lipids, the organism should be necessarily supplied with indispensable fatty acids - arachidonic, linoleic and linolenic. It is also important to take into consideration that absorption of vitamins A, D, K is connected with lipids (liposoluble vitamins) and avitaminosis develops in fat starvation. *Protein* starvation is the most serious. Prolonged malnutrition with a primary
deficit of proteins in food leads to *protein calorie deficiency.* It causes severe alimentary dystrophy. In children it develops quicker than in adults as they have an increased need in proteins (*Kwashiorkor disease).* It harmfully influences the development of the nervous system in early childhood, when the nervous cells grow
intensively. Depression of the synthesis of nucleoproteids, proteins and decreased enzymal activity accompany prolonged protein insufficiency. The quantity of cells is diminished and atrophic processes develop in organs. The growth and development of bones is suppressed. Avitaminosis develops. It is a basis for anemia development. Basal metabolism is decreased. Hepatic lipid degeneration occurs. The pancreas undergoes hyalinosis and fibrosis. Dystrophic changes of the heart and kidneys take place. It often leads to death. Only rational nourishment can save a child.

Mineral starvation manifests itself through a deficit of important ions - potassium (nervous and muscle excitability is depressed), calcium (osteoporosis and tetania develop), iron (hypochromic anemia develops), cobalt (hemopoiesis

disorder), iodine (endemic goiter and hypothyroidism), fluorine (bone formation disorder).

Vitamin insufficiency (avitaminosis and hypovitaminosis) can be exogenous (as a result of the absence or a low content of vitamins in food) or endogenous. Vitamins B p B6, B12 and PP are important for the nervous system, vitamins B6, B5 and E — for the endocrine system, vitamin B12 — for hemopoiesis, vitamins B1 and PP - for the digestive system.

Here are some example of avitaminosis:

• Beriberi (deficit of vitamin Bj is manifested as polyneuritis and dystrophic changes in the nervous fibers and myelin layers).

• Pellagra (deficit of vitamin PP is manifested as dermatitis, damage of the mucous membranes of the digestive tract with diarrhea).

• Rachitis (deficit of vitamin D2 is manifested as a disorder of the absorption of calcium and phosphorus in the small intestine and renal tubules with a disorder of bone mineralization).

• Scurvy (deficit of ascorbic acid is manifested as a disorder of oxidative processes,
collagen synthesis, due to which the vessels lose solidity and easily break resulting in hemorrhage syndrome).

Hypoxia is a typical pathological process developing due to insufficient oxygen supply to tissues or impaired oxygen use resulting in energy (in the form of ATP) production disorder.

Classification:

According to localization, hypoxia is divided into ***local*** and ***systemic.***
According to clinical course, it may be ***acute*** and ***chronic.***
According to pathogenesis hypoxia is divided into 5 types including:

- ***Hypoxic*** hypoxia in which the partial pressure of oxygen in arterial blood is reduced;
- ***Hemic*** hypoxia in which the amount of haemoglobin available to carry oxygen is reduced;
- ***Circulatory*** hypoxia in which the circulation of blood is slow or diminished;
- ***Tissue*** hypoxia in which the ability of tissues to utilise the delivered oxygen is diminished;
- ***Combined*** hypoxia.

Hypoxic hypoxia

In hypoxic hypoxia, the arterial blood is insufficiently oxygenated and the oxygen tension is low with the result that the saturation of hemoglobin with oxygen is also below normal. Hypoxic hypoxia may be due to:

a) Low partial pressure of atmospheric oxygen (such as at high altitude or replacement of oxygen in the breathing mix in the modified atmosphere of a sewer);

b) Disturbance in respiration and in ventilation of the alveoli (due to disorders in the apparatus of external respiration e.g., in chronic obstructive pulmonary disease)

c) Hindered passage of oxygen through the alveolar- capillary membranes into the blood (e.g., in pulmonary fibrosis) Hypoxic hypoxia after reasons, which described in b) and c) also known as "**respiratory hypoxia**" Low pO2 in the arterial blood i.e., *hypoxemia* is a characteristic of this type of hypoxia.

Hemic hypoxia

In hemic hypoxia, the arterial pO2 is normal but the *oxygen- carrying capacity* of the blood is reduced due to a decrease in hemoglobin (in anemias) or due to inactivation of hemoglobin.

Accordingly, there are two forms of hemic hypoxia:

a) *anemic type* (a decrease in oxygen capacity of the blood); Due to hereditary defect of hemoglobin, or massive demolition of red blood cells;

b) *hypoxia in inactivation of hemoglobin* (a reduction in oxygen- binding ability of hemoglobin):

• Interaction of hemoglobin with carbon monoxide (CO) results in *carboxyhemoglobin* formation;

• Oxidation ferric up to a trivalent state by exogenous oxidants (nitro compounds, amino compounds, oxidation- reduction stains, medicinal preparations) results in *methemoglobin* formation;

• Interaction of hemoglobin with a hydrogen sulfide results in *sulf hemoglobin* formation. In this form of hypoxia a degree of saturation of present or functioning hemoglobin is normal, but total oxygen content of the blood is decreased.

Circulatory hypoxia

In circulatory hypoxia, oxygenation of arterial blood is normal, but the total volume of oxygen carried to the tissue per unit of time is decreased. This form of hypoxia may result from general circulatory disorders (in cardiac or vascular failure) or in local circulatory disturbances (in venous congestion or ischemia). Accordingly, there are two forms of circulatory hypoxia:

a) *stagnant*, when insufficient drain of venous blood is observed;

b) *ischemic*, when deficiency of arterial blood is observed.

Diminished oxygen in a venous blood and an *increased arterio- venous difference* are a characteristic of circulatory hypoxia.

Tissue (histotoxic) hypoxia

In tissue hypoxia, as distinct from all other forms, the transport of oxygen is undisturbed and its concentration in the blood is normal, but the *ability of the tissues to utilize the delivered oxygen is diminished.* This is due to:

- Oppression of a biological oxidation (deficiency of coenzymes such as NAD, FMN, ubichinone; deficiency of Fe, Cu);

- Blockage of transport of electrons on a respiratory chain: action of poisons (cyanides, CO, a hydrogen sulfide)
- Uncoupling of oxidation and phosphorylation.
- *Decreased arterio- venous difference* and increased oxygen in venous blood are a characteristic of this type of hypoxia.

There are two stages of hypoxia development — *compensation* and *decompensation.*

At the stage of compensation, normal oxygen supply to tissues is maintained due to compensatory reactions. The stage of decompensation develops when adaptation is exhausted and oxygen deficit takes place.

As hypoxia causes are too numerous and this pathological process is too widely spread, a lot of defense reactions have developed in the process of evolution and embrace almost all physiological systems, fist of all, the systems of transport and utilization of oxygen. Compensatory reactions are divided into immediate (urgent) and delayed (nonurgent, but long-term).

I. ***The reactions providing an adaptation to short- term acute hypoxia include:***

1. Respiratory reactions:

• increase in frequency of respiration;

• deepening of respiration;

• mobilization of the reserve alveoli.

2. Hemodynamics reactions:

• increase in frequency of the cardiac contractions;

• increase in volume of circulating blood (mobilization of the blood from its depots);

• increase in the venous inflow;

• increase in the systolic and minute volume of the heart;

• increase in speed of circulation;

• mobilisation of the reserve capillaries;

• redistribution of the blood (an increased inflow of blood to vitally important organs -

heart, brain);

3.Hematic reactions:

• increase in oxygenic capacity of the blood (mobilization of erythrocytes from the bone marrow and blood depots – relative erythrocytosis);

• activation of erythropoiesis (absolute erythrocytosis);

• increase in property of the blood hemoglobin to combine with oxygen;

• increase in dissociation of the oxyhemoglobin (owing to acidosis);

• appearance of fetal hemoglobin.

4.Tissue reactions:

• increase in the ability of the tissues to absorb oxygen;

• reduction in the functional activity of the organs;

• increase in interface of oxidation and phosphorylation;

• increase in anaerobic glycolysis;

•stabilization of the membranes of lysosomes (due to increased secretion of glucocorticoids).

II. The reactions ensuring the constant adaptation to the less expressed, but the long- term or repeated hypoxia:

1. Respiratory reactions:
• hypertrophy of the pulmonary tissue;
• hypertrophy of the respiratory muscles;
• hypertrophy of the neurons of the respiratory center;
• increase in diffusion of oxygen (increase in permeability of the alveolary capillary membranes).
2. Hemodynamics reactions:
• hypertrophy of the myocardium;
• formation of the new capillaries, especially in the lungs.
3. Hematic reactions:
• hyperplasia of the bone marrow (a proof increase in hemoglobin and erythrocyte amounts).
4. Tissue reactions:
• increase in amount of myoglobin (which is combined with oxygen even in its low amount in the blood);
• increase in quantities of the mitochondria per unit of mass of the cell (increase in capacity of the system of oxygen utilisation).

Principles of hypoxic state treatment

It is possible to raise resistance to hypoxia by:
• improving adaptive reactions (by training in a pressure chamber);
• decreasing the organism requirement of oxygen.

If oxygen utilization is normal, it may be added. It is possible to correct metabolic disorders with the help of specific antihypoxic preparations. They stimulate the transport of electrons in the respiratory chain (cytochrome) and inhibit free radical oxidation (antioxidants). The following preparations are in use — phosphorylated carbohydrates, blockers of calcium canals as well as the substances increasing glycolysis and reducing organism requirement of oxygen.

KROK 1_mcqs (A is correct answer):

1.Prolonged fasting causes hypoglycemia which is amplified by alcohol consumption, as the following process is inhibited:

A. Gluconeogenesis
B. Glycolysis
C. Glycogenolysis
D. Lipolysis
E. Proteolysis

2. A 10-year-old girl has a history of repeated acute respiratory viral infection. After recovering she presents with multiple petechial hemorrhages on the sites of friction from clothing rubbing the skin. What kind of hypovitaminosis has this girl?

A. C
B. B6
C. B1
D. A
E. B2

3. As a result of continuous starvation the glomerular filtration rate has increased by 20%. The most probable cause of the glomerular filtration alteration under the mentioned conditions is:

A. Decrease in the oncotic pressure of blood plasma
B. Increase in the systemic arterial pressure
C. Increase in the permeability of the renal filter
D. Increase of the filtration quotient
E. Increase of the renal blood flow

4. A comatose patient was taken to the hospital. He has a history of diabetes mellitus. Objectively: Kussmaul breathing, low blood pressure, acetone odor of breath. After the emergency treatment the patient's condition improved. What drug had been administered to the patient?

A. Insulin
B. Adrenaline
C. Isadrinum
D. Glibenclamide
E. Furosemide

5. Diseases of the respiratory system and circulatory disorders impair the transport of oxygen, thus leading to hypoxia. Under these conditions the energy metabolism is carried out by anaerobic glycolysis. As a result, the following substance is generated and accumulated in blood:

A. Lactic acid
B. Pyruvic acid
C. Glutamic acid
D. Citric acid
E. Fumaric acid

6. Pyruvate concentration in the patient's urine has increased 10 times from normal amount.
What vitamin deficiency can be the reason of this change:

A. Vitamin B1
B. Vitamin C
C. Vitamin A
D. Vitamin E
E. Vitamin B6

7. Pyruvate concentration in the patient's urine has increased 10 times from normal amount.
What vitamin deficiency can be the reason of this change:

A. Vitamin *B*1
B. Vitamin C
C. Vitamin A
D. Vitamin E
E. Vitamin *B*6

8. Hydroxylation of endogenous substrates and xenobiotics requires a donor of protons. Which of the following vitamins can play this role?

A. Vitamin C
B. Vitamin P
C. Vitamin *B*6
D. Vitamin E
E. Vitamin A

9. Glomerular filtration rate (GFR)increased by 20% due to prolonged starvation of the person. The most evident cause of filtration changes under this conditions is:

A. Decrease of oncotic pressure of blood plasma
B. Increase of systemic blood pressure
C. Increase of penetration of the renal filter
D. Increase of filtration coefficient
E. Increase of renal plasma stream

10. A person felt thirsty after staying under the conditions of hot weather for a longtime.
Signals of what receptors caused it first of all?

A. Osmoreceptors of hypothalamus
B. Sodium receptors of hypothalamus
C. Osmoreceptors of liver
D. Glucoreceptors of hypothalamus
E. Baroreceptors of aortic arch

11. A 10-year-old girl often experiences acute respiratory infections with multiple punctate hemorrhages in the places of clothes friction. Hypovitaminosis of what vitamin has the girl?

A. C
B. B6
C. B1
D. A
E. B2

12. Testosterone and it's analogs increase the mass of skeletal muscles that allows to use them for treatment of dystrophy. Due to interaction of the hormone with what cell substrate is this action caused?

A. Nuclear receptors
B. Membrane receptors
C. Ribosomes
D. Chromatin
E. Proteins-activators of transcription

13. A patient who has been strictly keeping to a certain diet for 10 days went through examination of respiratory coefficient. It was determined that it was equal1.What have the patient been keeping to?

A. With domination of carbohydrates
B. With domination of proteins and fat
C. With domination of fat and carbohydrates
D. Mixed
E. With domination of proteins and carbohydrates

14. Most participants of Magellan expedition to America died from avitominosis. This disease declared itself by general weakness, subcutaneous hemorrhages, falling of teeth, gingival hemorrhages. What is the name of this avitiminosis?

A. Scurvy
B. Pellagra
C. Rachitis
D. Polyneuritis (beriberi)
E. Biermer's anemia

15. Concentration of pyruvate is increased in the patient's blood, the most of which is excreted with urine. What avitaminosis has the patient?

A. Avitaminosis B1
B. Avitaminosis *E*
C. Avitaminosis B3
D. Avitaminosis *B*6
E. Avitaminosis B2

16. A 44-year-old woman complains of common weakness, heart pain, considerable increase of body weight. Objectively :moon-like face, hirsutism, AP-165/100 mm Hg, height - 164 cm, weight- 103 kg; fat is mostly accumulated in the region of neck, upper shoulder girdle, stomach. What is the main pathogenic mechanism of obesity?

A. Increased production of glucocorticoids
B. Decreased production of thyroidal hormones
C. Increased production of insulin

D. Decreased production of glucagon
E. Increased production of mineralocorticoids

17. A 4 y.o. child with signs of durative protein starvation was admitted to the hospital. The signs were as follows: growth inhibition, anemia, edemata, mental deficiency. Choose a cause of edemata development:

A. Reduced synthesis of albumins
B. Reduced synthesis of globulins
C. Reduced synthesis of hemoglobin
D. Reduced synthesis of lipoproteins
E. Reduced synthesis of glycoproteins

18. A woman who has been keeping to a clean-rice diet for a long time was diagnosed with polyneuritis (beriberi).What vitamin deficit results in development of this disease?

A. Thiamine
B. Ascorbic acid
C. Pyridoxine
D. Folic acid
E. Riboflavin

19. Removal of gall bladder of a patient has disturbed processes of *Ca* absorption through the intestinal wall. What vitamin will stimulate this process?

A. *D*3
B. *PP*
C. *C*
D. *B*12
E. *K*

20. Examination of a man who hadn't been consuming fats but had been getting enoughcarbohydrates and proteins for a long time revealed dermatitis, poor wound healing, vision impairment. What is the probable cause of metabolic disorder?

A. Lack of linoleic acid, vitamins *A*, *D*, *E*,*K*
B. Lack of palmitic acid
C. Lack of vitamins *PP*, *H*
D. Low caloric value of diet
E. Lack of oleic acid

21. Examination of a patient with frequent hemorrhages from internals and mucous membranes revealed proline and lysine being a part of collagene fibers. What vitamin absence caused disturbance of their hydroxylation?

A. Vitamin *C*
B. Vitamin *K*
C. Vitamin *A*
D. Thiamine
E. Vitamin *E*

22. Long-term starvation cure of a patient resulted in diminished ratio of albumin sand globulines in plasma. What of the following will be result of these changes?

A. Increase of ESR
B. Decrease of ESR
C. Increase of hematocrit
D. Decrease of hematocrit
E. Hypercoagulation

23. A patient suffers from vision impairment- hemeralopy (night blindness).What vitamin preparation should be administered the patient in order to restore his vision?

A. Retinol acetate
B. Vicasol
C. Pyridoxine
D. Thiamine chloride
E. Tocopherol acetate

24. A chemical burn caused esophagus stenosis. Difficulty of ingestion led to the abrupt loss of weight. In blood: 3, 0 · 1012/l, Hb -

106 g/l, crude protein - 57 g/l. What type of starvation is it?

A. Incomplete
B. Proteinic
C. Complete
D. Water
E. Absolute

25. A doctor examined a child and revealed symptoms of rachitis. Development of this disease was caused by deficiency of the following compound:

A. 1,25 [OH]-dichydroxycholecalciferol
B. Biotin
C. Tocopherol
D. Naphtaquinone
E. Retinol

26. During starvation muscle proteins break up into free amino acids. These compounds will be the most probably involved into the following process:

A. Gluconeogenesis in liver
B. Gluconeogenesis in muscles
C. Synthesis of higher fatty acids
D. Glycogenolysis
E. Decarboxylation

27. In order to accelerate healing of a radiation ulcer a vitamin drug was administered. What drug is it?

A. Retinol acetate
B. Retabolil
C. Prednisolone
D. Levamisole
E. Methyluracil

28. The gluconeogenesis is activated in the liver after intensive physical trainings. What substance is utilized in gluconeogenesis first of all in this case:

A. Lactate
B. Pyruvate
C. Glucose
D. Glutamate
E. Alanine

29. A 19-year-old female suffers from tachycardia in rest condition, weight loss, excessive sweating, exophthalmos and irritability. What hormone would you expect to find elevated in her serum?

A. Thyroxin
B. Cortisol
C. Mineralocorticoids
D. ACTH
E. Insulin

30. Thyrotoxicosis leads to increased production of thyroidal hormones *T*3 and*T*4, weight loss, tachycardia, psychic excitement and so on. How do thyroidal hormones effect energy metabolism in the mitochondrion of cells?

A. Disconnect oxidation and oxidative phosphorylation
B. Activate substrate phosphorylation
C. Stop substrate phosphorylation
D. Stop respiratory chain
E. Activate oxidative phosphorylation

31. Power inputs of a boy increased from500 to 2000 kJ pro hour. What can be the cause of
it?

A. Physical exercise
B. Raise of outer temperature
C. Mental activity
D. Food intake
E. Transition from sleep to wakefulness

32. A patient is followed up in an endocrinological dispensary on account of hyperthyreosis. Weight loss, tachycardia, finger tremor are accompanied by hypoxia symptoms - headache, fatigue, eye flicker. What mechanism of thyroid hormones action underlies the development of hypoxia?

A. Disjunction oxydation and phosphorilation
B. Inhibition of respiratory ferment synthesis
C. Competitive inhibition of respiratory ferments
D. Intensification of respiratory ferment synthesis
E. Specific binding of active centres of respiratory ferments

33. Inhabitants of territories with cold climate have high content of an adaptive thermoregulatory hormone. What hormone is meant?
A. Thyroxin
B. Insulin
C. Glucagon
D. Somatotropin
E. Cortisol

34. A pregnant woman with several miscarriages in anamnesis is prescribed a therapy that includes vitamin preparations. What vitamin facilitates carrying of a pregnancy?
A. Alpha-tocopherol
B. Folic acid
C. Cyanocobalamin
D. Pyridoxal phosphate
E. Rutin

35.To lose some weight a woman has been limiting the amount of products in her diet. 3 months later she developed edemas and her diuresis increased. What dietary component deficiency is the cause of this?
A. Proteins
B. Fats
C. Carbohydrates
D. Vitamins
E. Minerals

36.During regular check-up a child is determined to have interrupted mineralization of the bones. What vitamin deficiency can be the cause?
A. Calciferol
B. Riboflavin
C. Tocopherol
D. Folic acid
E. Cobalamin

37.During ascent into mountains a person develops increased respiration rate and rapid heart rate. What is the cause of these changes?
A. Decrease of O2 partial pressure
B. Increase of CO2 partial pressure
C. Increase of blood pH
D. Increase of nitrogen content in air
E. Increase of air humidity

38.A patient with a chemical burn has developed esophageal stenosis. The patient presents with acute weight loss due to problematic food intake. Blood test: erythrocytes - 3.0 · 1012/L, Hb-106 g/L, total protein - 57 g/L. What type of starvation does this patient suffer from?
A. Incomplete starvation
B. Protein starvation
C. Complete starvation
D. Water starvation
E. Absolute starvation

39.A hereditary disease - homocystinuria - is caused by disturbed transformation of homocysteine into methionine. Accumulated homocysteine forms its dimer (homocystine) that can be found in urine. What vitamin preparation can decrease homocysteine production?
A. Vitamin B12
B. Vitamin C
C. Vitamin B1
D. Vitamin B2
E. Vitamin PP

40. A 25-year-old young man came to the doctor complaining of general

weakness, rapid fatigability, irritability, reduced working ability, and bleeding gums. What vitamin is likely to be deficient in this case?
A. Ascorbic acid
B. Riboflavin
C. Thiamine
D. Retinol
E. Folic acid

Tests for Self-Control

(give correct answers)

1. An unconscious man was taken to the hospital after poisoning with carbon monoxide. Appearance of what substance in the blood provokes hypoxia?
A. Carboxyhemoglobin.
B. Methemoglobin.
C. Carbohemoglobin.
D. Oxyhemoglobin.
E. Lactate.

2. A blocker of cytochrome oxidase was injected to an experimental animal. The animal died immediately. What substance caused death of the animal?
A. Potassium oxalate.
B. Potassium nitrite.
C. Potassium sulphate.
D. Potassium phosphate.
E. Potassium cyanide.

3. At a height of 6000 m above the sea level a mountain climber experiences euphoria, inadequate assessment of the situation, hallucinations. What is the main cause of the development of these mountain sickness symptoms?
A. Dilating of the air in the frontal sinuses.
B. Snow ophthalmia.
C. Decrease of p0 2 in the air.
D. Decrease of pC0 2 in the air.
E. Exercise stress.

4. A 50-year-old man was taken from a closed room full of smoke from a fire. He was unconscious. What kind of hypoxia did the victim develop?
A. Hypoxic.
B. Respiratory.
C. Hemic.
D. Histic.
E. Circulatory.

5. A sportsman was climbing a mountain for several hours. At a height of 4800 m he suffered from dyspnea, palpitation, bursting headache. What is the cause of such signs?
A. Decrease of barometric air pressure.
B. Decrease of p0 2 in the air.
C. Lack of ventilation.
D. Gas embolism.
E. Decrease of air temperature.

6. A patient demonstrates a decreased amount of erythrocytes and hemoglobin in the blood, reduced color index, low concentration of iron in the serum, microanisocytosis, poikilocytosis. These changes are accompanied by hypoxia development. What kind of hypoxia is observed in this case?
A. Exogenous.
B. Hypoxic
C. Circulatory.
D. Hemic.
E. Respiratory.

7. Potassium cyanide solution was injected to an animal. What type of hypoxia developed in this case?
A. Hemic.
B. Respiratory.
C. Hypoxic.
D. Histic.
E. Circulatory.

8. A patient had a lung surgery. The heart stopped. Its regular contractions were restored only in 10 minutes. What organ suffered from hypoxia most of all?
A. Spleen.
B. Heart.
C. Liver.

D. Kidneys.
E. Brain cortex.
9. A 40-year-old man complains of fever, general sickness, headache, cough, dyspnea. After a clinical inspection a diagnosis of bronchopneumonia was given. What form of hypoxia is it?
A. Hemic.
B. Circulatory.
C. Respiratory.
D. Histic.
E. Hypoxic.
10. A 3-year-old child was diagnosed with Kwashiorkor disease. Such symptoms are observed: keratinization and desquamation of the skin, hepatic adipose infiltration. What type of starvation is observed in this case?
A. Carbohydrate.
B. Protein.
C. Mineral.
D. Vitamin.
E. Fatty.
11. The basal metabolism of a rat after 48 h of starvation without water deprivation has decreased by 20 %. The respiratory quotient is 0.7; there is lipemia, negative nitrous balance. What period of complete starvation is it (according to the pathogenetic classification)?
A. Uneconomical energy expenditure.
B. Maximal adaptation.
C. Terminal.
D. Indifference.
E. Excitement.
12. After 10 days of experimental starvation without water deprivation the body mass (of a rat) and basic metabolism have decreased by 40 %, the respiratory quotient is 0.8, there is acidosis, edemas, ketonemia. What period of complete starvation is it (according to the pathogenetic classification)?
A. Uneconomical energy expenditure.
B. Maximal adaptation.
C. Terminal.
D. Indifference.
E. Excitement.
13. After 10 h of starvation without water deprivation the basal metabolism of a rat increased, the respiratory quotient is 1.0, there is a high level of glucocorticoids and catecholamines in the blood. The content of nitrogen in the urine is high. What period of complete starvation are such symptoms typical of (according to the pathogenetic classification)?
A. Uneconomical energy expenditure.
B. Maximal adaptation.
C. Terminal.
D. Indifference.
E. Inhibition.
14. During starvation the mass of organs and tissues as a rule decreases. What organ loses more mass?
A. Brain.
B. Kidneys.
C. Liver.
D. Heart.
E. Muscles.

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