MINISTRY OF HEALTH OF UKRAINE
Zaporizhzhia State Medical University
Pathophysiology Department

PATHOGENESIS OF INFLAMMATION AND PERIPHERAL CIRCULATION DISTURBANCES

Module № 1. General Pathophysiology
Submodule 2. Typical Pathological Processes

Manual for independent work for the students of the 3rd course of international faculty speciality "General medicine" English medium of instruction

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CONTENT

Introduction

Inflammation is a frequent form of the typical pathological process that occurs when the body reacts to any pathological stimulus. The inflammatory process is also the leading pathogenetic link of many diseases, and its localization in one or another body often determines the specificity and nosological form of the disease.

Every doctor no mater what specialization he have inevitably observes inflammation manifestation. The protective role of inflammation is incontestable. If it were no inflammatory response infections will obviously gain generalized character and result in sepsis development, traumas will transform only to shock conditions and tissue defects will not be reconstructed at all. Meanwhile, the mechanisms of inflammation development usually cause secondary injuries for the tissues, so doctors are forced to use anti-inflammatory drugs in order to prevent pathologic manifestation of this process.

Inflammation is a typical pathological process that occurs as a result of tissue damage and is manifested by three interrelated events: alteration, violation of microcirculation with exudation and emigration and proliferation. This universal vascular-mesenchymal reaction was formed in the process of phylogenesis and has protective and adaptive meaning. It’s aim is to eliminate the flogogenous (inflammatory) factor and restore the damaged tissue.

The violations of peripheral circulation include arterial and venous hyperemia, ischemia, stasis, thrombosis and embolism. Their occurrence and development may be caused by both violation of the neuromuscular regulation of local blood circulation, and the pathology of the relative organs and tissues.

Disturbances of local blood circulation require a detailed study, because they are an important link in the pathogenesis of many diseases. Knowledge of the general patterns of their pathogenesis is necessary for successful treatment and prevention of relevant disorders.

THE AIM AND LEARNING OBECTIVES OF PRACTICAL CLASS

1. **General aim:** to study the pathogenic mechanisms ofinflammation:
2. **Learning objectives** (basic educational and training issues for extracurricular self-study):

1) Students should know:

a) causes and origins of the inflammation development;

b) the main inflammatory mediators (cellular and humoral), their origin, principles of classification, their main effects;

c) stages of peripheral circulation disturbance in the inflammatory site and mechanisms of their development;

d) stages, paths, mechanisms of leukocyte migration during inflammation;

e) stages of phagocytosis, its mechanisms and biological significance;

f) biological meaning of inflammation;

g) causes and mechanisms of development of the basic forms of peripheral circulation disturbances;

h) causes and mechanisms of development of the basic forms of microcirculation disturbances.

2) Students should be able to:

a) correctly interpret the main known theories of pathogenesis of inflammation;

b) characterize the biological significance of inflammation;

c) to solve situational problems on the basis of pathophysiological analysis of clinical and model situations related to the development of inflammation;

d)to evaluate the main clinical and pathophysiological signs of arterial

and venous hyperemia, ischemia, thrombosis, embolism, stasis;

e)explain the mechanisms of development of arterial hyperemia, venous hyperemia, ischemia, modelled in the experiment;

f) to solve situational problems on the basis of pathophysiological analysis of clinical and model situations related to the development of peripheral circulation and microcirculation.

QUESTIONS TO STUDY:

1. Inflammation: definition, etiology, stages, signs.

2. Mediators of inflammation

3. Vascular events in inflammation

4. Cellular events in inflammation

5. Regeneration and repair mechanisms. Classification of inflammation

6. Chronic inflammation.

7. Disturbances of peripheral circulation. Arterial hyperemia

8. Disturbances of peripheral circulation.Venous hyperemia

9. Disturbances of peripheral circulation.Ischemia.

10. Disturbances of microcirculation. Stasis.

11. Disturbances of peripheral circulation.Thrombosis

12. Disturbances of peripheral circulation.Embolism

THEORETICAL MATERIAL

1. Inflammation: definition, etiology, stages, signs.

Inflammation is a local manifestation of the organism general reaction to the damage. Inflammation is a typical pathological process arising in any tissue and organ. The protective role of inflammation is incontestable. If there was no inflammatory response, infections will obviously gain generalized character and result in sepsis development and tissue defects will not be reconstructed at all.

The causes of inflammation are divided according to the origin: **exogenous** and **endogenous**, **infectious** and **non-infectious**.

Exogenous infectious factors include bacteria, viruses, ricketsia, parasites, fungi, etc.

Exogenous non-infectious factors include:

- physical (temperature, electricity, radiation, mechanical trauma);
- chemical (toxins, poisons, acids, alkali);
- biological (foreign proteins, psychic factors, animal poisons, transplantation of the tissues and organs).

The following **endogenous** factors cause inflammation:

- products of tissue decay as a result of mechanical trauma, burns, frostbites, infarctions, hemorrhages, thrombi, malignant tumors, immune complexes.
- endogenous chemical agents – the products of normal or disturbed metabolism if they are not eliminated from the organism. For example, renal failure results in accumulation of uric acid through the whole body and it leads to the development of inflammation in the lungs, GIT, and skin.

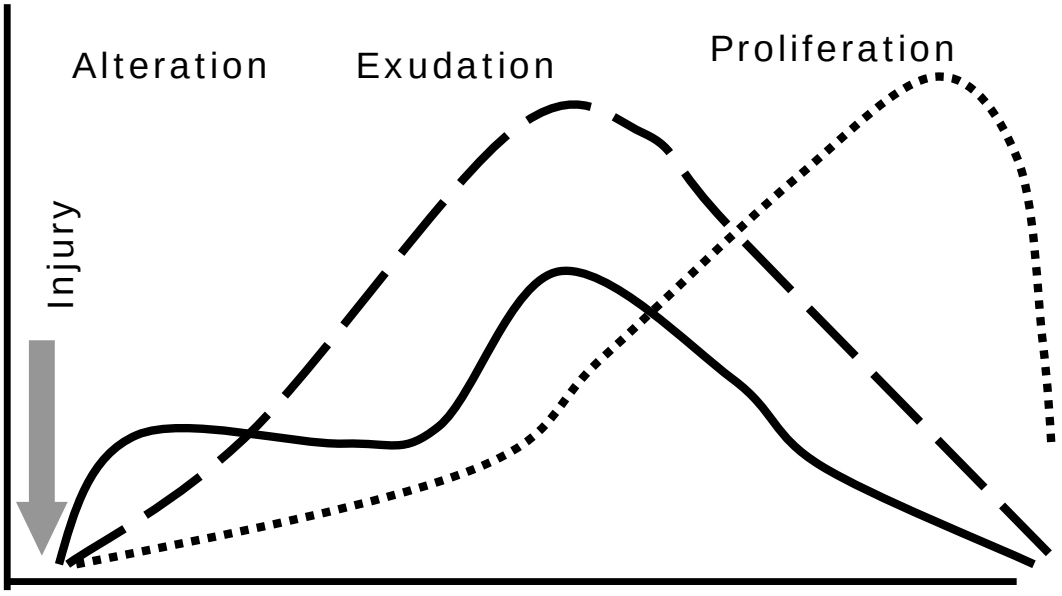

Figure 1. Interrelation between the inflammatory events

We can describe inflammation as the consecution of the following events or **stages: alteration** (primary and secondary), **exudation** (vascular reactions, vascular leakage, leukocyte exudation and phagocytosis) and **proliferation**.

Such consequence of events is typical only for the acute forms of in flammation.

Inflammation is characterized by the local and systemic signs.

The **local signs of inflammation** are:

- Calor (heat) – caused by increased intensity of metabolism in the site of inflammation;
- Rubor (redness) – due to dilation of arterioles, caused by the accumulation of metabolites
- Dolor (pain) – due to influence of specific mediators (histamine, kinines and prostoglandines) and possibly due to compression of pain receptors by exudate;
- Tumor (swelling) – caused by vascular leakage of fluid into the tissue - exudation;
- Functio laesa (loss of function) – caused by the disturbances of blood circulation, innervation, influence of inflammatory mediators and alteration of

metabolic processes in the site of inflammation.

The first four symptoms had been described many centuries ago by Roman doctor Caelcus, and later, Greek scientist Galen added the fifth sign “functio laesa” that means disturbances in functions of injured tissue.

The **systemic signs of inflammation** are:

- peripheral blood leukocytosis – it is caused by activation of leukopoiesis in the red bone marrow – leukocytes play the main role in the pathogenesis of inflammation;
- fever – leukocytes activated in the process of inflammation synthesize and release secondary pyrogens which shift the set point of the hypothalamus thermoregulation center;
- increase of blood proteins level (globulins) – reflects activation of immune response during inflammatory process and synthesis of immunoglobulins;
- increase of erythrocytes sedimentation rate – occurs due to increased amount of immunoglobulins in the patient’s blood which make complexes with erythrocytes that settle down in the test tube;
- increase of cateholamins and corticosteroids blood level – confirms active participation of endocrine system in the pathogenesis of inflammation and gives us an evidence of general character of inflammatory responce.

Alteration. Physical and chemical changes at inflammatory site

Alteration is the first phase of inflammation. It is characterized with the damage of tissues and cells in the site of inflammation.

Primary alteration is caused by the direct action of pathogenic factor. It initiates the inflammation and includes damage of cell membranes, release of intracellular enzymes, disturbances of water and electrolyte metabolism, disturbance of energy metabolism in the damaged tissue. The important result of primary alteration is the synthesis and activation of inflammatiory mediators that are responsible for vascular reaction at the inflammation and the beginning of

exudation.

Secondary alteration is mostly the result of primary alteration influence. It is mediated with the following mechanisms:

- disturbances of local nervous regulation (damage of peripheral nerves, disturbances with the synthesis and accumulation of neuromediators);
- step by step changes in microvascular bloodflow – disturbances of blood circulation;
- influence of inflammatory mediators and changes of physical and chemical parameters in the site of inflammation.

In many cases alteration develops with the help of so-called **lysosomal effect**. Lysosomal enzymes, released from destructed cells, injure the structures of the neighboring cells leading to their death.

All the **metabolic processes** (the "fire of metabolism") are sharply intensified and qualitatively changed in a focus of inflammation.

The alteration of **carbohydrate metabolism** manifests as activation of glycolysis in order to increase energy supply for the tissues in the site of inflammation. It leads to metabolic acidosis development.

Lipid metabolism is characterized with the activation of lipolysis and braking of lipids synthesis. It results in formation of toxic lipid metabolism products and arachidonic acids metabolites (leukotriens and prostaglandins) which regulate the process of inflammation.

Protein metabolism is also characterized with the prevalence of proteolysis and braking of proteins synthesis. The consequences of such changes are destruction of pathogenic proteins, activation of immune reactions in the site of inflammation. The products of proteolysis will further serve as a substrate for proteins re-synthesis in reparation process.

Generally, the rate of metabolism is usually increased many times in the site of inflammation. catabolic reactions prevail at the early period of inflammation,

and anabolic – at the final stages. The speed of metabolic reactions is very high due to the temperature increase. The prevalence of catabolic processes and high speed of reactions result in the accumulation of suboxidized products in the site of inflammation. It is manifested as metabolic acidosis (low pH) development, increase of osmotic (accumulation of ions) and oncotic (accumulation of proteins and products of proteolysis) pressure. Increased osmotic and oncotic pressure, in its turn, causes local intracellular and extracellular hyperhydration.

2. Mediators of inflammation

Inflammation mediators are biologically active substances which determine the development and the end of inflammation. The role of these mediators is activation of inflammation mechanisms and coordination of interactions between cells participating in inflammatory process. Almost all mediators perform their biological activity by initial binding to specific receptors on target cells.

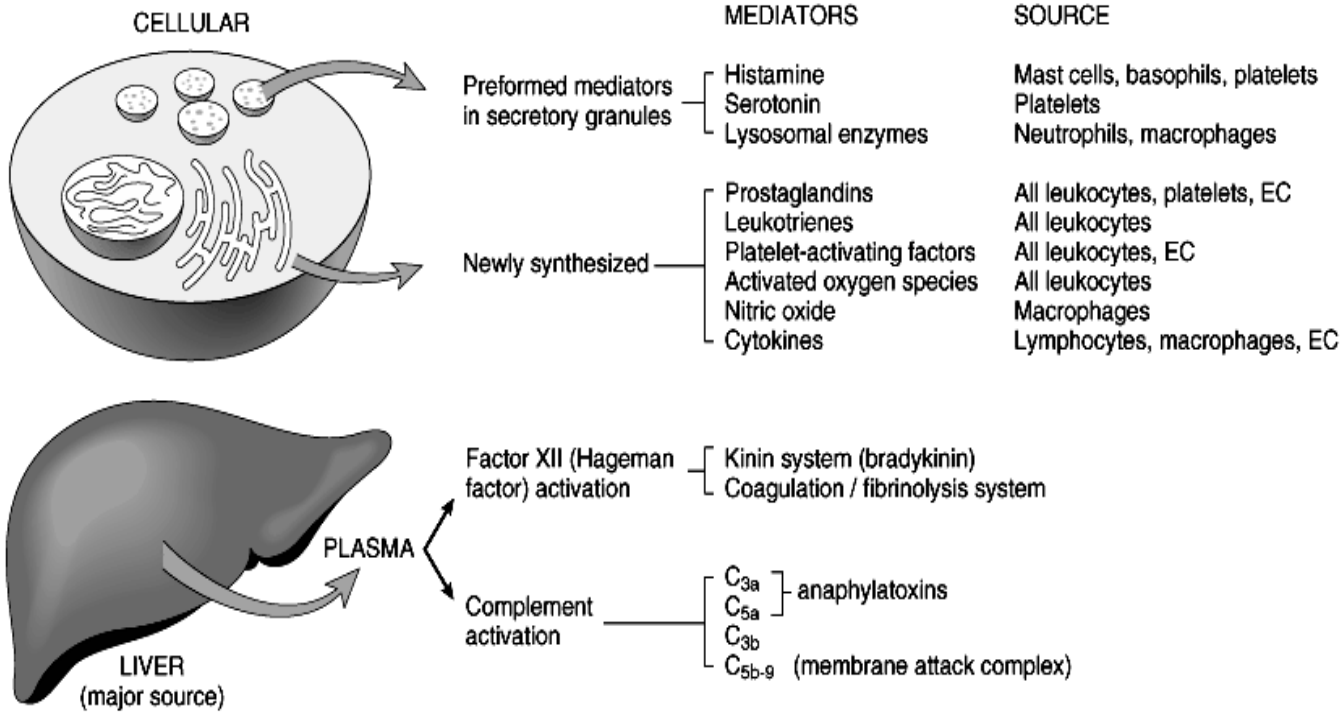

Figure 2. Sources of inflammatory mediators

The sources of inflammatory mediators are cells and blood plasma. **Cell-derived mediators** are divided into:

- preformed, sequestered in intracellular granules (histamine), which need to be secreted;
- newly synthesized (prostaglandins) in response to a stimulus.

Cellular mediators:

- histamine, serotonin;
- arachidonic acid metabolites **(**prostaglandins, leukotrienes);
- leukocytes products (cytokines, platelets activating factor, activated oxygen species, nitric oxide and lysosomal enzymes).

Histamine It's a biogenic amine, the product of aminoacid histidine decarboxilation. The main tissue storage of histamine are the mast cells of the connective tissue. Any kind of injury, mechanical, chemical, radiation or some biological active substances and toxins, including bacterial toxins, can provoke mast cell degranulationand histamine release from their granules. In turn, via H-1 receptors histamine acts to the endothelial cells that provokes the fist short-termed phase of vessels permeability and vasodilation. Vasodilation isn't direct property of histamine, but is also mediated by NO synthesizing in the endothelial cells. It must be added, that only NO and PgI-2 are the real vasodilators, but other biological active substances act to the H-1 receptors to synthesize NO with it's following vasoactive effect of vasodilation.Histamine supports an axon reflex due to mast cells degranulation. Last may be triggered by substance P-releasing from nociceptive endings when they are exitated by injuring factors. Moreover, histamine is a potent spasmogenic and algesiogenic substance, and it can provoke a pain, rather in form of itching..

Serotonin It's biogenic amine too, but it is mostly released by the platelates from aminoacid tryptophan. Its role in inflammation isn't such clear as a role of histamine, the universalmediator of injury, but it is known that serotonin increases the vessels permeability and provokesspasm of veinules, and in such way,

contributes to edema formation . It's realized through the weakness of exflux of the blood from the site of inflammation that increases hydrostatic pressure in microcirculatory bed. Serotonin also can cause pain.

Arachidonic acid (AA) metabolites.

When cells are activated by diverse stimuli, their lipid membranes can be rapidly remodeled to generate biologically active lipid mediators which have a variety of biologic processes some of which are seen in inflammation and hemostasis. These lipid mediators are thought to be short-range hormones that are formed rapidly and exert their effects locally and then are inactivated.

AA is a fatty acid that is present in large amounts in phospholipids of the cell membrane. It is released from membrane phospholipids due to the activation of cellular phospholipases by inflammatory stimuli or by other chemical mediators. AA metabolism proceeds along two major pathways, which are named after the enzymes that initiate the reaction. These arachidonic acid metabolites are collectively termed **eicosanoids**.

Cyclooxygenase pathway yields in three important products:

- Thromboxane A2 found in platelets and other cells is a potent platelet aggregator and vasoconstrictor
- Prostacyclin (PGI2) found predominantly in endothelial cells is a potent inhibitor of platelet aggregation and vasodilator.
- Prostaglandin effects are dilatation of vessels, the increasing of vessels permeability, the aggregation and adhesion of blood cells, fever development. Prostaglandins can also cause pain.

It should be noted that non-steroid anti-inflammatory drugs (aspirin, indomethacin) have anti-inflammatory properties because they inhibit the cyclooxygenase pathway of AA (inhibit biosynthesis of prostaglandins). Lipooxygenase is not affected by these antiinflammatory agents.

Lipooxygenase pathway yields in leukotrienes formation. Leukotrienes cause

vasoconstriction, bronchospasm, increased vessels permeability. Leukotrienes are up to 1000 times as potent as histamine in producing increased vascular permeability. They are also chemotaxins for neutrophiles and cause bronchospasm. The old name for these compounds was "**slow reacting substances of anaphylaxis**." To sum it up, prostaglandins and leukotrienes can mediate every step of acute inflammation.

Leukocytes products are produced by activated lymphocytes and monocytes.

Cytokines are polypeptide mediators which include interleukins, tumor necrosis factor and interferons.

Interferons (IFNs) are a class of natural proteins produced by immune cells in response to challenges by foreign agents such as viruses, bacteria, parasites and tumor cells. They generally have several effects: antiviral and antioncogenic properties, macrophage and natural killer lymphocyte activation.

Interleukins are a group of cytokines that were first seen to be expressed by leukocytes as a means of communication. Now it is known that interleukins are produced by a wide variety of body cells.

TNF (tumor necrosis factor) – is a pro-inflammatory cytokine that is produced by WBC and has an antineoplastic effect.

The **functions of cytokines** can be divided into the following groups:

- Mediation of natural immunity (IL-1, 6 and 8, TNF, a-interferons;
- Antiviral activity (interferons);
- Initiation of non-specific inflammatory response (IL-1, TNF, IL-8);
- Regulation of lymphocyte growth, activation, and differentiation (IL 2, 4);
- Activation of inflammatory cells (IFN-y, TNF-a, lymphotoxin, IL-5);
- Stimulation of hematopoiesis (granulocyte-macrophage stimulating and granulocyte stimulating factors);
- Increase of fibroblasts proliferation, collagen synthesis (IL-l).

It should be noted that some cytokines such as **IL-l** and **TNF** have a plenty of

effects.

Cytokines induce their effects in three ways:

1. They act on the same cell that produces them (**autocrine effect**), such as occurs when IL-2 produced by activated T cells promotes T-cell growth,

2. They affect other cells in their neighboring (**paracrine effect**), as occurs when IL-l produced by antigen-presenting cells affects T cells during the induction of an immune response

3. They affect many cells systemically (**endocrine effect**), the best examples in this category being IL-l and TNF-a, which produce the acute-phase response during inflammation (fever, increase acute phase protein amount).

Platelet activating factor is produced by a variety of cells, including platelets, basophils, mast cells, neutrophils, monocytes, macrophages and endothelial cells following necessary stimuli. Its effects are:

- Platelet aggregation and release;
- Bronchoconstriction and vasoconstriction;
- Vasodilation and increased vascular permeability;
- Increased leukocyte adhesion to endothelium;
- Leukocyte chemotaxis, degranulation and oxidative burst.

Activated neutrophiles and macrophages release **active oxygen radicals** which may contribute to inflammation by the following influences:

1. Endothelial cells damage resulting in increased vascular permeability;

2. Inactivation of antiproteases (such as antitripsin), which may lead to increased protease activity;

3. Injury of other cell types (red cells, parenchymal cells).

Lysosomal enzymes include elastase, collagenase, cathepsin which can mediate tissue injury, activate bradykinine generation, cause mast cells degranulation, possess chemotactic activity for moniocytes.

Nitric oxide produced by endothelium, macrophages and other cells causes

vasodilatation and is potentially cytotoxic both on parasites, bacteria, and own cells.

Plasma-derived mediators are present in plasma in precursor forms that should be activated to acquire their biological properties.

The **kinin system** generates vasoactive peptides from plasma proteins called kininogens by the action of specific proteases called kallikreins. This system results in the ultimate release of the vasoactive peptide bradykinin. Bradykinin has the following actions:

- Potent vasodilator;
- Increased vascular permeability due to the contraction of endothelial cells and extravascular smooth muscles contraction;
- Contraction of smooth muscles;
- Produces pain;
- Stimulates release of histamine from mast cells;
- Activate the arachidonic acid cascade reactions;
- Simulates phagocytes chemotaxis to the inflammation site.

The complement system consists of a series of plasma proteins that play an important role both in immunity and inflammation. Complement components present as inactive forms are numbered C1 to C9. The complement system can be activated by antigene-antibody reactions (through the classic pathway) or by other products, especially bacterial polysaccharides (through the alternative pathway). Complement-derived factors affect the following phenomena:

- Vascular phenomena. C3a and C5a increase vascular permeability and cause vasodilatation by releasing histamine from mast cells. C5a also activates lipooxigenase pathway of AA metabolism in neutrophiles and monocytes.
- Chemotactic influence on neutrophiles and monocytes (C5a).
- Phagocytosis. C3b, when fixed to bacterial cell wall, acts as an opsonin and favor phagocytosis by neutrophiles and macrophages, which bear cell surface receptor for C3b.

The clotting system and inflammation are closely connected. The intrinsic clotting system is a sequence of plasma proteins that can be activated by Hageman factor (factor XII). The final phase of the cascade is the conversion of fibrinogen into fibrin by the action of thrombin. During this conversion fibrinopeptides are formed which induce increased vascular permeability and are chemotactic for leukocytes. **Fibrin** binds to specific receptors on platelets, endothelial cells and smooth muscle cells as well as other cells. This binding produces the following effects: induction of cyclooxygenase-2 with subsequent production of prostaglandins; production of platelet activating factor and nitric oxide

Plasmin, the component of fibrinolytic system, which is important in lysing fibrin clots, has the following actions in the context of inflammation: activation of kinin system, degradation of fibrin to fibrinopeptides.

The summary of inflammatory mediators' activity:

Vasodilatation: histamine, bradykinin, prostaglandins, nitric oxide;

Increase of vessels permeability: histamine, bradykinin, C5a, leukotrienes;

Leukocyte adhesion: IL8, C5a, TNFα;

Chemotaxis: IL8, bacterial toxins, C3, C5;

Fever: IL1, TNF;

Tissue damage: oxygen free radicals, lysosomal enzymes;

Pain: Prostaglandins & bradykinin.

3. Vascular events in inflammation

Changes in vascular flow begin very early after the injury as a result of tissue alteration. They occur in the following order:

- Arterioles constriction
- Arterial hyperemia
- Venous hyperemia and pre-stasis
- Stasis.

The primary effect of injuring agent influence on the tissue results in a short-term (for a few seconds) increase of smooth muscles tone of the arterioles and pre-

capillaries. **Vessels constriction** or **spasm** is provided both with the activation of sympathetic nerves caused by alteration and with mediators influence (such as prostaglandis and leukotriens). The role of arterioles constriction is the localization of injuring agent and prevention of its spreading in the body.

The next stage is **arterial hyperemia** which is caused by dilation of pre-capillaries and arterioles diameter and is characterized with increased arterial blood inflow to the site of inflammation. Arterial hyperemia is mediated with vasoactive substances that cause vasodilatation. Bloodflow of the inflammation site is increased that is clinically manifested as heat and redness. The number of opened capillaries increases too. Increased arterial blood inflow brings more oxygen, mediators and immune cells to the inflammation site and helps to activate the general rate of metabolism.

Long vasodilatation is followed with the slowing of circulation and venous hyperemia development. **Venous hyperemia** is manifested as dilation of venules and post-capillaries. After some time penduliform movements of blood in the vessels (forward and backward) appear. Such movements are a sign of **pre-stasis** development.

Venous hyperemia is caused by the following reasons:

- Blood viscosity is increased with the leakage of protein-reach fluid into the extravascular tissues. It results in the concentration of blood cells and activation of thrombi formation.
- Vessel wall becomes swollen (impaired water ion metabolism) and its elasticity is decreased.
- Venules are squeezed with inflammatory exudates.

• The diameter of the venules is decreased due to leukocytes margination along the vessels walls.

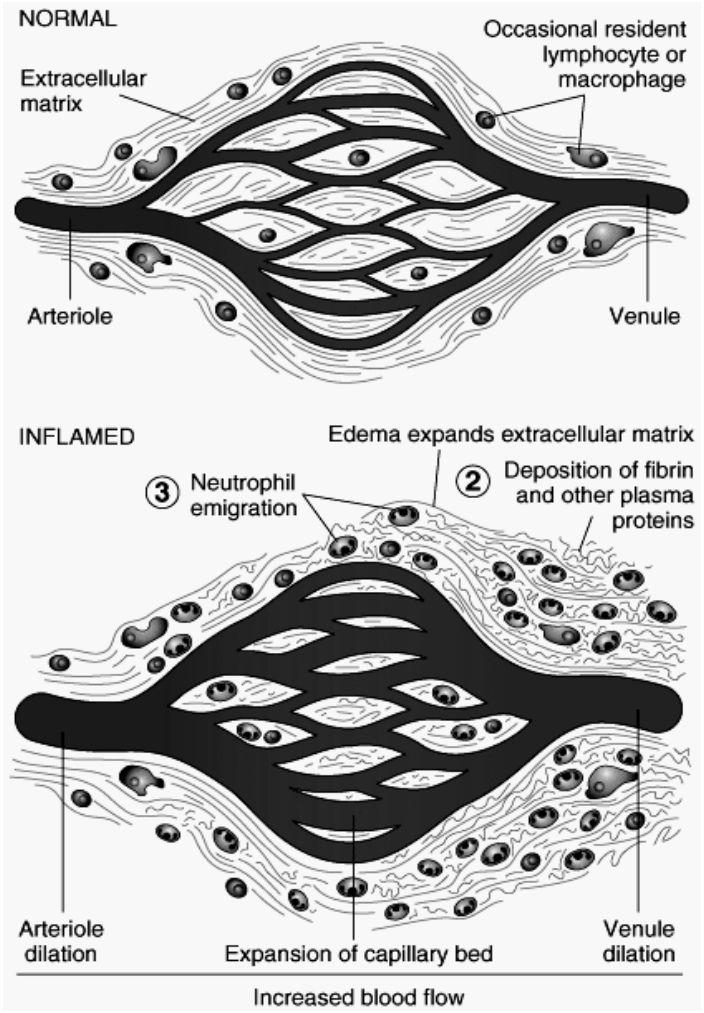

Figure 3. Microcirculation in the site of inflammation

The development of **stasis** is characterized by the peripheral orientation of blood cells in vessels (normally they possess central part of the vessel), thrombosis and complete stop of bloodflow.

The meaning of venous hyperemia and stasis development is isolation of damaged tissues (microbes, toxins, products of tissue decay, mediators are localized that prevents the surrounding tissues damage).

Exudation

Arterial and venous hyperemia are accompanied by the increase of vascular permeability and exudate formation.

The main mechanisms **of exudation** are:

- **Increased vascular permeability (vascular leakage);**
- **Increased intravascular hydrostatic pressure;**
- **Increased osmotic and oncotic pressure of interstitial fluid.**

Taken together these mechanisms lead to a marked outflow of fluid and its accumulation in the interstitial tissue with inflammatory edema development.

The most important feature of acute inflammation is increased permeability of the capillaries and postcapil-lary venules. Its degree may be measured either by the number of the particles which can pass through the vessel wall for the certain time or the time, when certain number of the particles can leak through. This phenomenon usually occurs in the small vessels, where the lack of smooth muscle weakens wall density, and it starts when arterial hyperemia begins to transform into venous hyperemia. The intensity of the vessels leakage depends on severity of injury and its target tissue. Mostly, it is a result not only pathogen of influence on the vessels wall but is also associated with inflammatyory mediators. There are three stages of high vessels permeability:

1. First, **early stage** is associated with release of histamine in the course of mast cells degranulation provoked either by primary injuring factor or secondarilyy. Secondary mast cell degranulation with histamine release is associated withC3a and C5a activated complement componets, different proteolytic enzymes, which appear in injured tissue later. It's short-termed period that usually lastsless than 30-40 minutes. Histamine initiates an appearance of the gaps between endothelial cells. Acting through the special histamine H-1 receptors, it transforms the oval shapes of the endothelial cells into the round ones, that ultimately leads to appearance of the small spaces (gaps) between the endothelial cells. The matter of the fact, that stimulation of H1- receptors provokes accumulation of intracellular Ca ions and then interaction of contractile structures inside the endothelium.As was said, this phenomenon is very short in time and permits only fluid and small proteins to pass through the small vessels wall, that indicates the start of inflammatory exudation. Histamine is the first vasoactive substance which dilates (via NO action) the microcirculatory vessels and increases their permeability. The matter of the fact, that histamine triggers the synthesis of NO inendothelium and the last, in turn, acting to the nearby situated smooth muscle cells, provokes their relaxation and arterioles dilation

2. Second stage is known as the late and prolonged. Itcan support high vessels permeability and their dilation for a long time (hours and days). It is mostly

associated with bradykinin formation from the kininogens of plasma. In addition it should be mentioned that bradykinin is responsible for nociceptive receptors stimulation, and in such way it provokes severe pain in the site of inflammation. It’s a very potent pain mediator.

3. Third stage oflate response seems to be supported by PgE2. As it’s known, it supports and prolongs many symptoms of inflammation, including redness and swelling due to prolongation of other mediators actions and pain because PgE2 sensitizes the nociceptive receptors to pain stimuli.

In the case ofserious injury of the blood vessels there is a damage of the vascular basal membrane which accompanied by exfoliation of lamina propria from the endoth-lial cells. Moreover, there may be destruction of collagen and elastic fibres, embedded into a basal membrane. Very often, the mucopolysaccharides lose their charge and become more permeable. If not only endothelial cells, but a basal membrane is injured completely, there is no possibility for tissue to be rcompletely repaired, and it usually results in a scar formation.

In the summary, vascular leakage is determined by the following mechanisms:

1. **Endothelial cells contraction**, leading to the formation of widened intracellular junctions, or intracellular gaps. This mechanism is mediated by histamine, bradykinin and other inflammatory mediators. This type of vascular leakage occurs rapidly after exposure to mediator (mediator binds to specific receptors on endothelial cells) and it is usually short in time (15 to 20 minutes) and reversible.

2. **Direct endothelial injury**, resulting in endothelial cell necrosis. This effect is observed in severe non-specific injuries, such as burns or bacterial infection. In most instances, leakage starts immediately after injury and is sustained at a high level for several hours or days until the damaged vessels are thrombosed or repaired. All levels of microcirculation are affected by this process including venules, capillaries and arterioles.

3. **Leukocyte-dependent endothelial injury**. Leukocytes aggregated and adhered to endothelium release toxic oxygen radicals and proteolytic enzymes, which cause endothelial injury or detachment resulting in increased permeability.

Increased blood vessels permeability is the most important factor of an exudate formation. But the other two factors of exudate formation are very important too. They are the following: increased hydrostatic pressure in the microcirculatory vessels, and increased osmotic and oncotic pressure in the surrounding tissue.

At the earliest phase of inflammation, the increase of hydrostatic pressure results in increased filtration of fluid from capillaries. This fluid contains little protein (less then 2 %) which is essentially an ultrafiltrate of blood plasma and is called **transudate**. Inflammatory exudates contain more then 2 % of protein.

The **hydrostatic pressure** in the vessels constantly increases with the slowing of bloodflow, and this factor also contributes to inflammatory edema development.

The loss of protein rich fluid from plasma and increasedrate of catabolic reactions increases **osmotic and oncotic pressure** in the site of inflammation anddecrease of these types of pressure in the blood vessels. Taken together they lead to a marked outflow of fluid and its accumulation in interstitial tissue.

Exudation in the inflammatory site plays both double role.

The **negative role of exudation** is squeezing of tissues and organs with the exudates, possibility of exudates outflow to body cavities and big vessels, abscess and phlegmon formation.

The **positive role of exudation** is:

- transport of plasma-derived inflammatory mediators (kinine system, complement proteins and components of the clotting system);
- transport of antibodies to inflammatory sites;
- elimination of toxins and metabolites from the inflammatory site;
- localization of the agent which caused inflammation.

4. Cellular events in inflammation

The changes which are characteristic to alteration and vessels reaction development lead to l**eukocytes emigration to the inflammation center.** In normally flowing blood, erythrocytes and leukocytes are confined to a central axis column, leaving a layer of plasma in contact with endothelium. Gradual slowing of blood flow in the site of inflammation results in peripheral arrangement of blood cells and their interaction with the vessel wall.

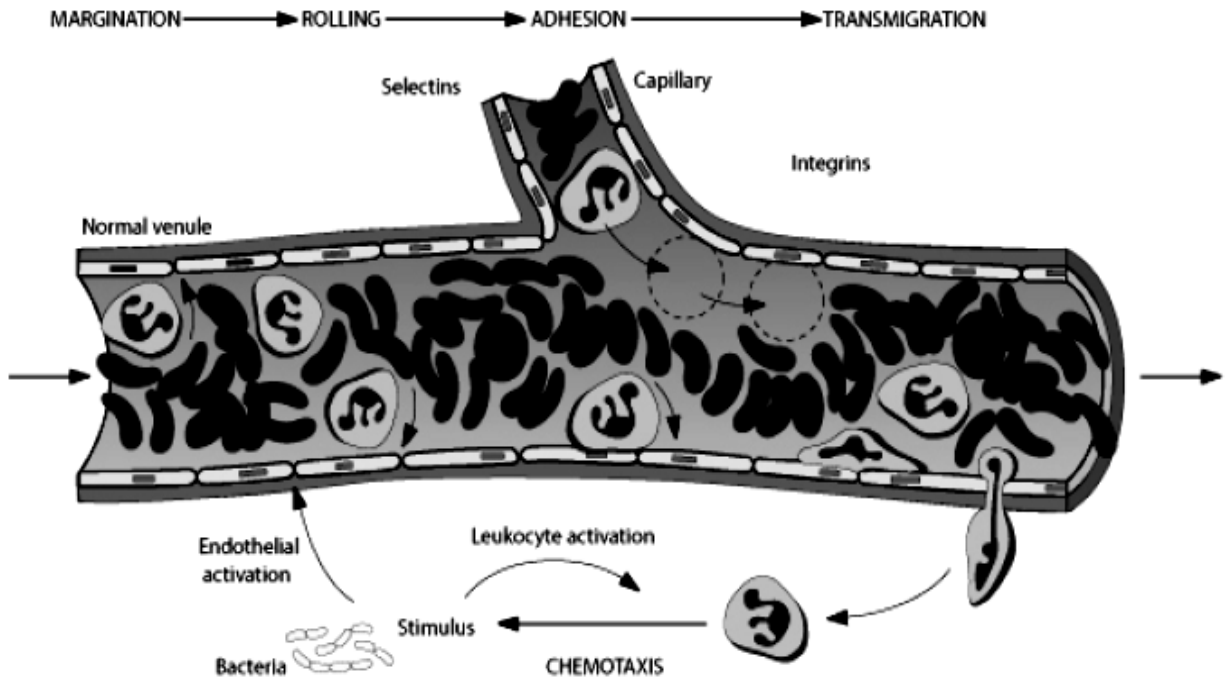

Figure 4. Stages of leukocytes extravasation

The extravasation of leukocytes involves four stages.

1. Margination. Laminar blood flow keeps RBCs in the center of the vessel and pushes WBC to the vessel walls. This allows the leukocytes to have a better opportunity while interacting with the endothelial cell lining.

2. Rolling. As bloodflow slows early in inflammation, WBC fall out of the central column. Endothelial cells and leukocytes have complementary surface adhesion molecules called **selectins** which briefly stick and release causing the leukocyte to roll along the endothelium until it stops.

3. Adhesion. Leukocytes stop rolling and become firmly attached to endothelial wall. Firm adhesion occurs due to the interaction between special molecules on endothelial cells and **integrins** on leukocytes.

4. Transmigration usually occurs in the postcapillary venule because it has an adequate number of inter-endothelial gaps and an adequate number of receptors, particularly due to histamine action. Leukocytes move along the endothelial surface, insert pseudopods into the junctions between the endothelial cells, squeeze through interendothelial junctions and assume the position between the endothelial cell and the basement membrane. Locomotion is a genetic property of the leukocyte. It was estimated that neutrophil can't be in the rest even in normal state and persists in form of "chaotic dance"when it throws out the pseudopods. But emigrated leukocyte has difficulties in navigation problem to arrive to correct extravascular location, and both chemattractants and their receptors on the leukocyte membrane are engaged in this moving. Chemokins or chemattractants in step by step manner call the leukocytes in the site of their high concentration via stimulation leukocyte locomotion. At first, the neutrophil enters the gap between the endothelial cells and then, being activated before by the chemattractants, releases hydrolytic enzymes on the basal membranes. These are the elastase, collagenase, depolarizing the mucopolysaccharides of the vessels walls. The proteolytic enzymes make vessels wall more permeable, and such way, facilitate a leakage of the leukocytes through the small vessels. If you try to observe the vessels wall in electron microscope before and after leukocyte passage, you hardly ever find any defect in the vessels wall.Monocytes can emigrate by the same way or by pinocytosis using their glycolytic reserve. Obviously, the antagonists of glycolysis can arrest a pinocytosis due to creating the lack of energy for monocyte active transport.In contrast to the neutrophils and monocytes, the lymphocytes emigrate only in small venules with special tall type of endothelium. Such endothelial cells possess by so called "homming" receptors that are necessary for lymphocyte transmigration. It must be added, that oppositely to the phagocytes, which have got "one way ticket " wandering only from the blood to the

interstitium, lymphocytes possess byso called “ ticket return” and can traverse the vessel there and back. Being the first in emigration, neutrophils predominate in the tissue and infiltrate it during first 6-24 hours but then, on 2-4-day they partially are replaced by the monocytes. Neutrophiles usually emigrate first and monocytes later, because chemotactic factors for neutrophiles and monocytes are activated at different phases of inflammation. Neutrophils peak of migration is 4-6 hours and monocytes cells peak is in 18-24 hours after beginning of inflammation.

Later the lasts are transformed into inflammatory tissue macrophages. In this conversion they change not only the size, becoming lager, but the shape of the nucleus. The macrophages have a long- tanding course in the tissue and dominate as the cellular unit in the site of chronic inflammation.

Leukocytes play an important role in inflammatory site:

- Protective function (finding, recognition, engulfment and the destruction of inflammatory agents and own damaged cells).
- Synthesis and secretion (release) of inflammatory mediators, which determine all stages of inflammation.
- Processing and presentation of foreign agents for the immune cells (development of immune reactions).
- During chemotaxis and phagocytosis activated leukocytes may cause tissue damage with the lysosomal enzymes, toxic oxygen radicals and products of AA metabolism (prostaglandins and leukotrienes).

Phagocytosis is a form of endocytosis in which cells engulf large solid objects such as bacteria and deliver the internalized objects to special digesting vacuoles. The objects of phagocytosis are microorganisms, insoluble particles, activated clotting factors. It is possible in certain cell types, such as macrophages and neutrophils. Phagocytosis is also an important part of the cleaning process after cellular destruction following inflammation, infection or any other process that leads to cellular death.

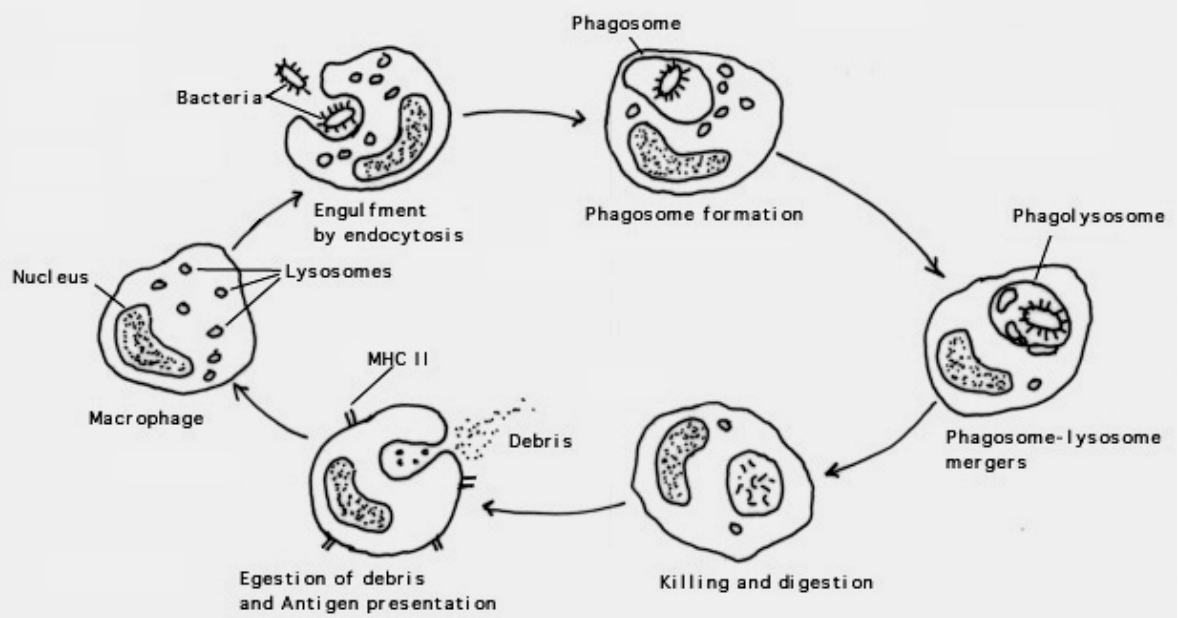

Figure 5 Stages of phagocytosis

There are several stages of phagocytosis:

1. Chemotaxis is the movement of cells along the gradient of chemotactic factors. Both exogenous and endogenous substances can act as chemotactic agents for leukocytes (**chemotaxins**). Exogenous achemotaxinsare the bacterial products; lipopolysaccharides and proteins. Endogenous chemical mediators in-clude:

• Activated complement system components, especially C5a and C3a - anaphylatoxins

• Products of lipooxygenase pathway metabolism, mainly LTB-4

• PAF

• Interleukin 1 and TNF-alpha as the late chemattractants

• All listed above substances are polyvalent chemattractants because they attract all types of obligatory phagocytes, including the neutrophils, eosino-phils, monocytes and macrophages

• As for neutrophils, IL-8 and neutrophil chemotactic factors, released from the mast cells,are the special or monovalent ones. Histamine, eosinophil chemotactic factor from the mast cells and eotaxin from endothelium are the

monovalent chemattractants for the eosinophils. Special monocytic chemo-tactic factor is working for the monocytes, but lymphotaxin for lymphocytes. These substances let phagocyte to “see or smell” a pathogen.

Chemotactic agents bind to specific receptors on the cell membrane of leukocytes. This reaction is followed by inducing calcium mobilization which causes the changes of the leukocyte cytoplasm state, the contraction of microfilaments and the progressive moving of the leukocyte.

2. Adherence works reasonably well for whole bacteria or viruses, but worse for proteins or encapsulated bacteria. Recognition and attachment of bacteria is accomplished when they are coated by certain factors called **opsonins**, which bind to the specific receptors on leukocytes. The major opsonins are: Fc fragment of IgG and C3b fragment of the complement.

3. Phagosome formation starts with pseudopodium formation. Fusion of the pseudopodium with a membrane enclosing the phagocyte "prey" leads to the formation of a structure termed a phagosome. The phagosome moves deeper into the cell, and fuses with a lysosome, forming a phago-lysosome. The phagolysosomal contents are digested and then eliminated by exocytosis. Some peptides however, undergo a very important separate process at this stage. Instead of being eliminated, they attach to a host molecule MHC class II and end up being expressed on the surface of the cell within a groove on the MHC molecule (**antigen presentation**).

4. Bacterial killing is provided with two mechanisms:

Oxygen-dependent mechanisms initiate production of reactive oxygen species – superoxide anion, hydroxyl ion and hydroperoxide with the help of NADPH oxidase enzyme. Oxygen consumption in this case increases 2 – 3 times. This process is known as the **oxidative burst**, and leads to killing and digestion of the phagolysosomal contents.

The steps of oxygen dependent killing proceeding in phagocytes:

1. Chemotaxins initiate the respiratory burst of a leukocyte, when it uptakes greedy an oxygen. It must be noted that in normal, not being activated, any leukocyte supports its energetic needs by the glycogenolysis with participation of hexosomonophosphate shunt.

2. After phagosome is arranged, the external membrane of the leukocyte contacts with cell cytoplasm due to cytoplasm invagination. That time, two components of NADPH- system (cytoplasm and membrane) meet each other, and it results in activation of NADPH -ase.

3. Activated NADPH-ase, in turn, transfers a single electron on an oxygen mole-cule with following superoxide radical formation.

4. Then part of the superoxide dismutases with such end product as hydrogen per-oxide formation

5. Eventually, in Fentone's reaction when transient metals iron and cooper are in-volved, hydroxil radical OH' is formed.

6. Reduction of NADP up to NADPH is realized through hexoso- mono-phosphate shunt activity

Above described reactions, result in the three primary radicals or active oxygen species formation. They possess very strong bactericidal properties. These reactions are going in any type of the obliged phagocytes, but the granulocytes possess a stronger weapon in their fighting against a pathogen. It is myeloperoxidase system.

The granulocytes: neutrophils and eosinophils, except the primary oxidants, produce the secondary oxidants, because they possess by the enzyme myeloperoxidase in their azurophilic granules. It's their marker, and yet in the bone marrow, they get it during maturation. Granulocytes' myeloperoxidase system consists of enzyme myeloperoxidase, hydrogen peroxide and halids (chlorides and bromines); the system is not specific and kill any pathogen. Assembly of hydrogen peroxide, myeloperoxidase and chlorides results in hypochloric anion (OCL-) and

hypochloric acid (HOCL-) formation; those in further interact with the aminogroups of proteins and form chloramines, very strong oxidants.

Hydroperoxide-myeloperoxidase-halide system is very effective in the struggle against such pathogens as worms, protozoa, fungi, and cells infected by the viruses.

Oxygen independent mechanisms are realized with the help of substances within leukocyte granules:

- Lysozyme - attacks bacterial cell walls - especially gram + bacteria;
- Bactericidal permeability increasing protein causes phospholipase activation, phospholipids degradation and increased permeability of the outer membrane of microorganisms;
- Lactoferrin - iron binding glycoprotein prevents the use of iron by bacteria.

Both oxygen-dependent and independent mechanisms result in damage of membrane proteins and lipids of the phagocyted object. The phagocyte itself is protected from destructive influence of the named substances with the help of antioxidative substances.

Some bacteria, such as Mycobacterium tuberculosis, have defense mechanisms against digestion after phagocytosis, and survive within the phagocyte undetectable by lymphocytes.

Defects in leukocyte function

Leukocytes play a cardinal role in a host defense against any pathogen. Defects in leukocyte functions, both genetic and acquired ultimately lead to increased vulnerability at face of infection. To sum up, the defects include both inherited and acquired variants of:

1. Defects of leukocyte adhesion,

2. Defects of phagocytosis.

Chediak-Higashi syndrome is an autosomal recessive condition characterized by neutropenia, defective granulocyte degranulation and delayed

microbial killing. In this syndrome the granules of neutrophils are very huge due to aberrant organelles fusion, moreover, the transport of lysosomal enzymes to phagocytic vacuoles is slowdown. The next is chronic granulomatous disease when defective synthesizing of several components of NADP-oxidase which is necessary for superoxide gen-eration.

Acquired deficiency may be represented by myeloid leukemia when the blood of patient is fool of immature granulocytes with a very weak myeloperoxidase activity. The matter of the fact, that the more mature granulocytes, the more the cells which rich of the myeloperoxidase activity. Besides, there is a low adhesion properties of both, leukocytes and endothelium are in the patients suffering of diabetes mellitus and chronic kidney insufficiency, so as, thermal injury and malnutrition.

The role of leukocytes in acute inflammation

Mast cells and basophils are the main source of histamine. During acute inflammation mast cells completely disappear of the site of injury, but a repair of tissue is manifested by the renewal of their population. There are two variants of mast cell degranulation: primary and secondary. The primary is under injuring agent but secondary is provoked by the mediators of acute inflammation, such as anaphylatoxins, PAF, cationic proteins of the neutrophils, oxidants, and different proteolytic activities released from the variety of cells involved in injury. Besides histamine, heparin and other mucopolysaccharides, possessing by opposite antiinflammatory properties, are present in mast cell granules. These cells, also content chymase and tryptase activities and the factors for neutrophil and eosinophil chemotaxis (NCF-chemotactic factor and ECF- eosinophl chemotactic factors). They provide with these cell-recruits an infiltration of tissue especially if they are of allergic or parasitic origin. Moreover, mast cells can be a source of such mediators as the eucosanoids, PAF and, at last, produce the mediators of an acute phase response. It mast be added, that the mast cells of connective tissue possess by the lot of receptors to Fc- fragments of IgE. High level of serum IgE, which characteristic of immune status of patient with allergy, contrib-utes an interaction

of antigen with fixed on the mast cells surface IgEs, that result-ing in mast cells degranulation and flooding of tissue with histamine.

Eosinophils in a large quantity are found in the tissue or exudates in course of allergy, parasitic disease, especially, in the patient with ascariasis. Histamine is the most important factor for their attraction to the site of inflammation. There are the lot of the receptors to the Fc-fragment of IgE also are situated on eosinophil membrane. IgE-antibodies in very high titer revealed in the patients with described pathology. Antigen-antibody reaction on the eosinophil membrane may result in their degranulation with release of their content. It includes the oxidants, main basic protein and such enzymes as histaminase and arylsulfotase. The lasts take part in inactivation correspondingly histamine and leukotriens. So, degranulation of the eosinophils has a double meaning. On the on hand, it leads to an injury of the pathogen, but the surrounding tissue may suffer too (positive and negative components of inflammatory response) but, on the other hand, it protects tissue from flooding of the site of inflammaton with an excess of the proinflammatory mediators (positive effect).

If the neutrophils are seemed to be the cells of the first line of defense in inflammation, the **macrophages** provide the second line. Neutrophils appear first on the stage of inflammatory "performance" because they are very sensitive to chemattractants and mobile, moreover, their life span is not longer than 1-3 days, and the population is replenished by bone marrow granulocytopoiesis. They are characterized by early emigration to the tissue, but if the wound isn't infected in 2-3 days the macrophages appear in the inflammatory site.

Then the macrophages turn into the inflammatory macrophages, very active in their function in compare with "quiet" tissue macrophages. In the site of inflammation they tend to be fused with giant cell formation.

The functions of macrophages in the site of inflammation

1. They are the obligate phagocytes and, like neutrophils, can elaborate free radicals, but in form of only primary oxidants; release hydrolytic enzymes and in-

gest the tissue unwilling elements with their following killing and degradation

2. They are called scavengers because of their ability to tissue cleaning of the debris. They produce collagenase, elastase and plasminogen activator providing the thrombi lysis and repair of microcirculation in the site of inflammation

3. Take part in the rebuilding of the connective tissue, producing angiogenetic factor of small vessels renewal, FGF (fibroblast growth factor) and fibronectin. The last plays role of the “railway” for the restoring of tissue with mast cells population via moving them from the blood to the connective tissue

4. The fulfill an antigen-presenting function. Wearing on their surface MHC class II molecules, they present the information about the “non-self” antigens to the lymphocytes, and such way, realize the connection between inflammation and immunity

5. Activated macrophages release and produce the mediators of an acute phase response which are very important for interrelation between the site of injury and whole organism

6. They take part in so called granulomatous inflammaton that is a variant of chronic inflammation, for example, intuberculosis, syphilis, leprosis, or brucellosis.

5. Regeneration and repair mechanisms. Classification of inflammation

Inflammation causes the damage that must be repaired. The damage can heal by the two following ways: regeneration and repair.

Regeneration is the replacement of dead cells with new ones. In this way function is completely restored. The process depends on the ability of nearby cells to divide, the condition of the surrounding stroma, and the number of remaining cells. If conditions are proper, damaged tissues will be restored to full structure and function by the mitosis of surrounding undamaged cells. Parenchymal cells of the liver as well as many connective tissue cells are an example of cells that can divide

in the required circumstances.

There are several populations of cells that never divide. Skeletal muscle cells, cardiac muscle cells and nervous system neurons never divide and can not regenerate. Rather, they will be replaced by **repair**. **Repair** is the replacement of dead cells with fibrous connective tissue cells and fibers. Fibrous connective tissue repair will restore the continuity of tissue but it will not restore its function. In heart attacks, a patch of cardiac muscle cells is damaged. Cardiac muscle cells cannot regenerate, that's why they are replaced by fibrous connective tissue which restores their continuity, but not their function. The process of repair results in the formation of a fibrous scar from granulation tissue.

Factors influencing healing. The rate of healing and the success of formation of scar tissue can be limited by many adverse factors. Some of the factors which are of clinical importance are as follows:

Local:

- Inadequate blood supply;
- Persisting infection, or other stimulus to inflammation;
- Excessive movement;
- Irradiation;
- Locally applied drugs, e.g. corticosteroids.

Systemic:

- Catabolic state associated with malignancies;
- Age: the healing becomes slower and less effective with ageing;
- Nutritional deficiencies, e.g. vitamin C, zinc, protein;
- Metabolic diseases, e.g. renal failure, diabetes mellitus;
- Systemic drugs, e.g. corticosteroids.

Repair is influenced by the number of factors. Some of them cause activation, others cause inhibition of repair. The wide group of **growth factors** is known. The term growth factor refers to a naturally occuring protein which is capable of

stimulating cellular proliferation and cellular differentiation. The main sources of these factors are macrophages, fibroblasts and liver cells. Leukotrienes 1-7 are also known as cell growth activators.

The important role in regulation of repair is played by **chalones.** Chalone is a specific inhibitor of cell proliferation which is thought to be responsible for regulating the size of a population of cells.

Tumor necrosis factor may both play the role of activator and inhibitor of cell growth; it depends on the type of the cells and its amount.

Glucocorticoids are known as potent inhibitors of cell growth, because they inhibit the processes of cellular division.

Inflammation classification principles

The classification based on the cause of inflammation:

- Infectious: non-specific (cocci) and specific (tuberculosis, syphilis);
- Non-infectious (aseptic) – caused by infarctions, hemorrhages, salt deposition.

The classification based on the prevailing mechanism:

Alterative – inflammation with prevailing alteration usually develops in the myocardium, liver, kidneys. It is seen in severe infections and in toxic states. The classic example of alterative inflammation is viral hepatitis.

Exudative - In this category of inflammation the predominant feature is loss of fluid and cells from the bloodstream into the interstitial tissues, According to the nature of the exudate further subdivision can be made.

In **proliferative** inflammation the characteristic feature is cellular proliferation. The proliferative cells are vascular endothelium, fibroblasts, histiocytes and occasionally papenchymal cells. Since proliferative changes are part of organization and repair, proliferative inflammation is synonymous with chronic inflammation. The reasons of it can be infectious (syphilis, tuberculosis, rheumatism, brucellosis, leprosy) and non-infectious – dust disease (silicosis,

asbestosis, talcosis).

The **classification of exudative inflammation** is based on the content of exudate which is in particular dependent on the degree of vessels permeability increase.

Serous inflammation (3-8% of protein, single neutrophiles in exudate). The reason of serous inflammation can be thermal injury (burns), chemical, infectious (viruses), allergic agents. A serous inflammation usually occurs in connection with serous membranes such as the peritoneum, pleura and pericardium.

Catarrhal inflammation develops on mucous membranes and is characterized by the presence of mucus in exudates. It also includes leukocytes, lymphocytes and epithelial cells. The examples of catarrhal inflammation are rhinitis, gastritis, and enterocolitis.

Fibrinous inflammation develops in case of severe injuries and greatly increased vascular permeability. Fibrinous exudate is characteristic of inflammation in pericardium and pleura exudate including fibrin. Fibrinous exudates may be removed by fibrinolisis (resolution) or converted to scar tissue (organization). The forms of fibrinous inflammation are:

- Croupous inflammation (develops in prismatic epithelium) – fibrinous pericarditis (hairy heart), croupous pneumonia.
- Diphtheritic inflammation (develops in squamous epithelium) – throat, pharynx, tonsils.

Purulent (suppurative) inflammation. In this type of exudative inflammation, there are large numbers of neutrophils and varying degrees of tissue necrosis. Suppuration refers to the presence of pus. Pus is a thick creamy yellow fluid containing leukocytes, tissue debris, bacteria. The fluid in which these elements are suspended is inflammatory exudate with a high concentration of nucleic acids derived from tissue breakdown and liquefaction. Bacteria which tend to produce suppuration are called pyogenic bacteria (staphylococci, kiebsiella species).

When the inflammatory process is severe and is localized, it produces a discrete focus of suppuration and necrosis which is called an **abscess. Phlegmonous inflammation** differs from abscess in that it is not localized, not accompanied by significant tissue necrosis, and it evolves more slowly. Phlegmonous inflammation occurs in skin and subcutaneous tissues, skeletal muscle and appendix. It is usually caused by streptococci which elaborate hyaluronidase and streptokinase. These enzymes digest tissue and allow the infection to spread.

Putrefactive inflammation develops as a result of putrefactive bacteria injury. Inflamed tissue is exposed to putrefactive decomposition; it gets dirty-green in color, and becomes flabby, as though it creeps away with the formation of bad smelling gases.

Haemorrhagic inflammation. This relatively rare type of inflammation is seen in toxic infections such as anthrax, plague, leptospirosis and the hemorrhagic fevers. Severe toxemia damages endothelium, causing hemorrhage.

Inflammation is considered to be local tissue reaction, at the same time it is determined by the general condition of an organism, and its reactivity. It is established, that inflammation can be hyperergic (in sensitized organism), or hypoergic (in the presence of immunity to the agent of inflammation).

Nervous and hormonal factors can influence the character of an inflammation. It is established that growth hormone and aldosteron are capable to strengthen inflammatory response. Such action is termed pro-inflammatory effect.

Glucocorticoids are widely used for the suppression of inflammation in chronic inflammatory diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease and autoimmune diseases. The mechanism of their action lies in decrease of inflammatory mediators' synthesis: cytokines, AA derivates (leukotriens, prostaglandins etc.) and other mediators. Glucocorticoids also inhibit cells proliferation and protein synthesis. These effects decrease the intensity of all the events, which are normally observed during inflammation: exudation,

phagocytosis and proliferation.

The influence of nervous factors on inflammation is not yet well studied. However it is known that in the violation of peripheral innervation, especially sensitive, inflammation aquires chronic character. E.g., trophic ulcers of low extremities which accompany traumatic damage of spinal cord, heal and repair for a very long time. Tissues deprived of sensitive innervation, have low metabolism level and high vascular permeability.

Chronic inflammation

Chronic inflammation may follow acute inflammation, or the response may be chronic almost from the onset. Generally it occur when the reason of tissue injury which initiates inflammation can't be completely eliminated.

The reasons of chronic inflammation development are:

- Various forms of phagocytosis disturbances.
- Chronic stress and other condition followed with high level of glucocorticoids and catecholamines, which inhibit phagocytosis and proliferation.
- Persistent infections (treponema pallidum) or intoxication.
- Prolonged exposure to nondegradable material (silica particles – silicosis)
- Autoimmune diseases.

In contrast to acute inflammation, which is manifested by vascular changes, edema, and predominantly neutrophilic infiltration, chronic inflammation is characterized by:

- Infiltration with mononuclear cells, which include macrophages, lymphocytes, and plasma cells.
- Tissue destruction, induced by the persistent offending agent or by the inflammatory cells.
- Attempts of healing by connective tissue replacement of damaged tissue, accomplished by proliferation of small blood vessels (angiogenesis) and, in particular, fibrosis.

The products of activated macrophages serve to eliminate injurious agents such as microbes and to initiate the process of repair, and are responsible for much of the tissue injury in chronic inflammation. Tissue destruction is one of the hallmarks of chronic inflammation.

In short-lived inflammation, if the irritant is eliminated, macrophages eventually disappear (either dying off or making their way into the lymph nodes). In chronic inflammation, macrophage accumulation persists.

The differences between acute and chronic inflammation

	Acute	**Chronic**
Duration	Short (days)	Long (weeks to months)
Inflammatory cells	Neutrophils, macrophages	Lymphocytes, plasma cells, macrophages, fibroblasts
Exudation and edema	Usually present	Usually absent
Local signs	Always present	Not observed
Systemic manifestations	Fever, often high	Low–grade fever, weight loss, anemia
Changes in peripheral blood	Neutrophil leukocytosis; lymphocytosis (in viral infections)	Frequently none; variable leukocyte changes, increased plasma immunoglobulins

7. Disturbances of peripheral circulation. Arterial hyperemia

Arterial hyperemia (active hyperemia) is an increased blood organ supply due to excessive blood inflow from arterial vessels. It is manifested with the increased number and diameter of arterial vessels, dilation of the lumen of arterioles and precapillaries, increased number of functioning capillaries, reddening of the organ, tissue due to increased flow of arterial blood. The site of arterial hyperemia is characterized with increased temperature which results from warmer temperature of arterial blood and higher metabolic intensity.

Arterial hyperemia can be caused by different reasons.

- Mechanical (friction)
- Physical (high temperature, UV radiation)
- Chemical (local influence of acids, alkalis, ethyl alcohol)
- Biological (microorganisms, that cause inflammation)
- Psycho-social (emotions)

Arterial hyperemia may be of physiological or pathological origin. The main mechanisms of **physiological arterial hyperemia** development are:

- Increased function of the organ (muscles – during exercises, GIT – during digestion, brain – during mental activity).
- Thermoregulation process (in order to decrease body temperature skin, arterial hyperemia occurs).

Arterial hyperemia caused by unusual (pathologic) irritants is named **pathologic**. It occurs in sites of inflammation, allergic reaction and burns.

Other types of arterial hyperemia are **adaptive (postischemic)** and **vacate** (use of cupping-glasses creating a vacuum in a cup over the skin).

The mechanisms of arterial hyperemia development are **neurogenic** and **humoral**. Neurogenic arterial hyperemia is caused by changes in nervous regulation of blood vessels tonus. It can be **neurotonic** – caused by the activation

of β-adrenoreceptors and M-cholinoreceptors with psychic, mechanical, chemical agents and high temperature. Direct irritation of parasympathetic nerves causes the dilatation of blood vessels too. Activation of sympathetic nerves causes the constriction of blood vessels. When sympathetic nerves are cut or blocked with drugs **neuroparalytic** arterial hyperemia occurs.

Not only nervous but humoral factors influence blood vessels tonus. The dilation of arteries is also caused by the following humoral agents:

- low blood oxygen level;
- high CO_2 blood level;
- lactate acid, nitric oxide (NO);
- biologically active substances (kinines, histamine, prostaglandines).

Acceleration of blood flow reduces the time of blood contact with the tissue and decreases the time of oxygen diffusion to the tissue. Meanwhile, this doesn't lead to worsening of metabolism because it is compensated for by a greater number of functioning capillaries for a tissue unit; on the contrary, the metabolism even increases. As a result, the level of oxygen in the venous blood is higher, the arteriole-venule oxygen difference is lower and the venous blood has a more scarlet color.

Arterial hyperemia causes intensification of metabolic processes and activation of the functions of an organ or tissue. For instance, arterial hyperemia which usually accompanies the initial stages of inflammation results in activation of local immunity (due to increased inflow of immunoglobulins, lymphocytes, phagocytes and other agents with arterial blood), acceleration of plastic processes, increase of lymphopoiesis and lymph outflow from tissues. Prolonged hyperemia can lead to hypertrophy, hyperplasia and even accelerated development of organs and tissues.

Positive effects of arterial hyperemia are used in treatment of different diseases. In these cases arterial hyperemia is caused artificially with the help of hot compress, mustard plasters, radiation with UV and IR rays, or by surgical

transaction of sympathetic nerves.

The negative effects of arterial hyperemia include overextension and microrupture of vascular walls of microcirculatory bloodstream, micro- and macro-hematomas, internal and external hemorrhages. Arterial hyperemia of the organs enclosed in a limited space is sometimes accompanied by unpleasant sensations – headaches, tinnitus (hyperemia in cerebral vessels), aches in joints.

8. Disturbances of peripheral circulation. Venous hyperemia

Venous hyperemia (passive hyperemia, congestion) means an increase of organ or tissue blood volume due to obstruction and inadequate venous blood outflow.

It can be caused by **external squeezing** with tumor, ligature, scar, edema or exudate; or **internal occlusion** (thrombus, embolus). Obstruction to the venous outflow may be local or systemic. The example of local congestion is a pooling of blood in the leg resulting from venous thrombosis which causes impaired venous return. Systemic venous congestion (hyperemia) is observed in the patients with heart failure.

Clinically venous hyperemia is manifested with the following features:

- Veins dilation, increase of blood hydrostatic pressure in veins which leads to increased permeability of the vein wall with subsequent swelling of the tissue and organ. Prolonged dilation of veins may result in sclerotic processes and varicosities development.
- Blood flow speed decrease in veins and microcirculatory vessels. The number of functional capillaries does not usually change.
- Decrease of oxygen in venous blood which is the result of the utilization of oxygen taken by tissues from the blood due to its slow flow through capillaries. The decrease of oxygen content (hypoxia) leads to alteration of tissue metabolism which may result in dystrophic and atrophic changes of tissue. Such changes are accompanied by extensive growth of connective tissue.

- Cyanosis and temperature decrease of the organ resulting from increased volume of colder (in comparison with arterial blood) venous blood and lower intensity of tissue metabolism.

Chronic local venous congestion may also lead to complete stop of bloodflow in microcirculation – stasis. Other important consequence of venous congestion is hemorrhage from the overextended venous vessels.

Slowing down of the blood flow prolongs the time of contact of blood with the tissue and, and thus, the time of diffusion of oxygen to this tissue. Arteriole-venule oxygen difference increases, the level of reduced hemoglobin in the venous blood grows up and cyanosis (bluish color of the skin) develops. The percentage of the reduced hemoglobin in the venous blood is more than 5-6%. The partial pressure of oxygen in the tissue and its pH moderately decreases and the local partial pressure of carbon dioxide increase.

Short-term consequences of venous hyperemia are moderate hypoxia of an organ or tissue, congestive stasis and edema. Chronic venous hyperemia is accompanied by diapedetic hemorrhages into organs and tissues, atrophy of parenchymal cells and proliferation of the stromal cells which leads to sclerotic changes in the organ.

9. Disturbances of peripheral circulation. Ischemia

Ischemia is the state of inadequate organ or tissue blood supply due to decreased bloodflow in arteries. It can be caused by:

- external factor (the compression of artery by a ligature, tumor, scar, foreign body, tourniquet) – **compressive type of ischemia**;
- internal factor (obstruction by thrombus, embolus or atherosclerotic plaque) – **obstructive type of ischemia**;
- **angiospastic ischemia** – spasm of arteries caused by:
    - emotional strain (anxiety, anger, agitation);
    - physical factors (trauma, cold, mechanichal irritation);

- chemicals (nicotine, vasopressin, ephedrine);
- biological factors (bacterial toxins).

The clinical manifestations of ischemia are:

- Paleness of ischemic site.
- Blood flow speed and temperature decrease.
- Paresthesia (an abnormal sensation, typically tingling or pricking - "pins and needles").
- Pain resulting from metabolism disorders.
- The decrease of blood oxygen level.
- Decrease of volume and tension of ischemic site.

In ischemia the inflow of blood is decreased and the outflow remains equal to the inflow. The pressure markedly drops in the arterioles to the periphery of the narrowing, less significantly – in the venules. Separation of the blood flow into axial and plasmatic layers disappears. In the ischemic area the blood flow is slow and erythrocytes are redistributed in the microvessels – the blood going to the capillaries is poor in erythrocytes and has low hematocrit. Then, because of the low intracapillary pressure some capillaries close and the number of functional capillaries decreases. Due to the low intravascular pressure filtration of fluid from vessels to the tissue also decreases. The amount of tissue fluid reduces and the lymph outflow becomes weaker and can stop.

The decrease of blood supply to organ or tissue will result in hypoxic cell injury with subsequent energy metabolism disturbance, decrease of protein synthesis and disturbance of cell/tissue/organ function. The most unfavorable consequence of ischemia is an infarction (necrosis).

The character, intensity and consequences of ischemia are dependent on the following factors:

The ischemia with higher **speed of development** causes more tissue injury. Infarction is usually caused by rapidly developing occlusions. If the occlusion develops slowly, it provides an opportunity for an alternative blood supply with

collateral circulation and anastomoses opening.

The diameter of affected arterial vessel. Ischemia of big arterial vessels will result in broad tissue injury.

The susceptibility of tissues to hypoxia. Nervous tissue is the most sensitive to hypoxia. 3 –4 minutes of blood supply deprivation causes neurons damage. Myocardial cells are sensitive to hypoxia too. In contrast, the fibroblasts within the myocardium are not affected with hypoxia.

The availability of collateral bloodflow. Collateral vessels play a significant role in supplying oxygen to an organ, particularly when its delivery is limited by disease in the normal vasculature. Collateral vessels can be pre-existing vessels that normally have little or no blood flow. Acute occlusion of normal vessels (e.g., thrombosis of a large artery) can cause a redistribution of pressure within the vascular bed thereby causing blood flow to occur in collateral vessels. Conditions of chronic stress (e.g., physical overstrain or chronic hypoxia) can cause the growth of new blood vessels (angiogenesis). Absolutely sufficient collateral blood flow exists in the lung, skeletal muscles and mesentery. Brain, kidney, spleen and myocardial tissue have limited availability of collateral blood flow.

Blood oxygen level is significant in determining ischemic damage too. The patients with cardiac decompensation are more vulnerable to infarction.

The consequence of short-term ischemia is a decrease in functional activity of the organ, the consequence of long-term ischemia is hypoxic necrobiosis. The local necrosis of tissues caused by acute disturbance of its blood supply is called infarction. Over time, postnecrotic sclerosis develops at the site of infarction. The most common forms of infarction are myocardial and pulmonary. Infarcts often occur in aged patients with atherosclerosis or cardiac decompensation.

Ischemia of a magistral arterial vessel causes collateral arterial hyperemia through myoparalytic mechanism (effect of accumulated metabolites). If collateral vessels are absolutely sufficient (their total diameter is not less than the diameter of the blocked magistral artery), infarction does not develop (in the limbs, liver, intestines, lungs). In the kidneys, retina, spleen, the basin of the medial cerebral artery

collaterals are absolutely insufficient, therefore, in these organs infarctions occur rather often. Some organs have relatively sufficient collaterals, for example, the heart. In this case myocardial infarction is caused by atherosclerotic damage to the vessels. As a result, the functions of the endothelium and monocytes are impaired. It promotes thrombosis and angiospasm and can cause significant narrowing of the coronary blood vessels (decrease in their diameter up to 75%).

10. Disturbances of microcirculation. Stasis

Stasis is a lowering and complete stop of bloodflow in small arteries, veins and capillaries. The following types of stasis are known:

Primary (genuine, true) – caused by pathologic changes in capillaries or blood viscosity characteristics.

Secondary – due to considerable decrease in blood flow speed, which form the conditions for erythrocytes aggregation in microcirculation**:**

- **Venous** or **congestive**– caused by inadequate venous blood outflow;
- **Ischemic** or **post-ischemic**– caused by inadequate blood inflow from arteries.

Arteriole- venule pressure difference as the driving force of blood flow is lost in congestive and post-ischemic stasis, but remains unchanged in genuine stasis. Congestive and post-ischemic stases are principally reversible – when the reason of venous or ischemic stasis is removed, normal blood flow is restored. Otherwise, progress of ischemic stasis leads to capillary stasis development. Primary stasis is reversible only at the beginning because as it develops, changes in blood cells and plasma occur which increase obstruction of capillaries and venules.

In real pathological processes all above named mechanisms can combine, generating mixed stasis.

Primary stasis may be caused damage to tissues by:

- Physical factors (extremes of high or low temperature);
- Chemical factors (poisons, ethanol, acids, alkali);
- Biological factors (endotoxins of microorganisms);

- Endogenous factors (slowing down of blood flow, increased hematocrit in polycythemias, changes in red blood cell properties in anemias, etc.).

Primary stasis is characterized by an **increase in capillary resistance** to blood flow. If the flow is unchanged, the main role in vascular resistance will be played by blood viscosity. **Blood viscosity increases**, firstly, due to slowing down of blood flow in microvessels which often precedes stasis (for example, in inflammation, stasis develops under conditions of venous hyperemia), and secondly, as a result of enhanced intravascular aggregation (clumping) of erythrocytes. Sometimes erythrocyte aggregation precedes low blood flow, sometimes these processes come in parallel.

Intensification of erythrocyte aggregation is caused by damage to erythrocytes and loss of their integrity. The surface of erythrocytes during aggregation becomes rough or "fluffy". It looks like erythrocytes have a viscous cover. Erythrocytes stick together forming rouleaux and move in a vessel not in a longitudinal, but in a transverse position , and these conglomerates can block the vessel.

The pathogenesis of primary stasis usually includes two events:

- Aggregation of blood cells in the capillaries with their subsequent hemolysis;
- Slowing down of blood flow in the capillaries due to hemoconcentration and increased vessels permeability.

Stasis develops more readily at low blood flow, higher hematocrit (for example, due to transudation), at vessel flexures, in the presence of adhesion molecules on leukocytes and endothelium, at increased blood concentrations of globulins and fibrinogen. At first blood stops in response to the action of damaging agents causing stasis. Once the stasis has developed, the blood flow stops in the whole capillary – below and above the focuses of the initial stasis. As the stasis is progressing, there appears "sludge". The sludged blood differs from normal. It contains aggregations of erythrocytes, leucocytes, platelets. There is no clear borderline between the surface of blood cells and their plasma, the rouleaux become homogeneous. Homogeneity of the blood flow is lost, aggregations

become more marked, then they are sedimentated . The liquid fraction of blood leaks through the venule walls to the surrounding tissue and the blood becomes more viscous. The vessel walls do not receive sufficient nutrition and begin to lose their normal shape.

Pathogenic significance of blood stasis largely depends on the organ in which it develops and time of its duration: prolonged stasis may result in necrosis development.. Stasis is especially dangerous in microvesssels of the brain, myocardium and kidneys. Besides, stasis contributes to thrombi formation.

11. Disturbances of peripheral circulation. Thrombosis

Thrombosis is the formation of a thrombus (clotted mass of blood) within the intact cardiovascular system. In some cases a part of thrombus can break to create an embolus. Such condition is termed thromboembolism.

The factors that contribute to thrombus formation are:

Endothelial injury is the main factor that influences thrombogenesis. The reasons of it are:

- atherosclerosis;
- traumatic or inflammatory (phlebitis) injury of the vessel;
- biological agents (endotoxins);
- chemical agents (products absorbed from tobacco smoke).

Endothelial damage causes the exposure of subendothelial collagen that activates the platelets adherence and further blood coagulation.

Slowing of bloodflow can manifest as the stasis or turbulence of bloodflow. In normal (laminar) bloodflow all blood cells are separated from the endothelial surface by a plasmatic zone. Slowing of bloodflow permits platelets to contact with endothelium and build-up platelet aggregates and promotes endothelial cell hypoxia and injury. This fact explains the higher frequency of thrombi formation in the veins than arteries. Thrombi often develop in the valves of the deep veins of the lower parts of legs; in the vessels with aneurysmal dilatations; in the auricular

appendages when there is a massive dilatation of the atria (mitral stenosis).

Increased blood coagulation (hypercoagulability) can be associated with an inherited lack of natural anticoagulant. Affected person presents venous thrombosis and recurrent thromboembolism.

Thrombogenesis includes two stages:

1. The cellular stage of adherence, aggregation and agglutination of platelets and other blood cells.

2. The plasma stage – the formation of active thrombin and fibrin; the formation of blood clot which retracts and becomes denser.

Thrombi are clinically important for two reasons: they cause **obstruction of arteries and veins** (causing ischemia and venous hyperemia) and provide **possible sources of emboli**. Most venous thrombi are occlusive. Those arising in the deep veins of legs cause pulmonary embolization and infarction. In contrast, the role of arterial thrombi is more important in obstruction (coronary arteries - myocardial infarction; arteries of the brain – cerebral infarction).

12. Disturbances of peripheral circulation. Embolism

Embolism is the passage of a solid, liquid or gaseous mass through the bloodstream to a site distant from its point of origin. The mass is called an **embolus**. In the overwhelming majority of cases emboli originate from thrombi. Rarely, other material may embolize. Emboli can be carried anywhere in the circulation, but they eventually stop in smaller vessels.

Emboli from the right heart or from the systemic veins stop in branches of the pulmonary artery. Thrombi from deep leg veins are a common source of emboli to the lungs. Arterial thrombi originate from the left side of the heart or from atheromatous plaques in the aorta and large arteries. Thrombi from the veins of GIT may embolize portal vein system.

There are exogenous and endogenous types of embolism. The **exogenic embolism** includes:

- air embolism (cervical veins damage, air injection, open heart surgery);

- gas embolism during fast decompression;
- microbial embolism (parasites, fungi, protozoa).

The **endogenous embolism** includes:

- thromboembolism;
- fat embolism (oil intravenous injection, long tubular bones fracture);
- tissue embolism (tumor metastases, bone particles, fragments from ulcerated and ruptured atheromatous plaques).

Pulmonary embolism is the most clinically important; it can cause:

- Hemorrhagic infarction of the lung;
- Sudden death due to acute respiratory failure;
- Bronchi spasm;
- Lung capillaries and arterioles spasm;
- Coronary artery branches spasm.

Caisson disease, or decompression sickness – is a particular form of gas embolism which can appear in deep sea divers and underwater construction workers. When deep sea divers descend to the depth, air pressure within the diving suit and helmet is increased to compensate water pressure. The gases of compressed air are dissolved in blood, tissue fluid, and fat. If the diver ascends to the surface too rapidly, the dissolved oxygen, carbon dioxide and nitrogen can come out of solution in the form of bubbles. Nitrogen bubbles may form in small blood vessels or in the tissues themselves. Tissues with a high fat content, such as those in the brain and spinal cord, are particularly likely to be affected, because nitrogen dissolves very readily in fats.

Gas bubbles stop in small vesels causing ischemia of tissues or organs. Clinically it manifests with pain in the joints of the arms or legs, back, or muscles. Less common symptoms include itching, swollen lymph nodes, rash, and extreme fatigue. In severe forms spinal cord is affected, symptoms can include numbness, tingling, weakness. Symptoms of brain involvement, most of which are similar to those of air embolism, include headache, confusion, trouble speaking, and double

vision.

The same condition may occur during the flights on high altitude when an airplane loses pressurization and **explosive decompression** develops (sudden exposure to low barometric presure).

Examples of situational tasks

Task 1

Patient A., 35 years old, has got a burn of arm, it size was 2×2 cm,. During repeated examination 2 days later it was observed that the size of inflammation site increased up to 4×3 cm, skin around it was cyanotic, painful, with high tension.

1. Why site of inflammation had been increased?
2. Which factors take part in this process?

Task 2

Some drops of turpentine (aggressive chemical) were put on the eye conjunctiva of laboratory animal. 15 minutes later expressed inflammation appeared: redness of conjunctiva, dilation of mucosal membrane's capillaries, swelling and pain.

1. Will the inflammation develop if the eye will be under anesthesia? Explain your answer.
2. What is the mechanism of pain development in this experiment?

Task 3

Patient F., 30 years old, had made tuberculin skin test – Mantoux reaction (intracutaneous injection 2 TU of tuberculin) – for diagnostic purpose. 24 hours late in site of injection painful red infiltration appeared, its size was 25 mm. Body temperature was increased to 37,2 oC. A doctor estimates such reaction as positive hyperergic.

1. Which signs are the evidence of inflammation's development in patient? Prove your answer.

2. What is mechanism of primary alteration in this case?

3. Explain the mechanism of inflammatory site increase.

Task 4

Patient S, 20 years old was hospitalized in the surgical department with the complaints about nausea and pain in the right side of the lower abdomen. Body temperature 37,80 C. Blood count: RBC – 3,9*1012/L, WBC – 25*109/L, erythrocytes sedimentation rate – 34 mm/hour.

1. Which typical pathological process has developed in the patient? Try to define the disease.

2. Which signs of inflammation are observed in the patient? Explain the mechanisms of their development.

Task 5

Patient C., 51 years old, with diagnosis "acute peritonitis". After paracentesis (puncture of abdominal cavity) liquid was obtained which had the following signs: yellow color with green tint, density 1,029; proteins content – 3,9 %. In sediment: high amount of neutrophils with degenerative forms presence and purulent bodies.

1. What type of liquid was obtained after paracentesis?
2. Explain the mechanism of liquid appearance in abdominal cavity.

Task 6

Patient U. was hospitalized to the hospital with the suspicion of diphtheria. The following signs were observed after examination: the mucosal membrane of throat was red and covered with grey thin coating, which was tightly connectedwith underlying tissues. Body temperature was 39oC, tachycardia, tachypnea, skin was pale and humid.

1. What typeof inflammation (alterative, exudative, proliferative) is present in this case? Prove your answer.

2. Explain the mechanism of thin coating formation on the mucosal membrane of the throat.

3. Which factor determines the type of exudative inflammation?

Task 7

Patient B., 65 years old, with diagnosis “heart failure”. During patient’s examination it had been revealed accumulation of liquid in abdominal cavity (ascites). After diagnostic puncture liquid obtained that had the following signs: transparent, color was light-yellow, density – 1,014; proteins content 1,8 %. In sediment: single cells (most of them are lymphocytes).

1. What type of liquid was obtained after paracentesis?
2. Does the patient have signs of inflammation?
3. Suppose the mechanism of liquid accumulation in abdominal cavity

Task 8

The experiment was held on laboratory mice: 0,2 ml of bacterial solution with5×108 pneumococci was injected intraperitoneally. The average life span after injection was about 8 hours. The same amount of bacterial solution was injected to another group of laboratory mice, which were previously (2 hours)injected with 0,5 ml of neutral dust particles sterile solution. The average life span in this was about 3 hours.

1. Explain the mechanism of life span shortening in the second group of experimental animals.

Task 9

Two rabbits with experimental inflammation modelled by burn on the right hind leg were injected with the same dose of lethal toxin. The injection of lethal toxin was made into the site of inflammation in one rabbit and out of the

inflammatory site – in another rabbit. In 20 hours it was reveled that one rabbit has died.

1. Which group of the animals has died and why?

Task 10

Patient C, 48 years, complains of the pain and limitation of movements in the right leg, periodical temperature increase (37,2- 37,7 0C). Clinical examination: enlargement of the right knee, pain during palpation, decreased volume of the muscles. Puncture of the knee joint: obtained 5 ml of the serous liquid with high amount of monocytes and lymphocytes, single neutrophils, single tubercle bacilli.

1. Define the type of inflammation in the patient.
2. Why this infectious agent causes chronic inflammation development?

Task 11

The driver T. has got a trauma of the neck with the damage of jugular vein.

1. Which kind of peripheral blood circulation disturbance will develop in the patient?
2. Explain the mechanism of its development.
3. Can this disturbance be prevented? If yes, how it can be done?

Task 12

The sportsman felt his extremities hot after body-building exercises; the color of the skin was red and hot to the touch.

1. What kind of peripheral blood circulation disturbance had developed in sportsman?
2. Are these signs normal?
3. Explain the mechanism of this condition development.

Task 13

The experiment was held on the rabbit: sympathetic nerves that innervate the left ear were cut.

1. Which violation of peripheral blood circulation will occur in the experiment?
2. Explain the mechanism of its development.
3. Which other types of this violation of peripheral blood circulation can you name?

Task 14

Patient A., 50 years, is suffering from diabetes mellitus for 5 years. He has been working as a salesman for 30 years. The patient complains about pains in the legs. Clinical examination of the legs: edema, skin is cyanotic and cool, small subcutaneous hemorrhages.

1. Which violation of peripheral blood circulation has developed in patient?
2. Explain the mechanism of its development.
3. Explain the mechanism of edema, low skin temperature and subcutaneous hemorrhages.

Task 15

Patient G. has got a wound of the arm. The nurse dressed a wound with a tight bandage. In a few hours he felt pain in the wounded arm, the skin color turn pale, its temperature decreased.

1. Which violation of peripheral blood circulation has developed in patient? Define the type of it.
2. Explain the pathogenesis of pain, low temperature and paleness of the skin.
3. Which other negative consequences can occur if the bandage will not be removed?

Task 16

Patient B., 30 tears old, has got a fracture of right femur bone. During reposition of bone's parts patient felt pain in the left side of chest, which was enhanced with breathing; palpitation, short breath and feeling of fair.

1. What kind of peripheral blood circulation disturbance had developed in patient?
2. Explain the mechanism of its development.
3. What possible complication can develop in this clinical case?

Task 17

The development of thrombosis was provided in the experiment on laboratory animal.

1. What conditions are favorable for thrombus formation? What is the role of endothelial damage in thrombosis pathogenesis?
2. What type of vessels do thrombi usually form in?
3. What complications of thrombosis do you know?

Task 18

The experiment was held on laboratory rat: ethyl alcohol was injected into the vessels of mesentery. Right after the injection the speed of bloodflow was decreased, erythrocytes become to aggregate.

1. What kind of peripheral blood circulation disturbance had developed in patient?
2. Define its type and name other possible causes of development

Examples of tests

Inflammation

1. Which sign from the given belongs to systemic signs of inflammation?

a. swelling

b. pain

c. *****leukocytosis

d. heat

e. redness

2. Which of the given local sign of inflammation is developed due to vascular leakage?

a. Calor (heat)

b. Rubor (redness)

c. Dolor (pain)

d. *****Tumor (swelling)

e. Functio laesa (loss of function)

3. Which event is primary in inflammatory pathogenesis?

a. disorders of blood circulation

b. phagocytosis

c. tissues acidosis development

d. increased vessels permeability

e. *****cell damage

4. Which factor can directly cause secondary alteration?

a. kinines

b. *****lysosomal enzymes

c. lymphokines

d. fibrinogen

e. cytokines

5. Patient B., 32 years old, complaints about dry cough, pain in muscles and joints, appetite loss, headache. Body temperature is 39 C, blood count:

leukocytosis, increased ESR. Which is the mechanism of primary alteration in the case of viral infection?

a. *****cell genetic program realization violation
b. cell membranes damage
c. cell energy supply violation
d. cell receptors damage
e. cell lysosome destruction

6. Which of the statements from listed below correctly describes the metabolic changes in the site of inflammation?

a. Decreased metabolism level during all inflammatory stages
b. Increased catabolism level during final inflammatory stage
c. *****Increased catabolism in early inflammatory stage
d. Increased anabolism in early inflammatory stage
e. Decreased anabolism in final stage of inflammation

7. Patient B., 32 years old, complaints about dry cough, pain in muscles and joints, appetite loss, headache. Body temperature is 39 C, blood count: leukocytosis, increased erythrocytes sedimentation rate. Which of inflammatory mediators can cause systemic effect?

a. catecholamines
b. neutrophil's proteins
c. prostaglandins
d. kinins
e. *****interleukins

8. Arachidonic acid metabolites (prostoglandins, leukotriens) are known as potent mediators of inflammation. Which enzyme will release arachidonic acid from cell membrane lipids?

a. Cyclooxygenase
b. Lipoxygenase
c. Adenylate cyclase
d. *****Phospholipase

e. Myeloperoxidase

9. Which inflammatory mediator is known to be normally sequestered in intracellular granules?

a. *****Histamine

b. Prostaglandin E2

c. Complement

d. Interleukin

e. Bradykinine

10. Which substances released from activated neutrophiles and macrophages may contribute to tissue damage during inflammation?

a. *****Free oxygen radicals

b. Platelet activating factors

c. Endothelial growth factors

d. Interleukines

e. Gamma interferons

11. The main reason of the rapid onset of vasodilation after tissue injury is:

a. *****release of histamine from mast cells

b. neural reflexes

c. release of leukotrienes

d. release of prostaglandins from mast cells

e. activation of complement system

12. The main reason of the rapid onset of arterioles spasm after tissue injury is:

a. release of histamine from mast cells

b. *****neural reflex

c. release of leukotrienes

d. release of prostaglandins from mast cells

e. activation of complement system

13. Which mechanism is the most important for inflammatory exudate formation?

a. prostaglandin’s synthesis

b. tissue basophils degranulation

c. lysosomal enzymes release

d. leukocytes migration

e. *****increased vessels permeability

14. The patient V. has painful vesicles filled with transparent liquid, surrounded with hyperemia zone, as a result of skin burn. Which mechanism is the leading one in inflammatory exudation process?

a. *****increased tissue colloid and osmotic pressure

b. prostaglandin's synthesis

c. decreased tissue proteins level

d. increased lysosomal enzymes amount

e. leukocytes migration from vessels

15. Leakage of fluid out of blood vessels during acute inflammation is due to:

a. *****increased vascular permeability, hydrostatic and tissue osmotic pressure

b. decreased tissue osmotic pressure

c. increased vascular permeability with decreased osmotic pressure

d. increased hydrostatic pressure and permeability

e. increased vascular permeability and hydrostatic pressure with decreased tissue osmotic pressure

16. Choose the negative consequence of exudate formation in the inflammatory process from the given:

a. transport of plasma-derived inflammatory mediators

b. transport of antibodies

c. elimination of toxins and metabolites from the vessels of inflammatory site

d. localization of the agent which caused inflammation

e. *****squeezing of tissues and organs with the exudate

17. Patient G., 32 years old. Diagnosis: acute peritonitis. Muddy yellow liquor with pH 3.0 was got after abdominal cavity puncture. Which cells should be predominately found in inflammatory exudate of the patient with acute inflammation?

a. macrophages
b. monocytes
c. lymphocytes
d. *****neutrophiles
e. eosinophiles

18. Patient P., 45 years old, during last year had pyelonephritis exacerbation three times. Which leukocytes are predominately found in the inflammatory center in chronic inflammation?

a. neutrophiles and adipose cells
b. neutrophiles and fibroblasts
c. adipose cells and lymphocytes
d. eosinophiles and macrophages
e. *****monocytes and lymphocytes

19. Patient K., 28 years old. Diagnosis: pleuritis. In pleural punctate the quantity of neutrophils is high, some neutrophiles include intact microbe cells inside. Define the state of phagocytosis in this case:

a. phagocytosis activation
b. phagocytosis inhibition
c. *****incomplete phagocytosis
d. immune phagocytosis

20. Patient F., with acute inflammation of appendix was operated in a surgical department. The abdominal cavity contained exudate with dark yellow color. Microscopic analysis revealed big amount of microorganisms, neutrophiles, monocytes and purulent bodies. Which kind of inflammation does the patient have?

a. fibrinous
b. *****purulent
c. serous
d. putrescent
e. hemorrhagic

21. Patient K., 28 years old, has quickly healed wound without scar formation after furuncle cutting. Point out cells, which play important role in proliferation process:

a. neutrophiles
b. eosinophils
c. *****fibroblasts
d. lymphocytes
e. monocytes

22. Which disease is an example of an autoimmune disease that leads to chronic inflammation?

a. Viral pneumonia
b. Chronic pyelonephritis
c. Silicosis
d. *****Rheumatoid arthritis
e. Asbestosis

23. Substances or conditions that typically lead to or cause chronic inflammation include all of the following EXCEPT of:

a. foreign bodies
b. *****highly virulent bacteria such as Staphylococcus aureus
c. persistent infections
d. factors that lead to autoimmune reactions
e. inert, inhaled particles

KROK -1 tests on inflammation

1. Inflammation development was studied after skin septic damage in experiment on rabbits. Which hormones have anti-inflammatory effect?

a. thyroid hormones
b. catecholamines
c. mineralocorticoids
d. *****glucocorticoids
e. posterior pituitary hormones

2. Patient S., with rheumatoid arthritis was prescribed glucocorticoids. What is the main mechanism of glucocorticoids anti-inflammatory effect?

a. inhibition of histamine secretion
b. microcirculation improvement
c. secondary proliferation decrease
d. *****immune system activity depression
e. tissue acidosis prevention

3. Inflammatory process development was studied in experiment on rats. Inflammation was caused with 0,1% formalin solution subcutaneous injection. Which hormones can be used to strengthen inflammation in the process of modeling?

a. *****mineralocorticoids
b. female sexual hormones
c. glucocorticoids
d. male sexual hormones
e. posterior pituitary hormones

4. In postoperative scar region one could find granulation tissue intensive growth. In order to inhibit stage of proliferation in inflammation usually glucocorticoid treatment is prescribed. Which mechanism of proliferation processes is inhibited by glucocorticoids?

a. macrophages proliferation
b. *****fibroblasts proliferation
c. collagen resorption stimulation by eosinophils
d. collagen fibers synthesis increase
e. collagenases activation

5. It is know that inflammation is characterized with a series of microcirculation alterations. What is the first response of arterioles to injury?

a. *****vasoconstriction
b. vasodilation
c. redness

d. edema

e. hyperemia

6. Leukocytes are taking active part in inflammatory process. What is the name of the phenomenon where WBC's marginate and become attached to the edge of the endothelium?

a. cementing

b. pavementing

c. margination

d. *****adhesion

e. rolling

7. Leukocytes are taking active part in inflammatory process. They can move from the bloodstream to the site of inflammation. Active movement of neutrophils along a concentration gradient is known as…

a. passive diffusion

b. *****chemotaxis

c. facilitated diffusion

d. chemotactic diffusion

e. adhesion

8. Leukocytes are taking active part in inflammatory process by neutralizing bacteria and clearing the cell's debris from the site of inflammation. The process by which polymorphonuclear leukocyte's cytoplasm surrounds the bacteria and encloses it into an invagination of the cell membrane is known as…

a. phagolysosome

b. phagolysis

c. phagolum

d. *****phagocytosis

e. phagophobia

9. Inflammation is characterized by increased vessels permeability and increase of hydrostatic blood pressure in them. Increase of the osmotic and oncotic

pressure is present in the intercellular fluid. What kind of edema will appear in this case?

a. hydrodynamic

b. colloid-osmotic

c. lymphogenic

d. *****membranogenic

e. mixed

10. Necrosis focus appeared in the area of hyperemia and skin edema as a result of a thermal burn. What is the main mechanism that causes destructive process in the inflammation area in a few hours after the burn has appeared?

a. primary alteration

b. *****secondary alteration

c. emigration of lymphocytes

d. diapedesis of erythrocytes

e. proliferation of fibroblasts

11. In a patient who had undergone trauma of the knee with subsequent hemorrhagic bursitis complains of the limited ability of movements in the joint due to scar formation. Which inflammatory event was responsible for this complication?

a. primary alteration

b. secondary alteration

c. violation ofmicrocirculation

d. exudation

e. *****proliferation

12. A 6-year-old child had hyperergic inflammation of the upper respiratory tract. There was a threat of serious respiratory disorder so the doctor had to use anti-inflammatory hormone for the immediate therapy. Which from the given hormones has anti-inflammatory action?

a. epinephrine

b. *****cortisone

c. insulun

d. thyroid hormone

e. vasopressin

13. Modeling of inflammation on the intestine mesentery of a frog revealed peripheral orientation of leukocytes and their migration through the vascular wall. Which factor from the given determines this process?

a. decrease of oncotic pressure in the vessels

b. increase of oncotic pressure in the site of inflammation

c. *****increase of chemotactic substances in the site of inflammation

d. increase of hydrostatic pressure in the vessels

e. decrease of hydrostatic pressure in the vessels

14. An experimental model of inflammation with abscess formation was provided on laboratory animal. Then a lethal dose of tetanin was injected into the abscess cavity, but the animal didn't die. How can you explain the absence of animal lethal outcome in this case?

a. activation of antibodies synthesis

b. *****formation of a barrier around the site of inflammation

c. stimulation of leukopoiesis

d. intensification of vascularization in the site of inflammation

e. activation of phagocytosis the site of inflammation

15. Killing of pyogenic bacteria by neutrophils in the site of inflammation is brought about by the following mechanism:

a. by active oxygen radicals

b. by nitric oxide mechanism

c. by oxygen independent bactericidal mechanism

d. by hydrolytic enzymes

e. *****all from the listed

16. The patient with ascites was made abdominal cavity puncture. 100 ml of fluid were obtained with the following properties. Which of them is used a typical sign for differentiation of transudate from exudate?

a. single cells presence

b. *low protein content

c. specific gravity

d. fluid color

e. fluid transparency

17. 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. traumatic edema

b. vacuolar degeneration

c. alterative inflammation

d. *exudative inflammation

e. proliferative inflammation

18. A 7-year-old child has acute onset of disease: temperature rise up to 38 C, 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. serous inflammation

b. *catarrhal inflammation

c. suppuratuve inflammation

d. hemorrhagic inflammation

e. fibrinous inflammation

19. Cellular composition of exudate largely depends on the ethiological factor of inflammation. Which leukocytes are the first to be involved in the focus of inflammation caused by pyogenic bacteria?

a. eosinophilic granulocytes

b. basophils

c. myelocytes

d. monocytes

e. *neutrophil granulocytes

Peripheral circulation disturbances

1. Patient G. has inflammatory infiltration on the right forearm. Skin around inflammatory center is red, hot and painful. What kind of blood circulation disorder does this patient have?

a. venous hyperemia
b. sludge syndrome
c. ischemia
d. *****arterial hyperemia
e. embolism

2. What are the main conditions of a thrombus formation?

a. vessel wall injury, BAS influence, anti-coagulation system activation
b. coagulation deficiency, platelets activation, hemodilution
c. anti-coagulation system activation, BAS influence, vessel wall injury
d. hemoconcentration, turbulent blood flow, vessel wall injury
e. *****vessel wall injury, coagulation system activation, slow bloodflow

3. Patient with diabetes mellitus has venous hyperemia in lower extremities. What signs of this pathology would this patient have?

a. redness, local temperature increase, tissues edema
b. paleness, local temperature decrease, tissue elasticity decrease
c. *****cyanosis, local temperature decrease, tissues edema
d. redness, local temperature increase, tissue volume increase
e. cyanosis, local temperature increase, tissue volume decrease

4. Patient M. has angina pectoris attack as a result of myocardium ischemia after a physical load. Choose the correct ischemia definition:

a. *****imbalance between tissues blood supply and demand
b. erythrocytes quantity decrease in circulation blood
c. local vasodilatation under BAS influence
d. oxygen partial pressure decrease in blood under physical load
e. imbalance between blood oxygen capacity and oxygen tissue need

5. Patient 65 years old with diabetes mellitus and diabetic angiopathy has acute respiratory insufficiency as a result of pulmonary embolism. What blood system region could be a place for primary thrombus formation?

a. *****lower extremities veins

b. portal vein system

c. mesenteric arteries

d. pulmonary veins

e. lower extremities arteries

6. Skin-diver 10 minutes after the lifting from a depth of 15 m developed such clinical features: pain in joints and muscles, transient consciousness loss. Choose the appropriate pathology from listed below:

a. gas mixture poisoning

b. lung vessels thrombosis

c. *****gas embolism

d. cerebral vessels spasm

e. respiratory acidosis

7. Patient A. 60 years old with varicose veins of the lower extremities has cyanosis, decreased skin temperature, solitary petechiae, edema. What kind of hemodynamic disorder does the patient have?

a. compression ischemia

b. obstructive ischemia

c. thrombus embolism

d. arterial hyperemia

e. *****venous hyperemia

8. Student X. during the exam couldn’t answer the questions correctly. He turned red, felt hot and embarrassed. Which type of arterial hyperemia this student had developed?

a. neuroparalytic

b. *****neurotonic

c. metabolic

d. pathological

e. post-ischemic

9. Patient P. 40 years old with opened fracture of the hip suddenly developed pulmonary embolism. Choose the possible type of embolism:

a. thromboembolism

b. air embolism

c. tissue embolism

d. *****fat embolism

e. foreign body embolism

10. Patient G. has inflammatory infiltration on the right forearm. Skin around inflammatory center is red, hot and painful. What sign additionally describes the arterial hyperemia development?

a. arterioles constriction

b. venules dilation

c. erythrocytes aggregation in capillaries

d. *****functioning capillaries quantity increase

e. new capillaries growth

11. Sportsman had arterial hyperemia features in humeral region after the intensive training. Which mechanism could lead to working arterial hyperemia development?

a. neurogenic

b. substrative

c. neurotonic

d. neuroparalytic

e. *****metabolic

12. Sportsman had arterial hyperemia features in humeral region after the intensive training. What is the possible negative consequence of arterial hyperemia in organs and tissues?

a. excessive lymph formation with edema development

b. *****ruptures of microcirculation vessels walls

c. cells and tissues hypertrophy and hyperplasia

d. immunity depression

e. cells function activity increase

13. Ischemia is characterized with the following signs EXCEPT:

a. paleness

b. *****redness

c. local hypothermia

d. pain

e. slowing of the bloodflow

KROK 1 tests on Peripheral circulation disturbances

1. Pain in the leg at walking, cyanosis and edema of shins appeared in a patient with varicosity. His foot is cold. What kind of disturbances of regional blood flow appeared in the patient?

a. Angiospastic ischemia

b. Ischemic stasis

c. Compressive ischemia

d. *****Venous hyperemia

e. Obstructive ischemia

2. Edema and cyanosis of low extremities appear in a food shop assistant at the end of a workday. What is the main factor of the edema development in this patient?

a. Dilatation of resistant vessels

b. *****Orthostatic increase of venous pressure

c. Increase of number of functional capillaries

d. Increase of collateral blood flow

e. Increase of tissue drainage

3. Redness and increase in volume of affected place of tissue and increase in local temperature were observed in a patient with burn of thigh. Which pathological process do indicated symptoms correspond to?

a. *****Arterial hyperemia

b. Venous hyperemia

c. Thrombosis

d. Ischemia

e. Stasis

4. Patient's arm was put in plaster cast on account of humeral bone fracture. Swelling, cyanosis and decrease of the temperature of the traumatized arm appeared next day. What kind of disturbances of regional blood flow appeared in the patient?

a. Thrombosis

b. *****Venous hyperemia

c. Ischemia

d. Embolism

e. Arterial hyperemia

5. One of the most dangerous points in myocardial infarction pathogenesis is enlargement of the zone of necrosis, dystrophy and ischemia. Increase in myocardial oxygen consumption plays important role in the development of indicated processes. Which substances contribute to this process?

a. Chloride ions

b. Lipoproteins

c. *****Catecholamines

d. Acetylcholine

e. Adenosine

6. After surgical removing of coronary artery occlusion in a patient with ischemic heart disease, the development of secondary myocardium injury (reperfusion syndrome) characterized by necrobiotic changes in the focus of previous ischemia. This complication results from:

a. Accumulation of hydrogen ions

b. Deficiency of potassium ions

c. Deficiency of adenosine triphosphate

d. *****Excessive accumulation of calcium ions

e. Deficiency of creatinephosphate

7. A 57-year-old man complains of heart pain that has developed after prolonged negative emotions. An emergency doctor diagnosed ischemic heart disease. What kind of ischemia is the most probable in this patient?

a. Compressive

b. Obliterative

c. Angiospastic

d. Obturative

e. Metabolic

8. The theory exists that atherosclerosis plays an important role in periodontitis development, affecting vessels of gums. Which regional blood flow disturbance develops under atherosclerosis of vessels?

a. Active hyperemia

b. Passive hyperemia

c. Embolism

d. *****Ischemia

e. Disorders of lymph outflow

9. Instantaneous death of pilots occurs under depressurization of an airplane at the altitude of 19 km. What is the reason of the death in this case?

a. *****Multiple gas embolism

b. Hemorrhage to the brain

c. Gas embolism of cerebral veins

d. Bleeding

e. Paralysis of respiratory center

10. Gas embolism developed in a diver who was lifted up to the surface very fast. In this case it is a result of a fast changing:

a. *****from increased atmospheric pressure to normal

b. from normal atmospheric pressure to increased

c. from normal atmospheric pressure to decreased

d. from decreased atmospheric pressure to normal

11. Examination of the lower extremities of a 40-year-old patient with vascular disease of lower limbs (obliterating endarteritis) revealed skin pallor and dystrophy, local temperature decrease, and pain. The patient is likely to have the following disorder of the peripheral blood flow:

a. *****Obstruction ischemia

b. Compression ischemia

c. Angiospastic ischemia

d. Venous hyperemia

e. Arterial hyperemia

12. A female patient consulted by doctor about leg pain, edema of feet and shins that arises usually in the end of the workday. On the clinical examination: leg skin is cyanotic and cold to the touch. What type of peripheral blood flow disorder does this patient have?

a. *****Venous hyperemia

b. Arterial hyperemia

c. Ischaemia

d. Stasis

e. Thrombosis

13. Upper neck node of sympathetic trunk was removed from the rabbit on experiment. Redness and increased temperature of the skin of head is observed. What form of peripheral blood flow disorder developed in the rabbit?

a. *****Neuroparalytic arterial hyperemia

b. Neurotonic arterial hyperemia

c. Metabolic arterial hyperemia

d. Venous hyperemia

e. Stasis

14. A 42 year old woman with neuralgia of trigeminal nerve complains of recurrent reddening and sensation of heat in the right part of her face and neck, and hypersensitivity of the skin. Which type of arterial hyperemia causes these symptoms?

a. Metabolic

b. *****Neurotonic

c. Neuroparalytic

d. Functional

e. Reactive

15. A patient with obliterating endarteritis underwent ganglionary sympathectomy of femoral artery. The positive therapeutic effect of this operation is related to development of arterial hyperemia of the lower extremities. Which type of arterial hyperemia would develop in the patient after operation?

a. Metabolic

b. Neurotonic

c. *****Neuroparalytic

d. Functional

e. Reactive

16. After physical activity, a patient with the thrombophlebitis of the lower extremities suddenly developed dyspnea, acute pain in the chest, cyanosis, swelling of cervical veins. What type of circulation pathology can develop in this situation?

a. thromboembolism of mesenterial vessels

b. thromboembolism of coronary vessels

c. thromboembolism of the brain vessels

d. *****thromboembolism of the pulmonary artery

e. thromboembolism of the portal vein

17. 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. air

b. gaseous

c. *****fat

d. tissue

e. thromboembolism

18. The patient developed brain stroke as a result of thromboembolism in basilar artery system. Choose the most common place of thrombi formation in this case:

a. aortic aneurysm

b. pulmonary veins

c. *****cardiac thrombi

d. aortic atherosclerotic plaques

e. leg veins

19. 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 artery. The most probable cause of these changes is:

a. venous hyperemia

b. arterial hyperemia

c. *****ischemia

d. embolism

20. 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. gas embolism

b. air embolism

c. tissue embolism

d. thromboembolism

e. *****fat embolism

RECOMMENDED LITERATURE

Basical:

1. General and clinical pathophysiology : textbook for students of higher educational institutions, of IV th level of accreditation / A. V. Kubyshkin [et al.] ; ed. by.: A. V. Kubyshkin, A. I. Gozhenko. - 2nd ed. - Vinnytsya : Nova Knyha Publishers, 2016. - 656 p.
2. Simeonova, N. K. Pathophysiology : textbook for students of higher medical educational institutions of the III-IV accreditation levels / N. K. Simeonova ; ed. by.: V. A. Mikhnev. - 2nd ed. - Kyiv : AUS Medicine Publishing, 2015. - 544 p.

Additional:

1. Damjianov, Ivan. Pathophysiology / I. Damjianov ; ill. M. Chansky. - Philadelphia : Saunders, 2009. - 464 p.
2. General and Clinical Pathophysiology : Workbook for medical students and practitioners. - Odessa : The Odessa State Medical University, 2002. - 243 p.
3. Gozhenko, A. I. Pathophysiology / A.I. Gozhenko, I.P. Gurkalova. - Odessa : The Odessa State Medical University, 2005. - 325 p.
4. Kumar V. Robbins and Cotran Pathologic Basis of Disease. V. II / V. Kumar, A. K. Abbas, J. C. Aster. - South Asia ed. - India : Elsevier, 2015. - 1391 p.
5. Kumar V. Robbins and Cotran Pathologic Basis of Disease. Vol. I / V. Kumar, A. K. Abbas, J. C. Aster. - South Asia ed. - India : Elsevier, 2015. - 1391 p.
6. McPhee, Stephen J. Pathophysiology of Disease An Introduction to Clinical Medicine [Electronic resource] : учебник / Stephen J. McPhee. - 2nd ed. - 107 МБ. - NY : Appleton & Lange, 2000.
7. Mufson, Maurice A. Pathophysiology : PreTest Self-Assessment & Review / M.A. Mufson, C. A. Heck, S. M. Nesler. - 3th ed. - Chicago : Medical Publishing Division, 2002. - 268 p.
8. Pathophysiology: textbook for students / P.F. Litvitsky, S.V. Pirozhkov, E.B. Tezikov). - Moscow:Geotar-Media, 2016. – 432 p.