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INFLAMMATION

(pathophysiological aspects)

Minsk BSMU 2015

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
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КАФЕДРА ПАТОЛОГИЧЕСКОЙ ФИЗИОЛОГИИ

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ВОСПАЛЕНИЕ
(патофизиологические аспекты)

INFLAMMATION
(pathophysiological aspects)

Учебно-методическое пособие

Минск БГМУ 2015

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Рассматриваются основные вопросы патофизиологии воспаления: клинические признаки, этиология и патогенез воспалительной реакции, процесс фагоцитоза, виды воспаления, его возможные исходы, а также влияние нервной и эндокринной систем на характер течения воспаления.

Предназначено для студентов 2–3-го курсов медицинского факультета иностранных учащихся, обучающихся на английском языке.

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MOTIVATIONAL CHARACTERISTIC OF THE TOPIC

Teaching manual is designed to optimize the learning process and is offered to prepare students for laboratory lesson on the topic.

Lesson purpose: learn the basic causes, mechanisms of development, clinical manifestations, stages and biological essence of inflammation as a typical pathological process and based on this knowledge to form the ability to analyze and model the clinical situation related to the development of inflammation, to solve professional problems doctor.

Lesson objectives: the student should:

1. Know:

 definition of the notions: «inflammation», «alteration», «exudation» «phagocytosis»;

 causes and mechanisms of the inflammatory process development;

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

 the main effects of «inflammatory mediators»;

 the main endogenous anti-inflammatory factors;

 the stages of inflammation;

 stages of peripheral blood circulation in the inflammation and the mechanisms of their development;

 types of exudates, their difference from transudate;

 stages of phagocytosis and their mechanisms and biological significance;

 stages, ways and the mechanisms of emigration of leukocytes in inflammation;

 causes and types of phagocytosis violations;

 mechanisms of proliferation, its stimulators and inhibitors;

 pathogenetic features of acute and chronic inflammation;

 the basic theories of inflammation pathogenesis.

2. Be able to:

 to interpret the main existing theories of the pathogenesis of inflammation;

 to characterize the biological significance of inflammation;

 to solve professional problems based on analysis of clinical and pathophysiological model situations related to the development of inflammation.

3. Be familiar with:

 clinical manifestations and basic principles of detection of inflammation;

 clinical features of acute and chronic inflammatory process in children and older people.

Requirements for the initial level of the knowledge. For complete mastering of the theme the student must go over the next notions from Medical Biology, Histology and Normal Physiology again: «leukocytosis», «immune system», «phagocytosis».

The control questions from related disciplines:

1. The internal environment of the organism and the mechanisms to maintain homeostasis.
2. Basis of regulation of vital activity.
3. Functions of the blood.
4. The physiologically active substances affecting the tone and vascular permeability.
5. Nervous and humoral mechanisms of regulation of vascular tone.
6. Factors of leukocyte adhesion to the endothelium.
7. Leukocytosis. Its kinds.
8. Phagocytosis as a protective reaction of the body.
9. Immunity and immune deficiency conditions.

Control questions:

1. The definition of the notion and general characteristic of components of inflammation.
2. Inflammation as a typical pathological process. Local and systemic manifestations of inflammation.
3. Etiology of inflammation. Primary and secondary alteration in inflammation.
4. Basic mediators of inflammation, their origin, principles of classification.
5. The significance of inflammation mediators in the development of secondary alteration.
6. Metabolic changes in the focus of inflammation.
7. Physical and chemical changes in the focus of inflammation, mechanisms of their development and significance.
8. Functional element of the organ as a substrate of alteration and formation of inflammatory reaction.
9. Impairment stages of peripheral blood circulation in the focus of inflammation and mechanisms of their development.
10. The reasons and mechanisms of increasing the permeability of a vascular wall in the focus of inflammation.
11. The definition, mechanism and significance of exudation in inflammation.
12. Types of exudates, their distinctions from transudate.
13. The definition of the notion and biological significance of phagocytosis.
14. I. I. Mechnikov’s study about phagocytosis as a protective reaction of the organism.
15. Stages, ways and mechanisms of leukocytes emigration in inflammation.
16. Factors regulating activity of phagocytes in the focus of inflammation. Chemotaxis mechanisms, factors stimulating and oppressing chemotaxis.
17. Stages of phagocytosis and their mechanisms.
18. The reasons and types of phagocytosis impairments.
19. The proliferation stage, its basic signs and development mechanisms.
20. General manifestations of inflammation, mechanisms of its development and the significance for the organism.

21. Endogenic pro- and anti-inflammatory factors.
22. Relationship of local and general phenomena in inflammation. The role of the nervous, endocrine and immune systems in the development of inflammation. General biological significance of inflammation.
23. Positive and negative significance of inflammation for the organism.
24. The basic theories pathogenesis of inflammation. Modern conceptions of inflammation mechanisms.

GENERAL CHARACTERISTICS OF INFLAMMATION

The ability of the body to sustain injury, resist attack by microbial agents, and repair damaged tissue is dependent upon the inflammatory reaction, the immune system response, and tissue repair and wound healing. Although the effects of inflammation are often viewed as undesirable because they are unpleasant and cause discomfort, the process is essentially a beneficial one that allows a person to live with the effects of everyday stress. Without the inflammatory response, wounds would not heal, and minor infections would become overwhelming.

Inflammation (Greek — phlogosis; Latin — inflammation) is one of the most complex processes, commonly used in human pathology and are often the cause of many disorders of the human body and animals.

Today, most experts believe that inflammation is a protective and adaptive reaction of the body to injury which formed in the course of evolution. This reaction causes the certain changes in the terminal vessels, blood, connective tissue, which destroy the agent causing the damage, and then restores the damaged tissue.

Biological meaning of inflammation is the elimination or restriction of lesion and pathogens. Inflammation is aimed at localization, destruction and removal of factors caused it. Inflammation also produces undesirable effects. Inflammatory reactions, for example, underlie life-threatening hypersensitivity reactions to insect bites, drugs, and toxins as well as some common chronic diseases, such as rheumatoid arthritis, atherosclerosis, and lung fibrosis.

Repair by fibrosis may lead to disfiguring scars or fibrous bands that cause intestinal obstruction or limit the mobility of joints.

Thus, inflammation in the history of the animal world was formed as a dual process in which there are, and always protective and harmful elements act.

On one hand, this is a damage threatening the organ and even the whole body, and on the other hand — is a favorable process, which helps the body to fight for its survival. In general pathology the inflammation is usually regarded as a «key» general pathological process, as it possess all the features characterized the typical pathological processes.

Inflammation is the typical pathological process formed in the evolution both protective and adaptive response of the body to the effects of pathogens (phlogogenic) factors, aimed at localization, destruction and removal of

phlogogenic agent, as well as the elimination of the consequences of its actions and is characterized by alteration, exudation and proliferation.

For inflammation in any tissue or organ is used their Latin or Greek name and add the ending ***-itis***. For example, inflammation of the skin — dermatitis, liver — hepatitis, infarction — myocarditis.

THE ETIOLOGY OF INFLAMMATION

The inflammation can arise as result of influence of any agent. Force and duration of such influence should be stronger, than adaptive possibilities of the tissue, organ. Inflammation occurs as the body's response to pathogenic stimulus and damage caused by it. Pathogenic stimuli, i.e. causes of inflammation may be various: biological, physical, and chemical both exogenous and endogenous origin.

Exogenous factors include: *biological factors* (microorganisms — bacteria, viruses, rickettsia, protozoa; animal organisms — worms, parasites, foreign proteins, endotoxins, insect poisons, snakes), *chemicals* (acids, alkalis, salts of heavy metals), *physical factors: mechanical* (trauma, foreign body, pressure, rupture), *thermal* (cold, heat), *electrical* (natural electricity, industrial and household current) and the *impact of radiation* (X-rays, α-, β- and γ-rays, ultraviolet rays).

Endogenous factors, factors arising in the organism as a result of another disease are related to tissue decay products, blood clots, heart attacks, hemorrhage, bile and urinary stones, salt deposits, antigen-antibody complexes.

The development of inflammation, its severity, the nature, course and outcomes are determined not only by an etiologic factor (force of phlogogenic stimulus, its features), but the reactivity of the organism, conditions and specific circumstances of its origin and development.

THE MAIN CLINICAL SIGNS OF INFLAMMATION

Inflammation is predominantly a local manifestation of a general reaction of the body to the action of pathogenic, emergency stimulus. Under optimal conditions, the inflammatory response remains confined to a localized area. However, in some cases local injury can result in prominent systemic manifestations as inflammatory mediators released into the circulation.

Local signs of inflammation. The main signs of inflammation have long been known. Yet Roman scientist encyclopaedist A. Celsus in his treatise «On Medicine» has identified the following main local symptoms of inflammation: *redness (rubor), swelling (tumor), heat (color), and pain (dolor).*

The Roman physician and naturalist K. Galen added the fifth one — *the impairment of a function* (*function laesa*). Although these symptoms characteristic of an acute inflammation of the external coverings have been known for over 2000 years, they have not lost their significance today.

Redness — an evident clinical sign of inflammation associated with the expansion of the arterioles, the development of arterial hyperemia and «arterialization» of venous blood in the area of inflammation.

Swelling is caused by the enlargement of a tissue blood supply, infiltration due to the development of an exudation and an edema and swelling of the tissue elements.

Heat — an increase of temperature of the inflammatory area, develops as a result of the inflow of warm arterial blood as well as the metabolism activation, an increase of heat production and heat loss in the focus of inflammation.

Pain appears due to the irritations of sensitive nerve endings by various biologically active substances (histamine, serotonin, bradykinin, some prostaglandins and others), shift of pH of the internal environment in the acidic side, the mechanical compression of receptors of nerve fibers by the inflammatory edema.

Impairment of function caused by the inflammation occurs as a rule, sometimes it may be limited by the disorders of the function of the diseased tissue, but more often the whole body suffers from it, especially when the inflammation occurs in the vital organs.

Function impairment of the inflamed organ is associated with the structural damage, the development of pain, impairment of its neuroendocrine regulation.

In chronic inflammation and inflammation of the inner organs some of the mentioned signs may be absent.

General signs of inflammation. Inflammation is a process which is manifested not only by bright marked local symptoms, but also very typical and often significant changes in the body.

The most prominent systemic manifestations of inflammation are:

1. ***Changing of the number of leukocytes in the peripheral blood.*** The vast majority of inflammatory processes are accompanied by leukocytosis, more rarely leukopenia in inflammation of a viral origin. By its nature, leukocytosis is mainly redistributive, i. e. is due to the redistribution of white blood cells in the body, releasing of them into the blood stream. Stimulation of sympathoadrenal system, the effects of some bacterial toxins, products of tissue decay, as well as a number of inflammatory mediators (IL-Iβ, etc.) are the main reasons of the development of leukocytosis. Activation of leukopoesis contributes to the increase of the number of leukocytes in peripheral blood.

2. ***Fever,*** which develops under the influence of the inflammatory focus incoming pyrogenic factors: primary pyrogens of endogenous and exogenous origin (endotoxins — lipopolysaccharide nature structural elements of cell membranes of various bacteria, various microbial antigens and non-microbial origin, different exotoxins, etc.) and secondary pyrogens (interleukin-Iβ, interleukin-6, tumor necrosis factor).

3. ***Change in the number and quality of blood plasma proteins*** (dysproteinemia). Synthesized by hepatocytes, macrophages and other cells of the so-called «acute phase proteins» are accumulated in the blood in case of

an acute inflammatory process. Chronic inflammation is characterized by the increased amount of α-and particularly γ-globulin, the imbalance of albumins and globulins in the blood flow.

4. ***The increase of erythrocyte sedimentation rate*** **(ESR),** particularly in chronic inflammatory processes, due to the increased blood viscosity, reduced negative charge and agglomeration of red blood cells, changes in physical and chemical constants of proteins (dysproteinemia) of blood, an elevation of body temperature.

5. ***Changes of hormone levels in the blood*** consist of an increase concentration of catecholamines and corticosteroids.

6. ***Intoxication of an organism***.

7. ***Sepsis and septic shock***, also called the systemic inflammatory response, represent the severe systemic manifestations of inflammation.

THE PATHOGENESIS OF INFLAMMATION

The inflammation, as typical pathological process, consists of three components (stages) — ***alteration***, ***exudation*** and ***proliferation***. They are closely interrelated, mutually complement and pass into each other, there are no clear boarders between them. Depending on the process, predominating at a certain stage of inflammation, the following stages are distinguished:

1. ***Stage of alteration*** (damage): a) *primary alteration*, b) *secondary alteration*.

2. ***Stage of exudation and emigration*** (*vascular and cellular responses*).

3. ***Stage of proliferation and repair***: a) *proliferation*, b) *completion of inflammation*.

STAGE OF ALTERATION

Inflammation always begins with a tissue injury, which is a complex of metabolic, physicochemical, structural and functional changes, i. e. with alteration (from the Latin. alteratio — changes) tissue, which plays a role of the inflammatory trigger.

Alteration is a stage, with which all forms of an inflammation begin. This stage is characterized by the violation of cells structure and function, of fibrous structures of the microcirculatory system, nervous derivations. The damages of tissues are characterized by the disorder of proteins, fats, and carbohydrates metabolism, physicochemical and morphological changes of tissues. The more complicated protein fibrous derivations (collagen, elastin) can be destroyed also. Necrobiosis and necrosis can take place in tissues.

It is the ***reversible*** (sublethal) damage of cells if they can adapt and restore their structure and function, and the ***irreversible*** (lethal) damage of cells, which is characterized by irrevocable change of cells structure.

There are two types of the alteration: ***primary*** and ***secondary***.

The primary alteration is the result of the influence of the pathological (flogogenic) agent on a tissue. Metabolic and structural changes arise therefore. Various cells react differently: some cells perish, others — remain alive, and others become activated. The activated cells are responsible for the creation of following stages of an inflammation.

The secondary alteration is the consequence of the primary alteration and it arises even at the absence of the damaging agent.

The signs of cells damage are the follows: the lessening of pO_2; limitation or termination of O_2 consumption by cells; the decrease of ATP and ADP and the increase of the inorganic phosphorus concentration; the intensification of glycolysis, which cause the accumulation of lactic acid and pyruvate acid; the decrease of cells pH.

The decrease of ATP concentration reduces the activity of ionic pumps of cells membranes, the parity of Na^+, K^+, Ca^{2+} and Mg^{2+} in cytoplasm is violated, and the activity of biochemical systems of cells is violated too. Then content of water in cells changes, the synthesis of protein decreases, the density of cytoplasm is raises, the amount of H^+ increases, the outlines of the cell are changed. These changes are reversible.

The constant deficiency of energy provokes the rise of permeability of organelles membranes and swelling of the cell takes place. These changes are the result of the significant damage of cells membrane structures. Free radicals and peroxides play the significant role in this process. They are the result of hypoxia of the damaged tissues and the violation of biochemical processes in cells. The accumulation of free radical substances exceeds the possibility of the cell to neutralize them.

Therefore these substances damage membrane structures of the cell. Damage of lysosomal membranes is especially dangerous. Enzymes, which are localized in lysosomes, can acts on all kinds of macromolecules of cytoplasm. Primary lysis of the cell can be result of the lysosome membrane destruction by the pathological agent. Lysosome enzymes can get in the intracellular space. The secondary lysis of cells is the result of destruction of lysosomal membrane by free radicals.

When inflammation factors of the complement system plays a significant role in non-specific inactivation and destruction of flogogenic agent, dead cells and damaged tissues. *Complement's system* is protein complex in blood of the man, which consists from 20 proteins. These proteins are activated during the invasion of microorganisms, promote damage of cells membranes and stimulate the protective phagocytic response. The main task of the complement's system is destruction of all foreign agents, which get or derivate in human organism. These proteins, as well as lysosomes enzymes, promote development of the first stage of an inflammation. The damage of cells is accompanied by disorder of metabolism. Lisosomal enzymes destroy carbohydrates, proteins, fats, nucleic acids uncontrollably, and the activity of enzymes of glycolysis rises.

The inflammation always begins with the rise of metabolic processes. The main characteristic of *alteration* is the activation of metabolism. These are

the processes of substances disintegration. As a result of destruction of glycoproteins and glycosaminoglycan's complexes free amino acids and polypeptides are formed. Some of these substances are *mediators of inflammation*, which determine dynamics of inflammatory process.

MEDIATORS OF INFLAMMATION

At present, a large number of these «mediators» have been found. They are the intermediaries in the implementation of the actions of the agents resulting in the inflammation.

Releasing under the influence of the damaging agent, «mediators» change a variety of processes in the tissues — vascular tone, the permeability of the walls, blood supply, the emigration of white blood cells and other blood cells, their adhesion and phagocytic activity, cause pain, etc.

Mediators originate either from plasma or from cells (fig. 1). Plasma-derived mediators (e. g., complement) are present in plasma in precursor forms that must be activated, usually by a series of proteolytic cleavages, to acquire their biologic properties.

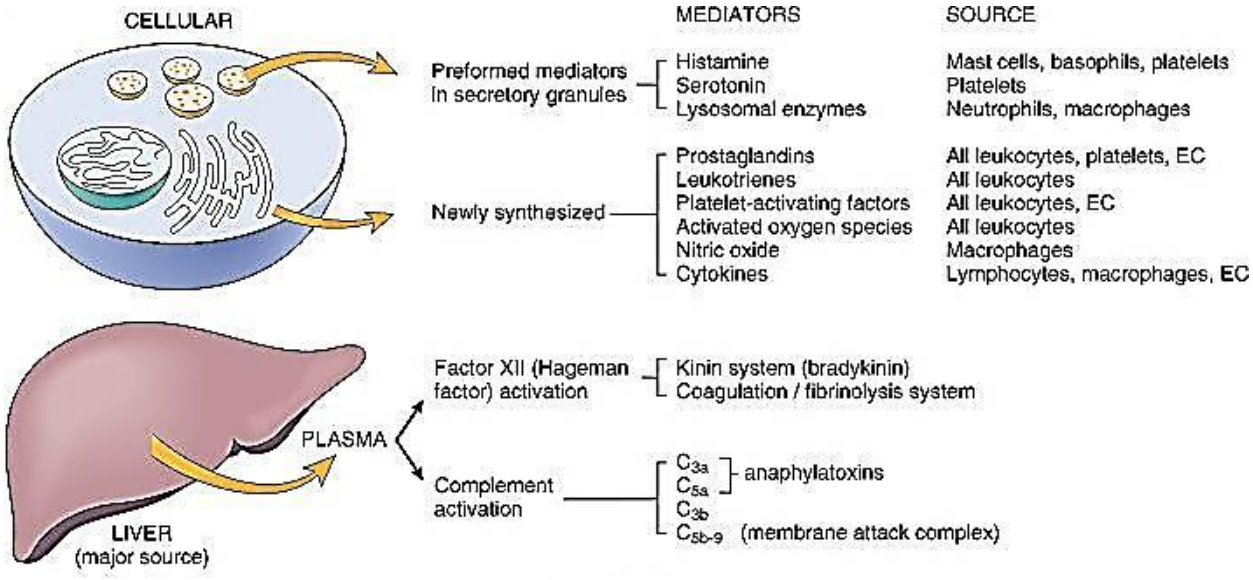

Fig. 1. Mediators of inflammation (EC-endothelial cells)

Cell-derived mediators are normally sequestered in intracellular granules that need to be secreted (e. g., histamine in mast cell granules) or are synthesized de novo (e. g., prostaglandins, cytokines) in response to a stimulus.

The major cellular mediators sources are platelets, neutrophils, monocytes/ macrophages, and mast cells, but mesenchymal cells (endothelium, smooth muscle, fibroblasts) and most epithelia can also be induced to elaborate some of the mediators.

Most mediators perform their biologic activity by initially binding to specific receptors on target cells. Some, however, have direct enzymatic activity (e. g., lysosomal proteases) or mediate oxidative damage (e. g., oxygen metabolites).

A chemical mediator can stimulate the release of mediators by target cells themselves. These secondary mediators may be identical or similar to the initial mediators but may also have opposing activities. They provide mechanisms for amplifying or in certain instances counteracting the initial mediator action.

Mediators can act on one or few target cell types, have widespread targets, or may even have differing effects, depending on cell and tissue types.

Once activated and released from the cell, most of these mediators are short-lived. They quickly decay (e. g., arachidonic acid metabolites) or are inactivated by enzymes (e. g., kininase inactivates bradykinin), or they are otherwise scavenged (e. g., antioxidants scavenge toxic oxygen metabolites) or inhibited (e. g., complement inhibitors). There is thus a system of checks and balances in the regulation of mediator actions. Most mediators have the potential to cause harmful effects.

CLASSIFICATION OF MEDIATORS

There are different approaches to systematization of «mediators of inflammation».

1. According to **the chemical structure** they are classified as: 1) *biogenic amines* (histamine, serotonin); 2) *polypeptides* (bradykinin, kallidin, methionyl-lysyl-bradykinin); 3) *proteins* (the components of the complement system, lysosomal enzymes, cationic proteins granulocytic origin, monokines, lymphokines); 4) *polyunsaturated derivatives of fatty acids* (prostaglandins, thromboxanes, leukotrienes).

2. **By their origin** «mediators» are divided into: 1) *cellular* (histamine, serotonin, granulocyte factors, monokines, lymphokines), 2) *humoral or plasma* (C3a and C5a fraction of the complement, anaphylatoxins, kinin, and blood coagulation factors) (table 1).

Table 1

Basic cellular and humoral inflammatory mediators

Name	The main effects	The main sources of their origin
Histamine	Smooth muscle spasm (increases the formation of prostaglandins E_2 and $E_{2\alpha}$, thromboxane). Vasodilation (widening of precapillary arterioles). Increase of permeability of blood vessels, inhibition of chemotaxis and phagocytic activity of neutrophils and production of lymphokines	Mast cells, basophilic leukocytes
Thrombotonin	The narrowing of post-capillary venules, increase of permeability of blood vessels. Pain. Itching	Platelets, mast cells
Kinins (bradykinin, bradykinin-metionillizil)	Vasodilation. Increase of vascular permeability. Pain. Smooth muscle spasm	α2-globulin, plasma

Name	The main effects	The main sources of their origin
The components of the complement system (C3a, C5a)	Degranulation of mast cells (histamine release). Increase of vascular permeability. Smooth muscle spasm. Leukocyte chemotaxis stimulation	Plasma proteins
Monokines, interleukins, IL-1β, tumor necrosis factor-α (TNF-α) and others	Stimulation of the synthesis of prostaglandins, phagocytosis, activation and fibroblast proliferation. Pyrogenesis	Macrophages, monocytes, neutrophil granulocytes
Lymphokines, IL-2, macrophage activating factor	The activation of natural killer cells. Stimulation of granulocytes	Lymphocytes
Prostaglandins (PGE, $PGE_{2\alpha}$)	Vasodilation. Increase of vascular permeability. Pyrogenesis	Polyunsaturated fatty acids of phospholipids and plasma membranes
The leukotrienes (LTB4, etc.)	Smooth muscle spasm. Increased vascular permeability. The activation of leukocytes	Granulocytes. Monocytes. Platelets. mast cells
Thromboxane	Vasoconstriction. Platelet aggregation. activation of granulocytes	Macrophages, monocytes, granulocytes
Lysosomal factors (acid hydrolases, cationic non-enzymatic proteins)	Secondary alteration, «generation», «inflammatory mediators». Contributes to vasodilation, increase of vascular permeability, the development of edema and leukocyte emigration, microthrombogenesis. Microbicide	Neutrophil granulocytes. Monocytes, macrophages

Humoral «mediators» are usually characterized by generalized effects and spectrum of their action is potentially wider than cellular mediators, the effects of which are mainly local. In turn, the cellular mediators can be separated by the type of cells releasing «inflammatory mediators» (factors of polymorphonuclear leukocytes, macrophage phagocytic systems, mast cells and platelets).

3. ***On the features of their release from the cells*** «inflammatory mediators» can be classified as: 1) *non-cytotoxic*, 2) *cytotoxic* mediators of releasing.

In the first case there is a corresponding receptor-stimulated cells output of «mediators» by the physiological exocytosis, in the second one — cell destruction occurs, whereby mediators out of it into the environment. Meanwhile, the same «mediator» (histamine and serotonin) can pass into it by both ways (from mast cell or platelet).

PHYSICOCHEMICAL CHANGES AT INFLAMMATION

The complex of physicochemical changes at inflammation includes ***acidosis, hyperioniya, disioniya, hyperosmiya, hyperonkiya, changes of the surface charge and the electric potential cell.***

At the very initial period of the inflammatory response a *short primary acidosis* associated with ischemia develops. In this process a content of acidic products increases in the tissues. On developing of arterial hyperemia acid-base

condition in the tissues of the inflammatory focus is normalized, and then a transitory metabolic acidosis develops, which is initially compensated (a decrease in alkaline reserves of tissues takes place, but their pH does not change). With the progression of the inflammatory process *uncompensated acidosis* has been developing due to the growth of the concentration of free hydrogen ions and depletion of tissue alkaline reserves. In alteration of cells large amount of intracellular potassium is released.

In combination with an increase of the amount of hydrogen ions, this leads to *hyperionia* in the inflammatory focus, the latter causes an increase of *osmotic pressure*. Accumulation of oligo-and monopeptides in the process of polypeptides proteolysis as a result of action of lysosomal hydrolases activated in acidosis leads to an increase of oncotic pressure (*hyperonkiya*). Under the influence of changes in the metabolic processes initiated by exposure of phlogogenic stimulus and lysosomal enzymes, the intensification of lytic processes, cell membranes become damaged.

This, on the one hand, increases the alteration, and on the other — contributes to the further enhancement of vascular-tissue permeability caused by the «inflammatory mediators» (histamine, bradykinin, PGE_2, etc.). Structural and functional changes in inflammation are very variable (from minimal structural abnormalities till destruction and necrosis), and may develop at the subcellular (mitochondria, lysosomes, endoplasmic reticulum, etc.), cellular and organic levels.

Structural changes are observed both in the parenchymal cells and stromal tissues and organs; characteristic changes in the cytosol and organelles, changes of their shape, size and number are characteristic for cells.

Thus, alteration as an initial stage and a component of the inflammatory process is characterized by the development of regular metabolic changes, physicochemical properties, formation and realization of effects of physiologically active substances («inflammatory mediators»), a deviation from the shape of the structure and function of tissue in the inflammatory focus.

Such changes, on the one hand, provide extra activation of processes directed to localization, inactivation and destruction of a pathogenic agent, and the other — are the base of the other components of inflammation-vascular reactions, exudation of fluid, leukocyte emigration, phagocytosis, cell proliferation and repair of damaged tissue.

STAGE OF EXUDATION AND EMIGRATION

Exudation (from Lat. exsudatio) or sweating is the escape of fluid, proteins, and blood cells from the vascular system into the interstitial tissue or body cavities. Changes in vascular flow and caliber begin early after injury and develop at varying rates, depending on the severity of the injury.

Exudation includes inflammation triad:

1) *vascular responses* and changes in blood circulation in the inflammatory focus;

2*) the actual exudation* — the output of the liquid portion of the blood vessels;

3) *the emigration of leukocytes* (from Lat. emigration — evictions) — output of leukocytes in the area of inflammation and the development of phagocytosis.

VASCULAR REACTIONS AT INFLAMMATION

Dynamics of vascular reactions and changes in blood circulation in developing of inflammation is stereotyped: in the beginning ***a short-time reflex spasm of arterioles and precapillaries*** arises, then replacing each other's an ***arterial and venous hyperemia, prestasis and stasis*** (arresting of blood flow) developing.

When exposed to the tissue by phlogogenic agent, as a rule, transient increase of tone of arteriolar walls and precapillaries develops, i. e. local ***vasoconstriction or spasm***. Local vasoconstriction lasting a few seconds, usually leads to impairment of blood flow — ischemia. The reason for vasoconstriction is stress reactions, the release under the influence of damaging factor of biologically active substances of vasoconstricting action: catecholamines, thromboxane, and some prostaglandins.

After an inconstant and transient vasoconstriction of arterioles, lasting a few seconds, vasodilation occurs (fig. 2).

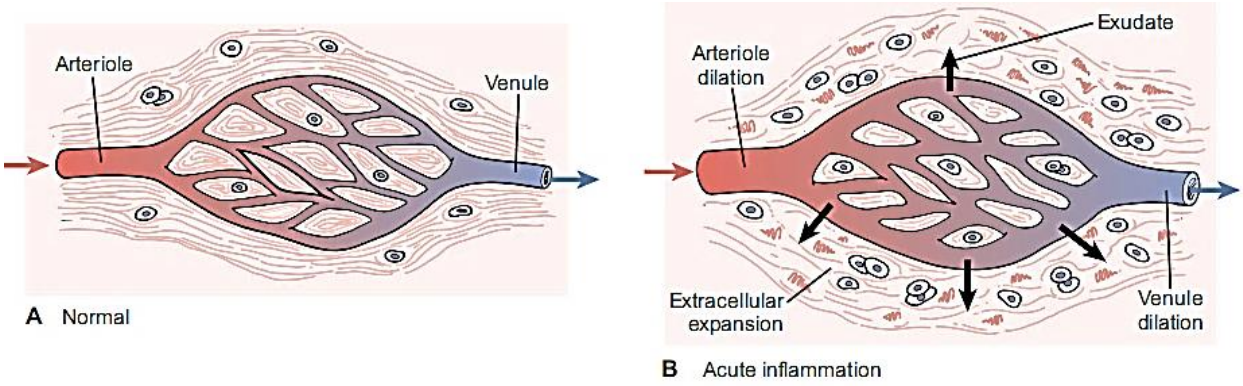

Fig. 2. Vascular phase of acute inflammation:
A — normal capillary bed; B — acute inflammation with vascular dilation causing increased redness (erythema) and heat (calor), movement of fluid into the interstitial spaces (swelling), extravasation of plasma proteins into the extracellular spaces (exudate), and emigration of leukocytes

Vasodilation or *arterial hyperemia* first involves the arterioles and then results in opening of new capillary beds in the area. ***Arterial hyperemia*** arises due to the formation and action in the inflammatory area of a large number of vasoactive substances — *«inflammatory mediators»* which suppress the automaticity of smooth muscle walls of the arterioles and precapillaries and cause their relaxation. This leads to an increase in the inflow of arterial blood,

speeding up its motion, opens up previously not functioning capillaries, increases the pressure in them. In addition, the vessels dilate as a result of «paralysis» of vasoconstrictors, dominance of parasympathetic effects on the vascular wall, acidosis, hyperpotassioioniya, reduction of the connective tissue elasticity surrounding the blood vessels. Thus, the main mechanisms leading to the development of arterial hyperemia are *neurogenic, humoral and mioparalitic*.

How long vasodilation lasts depends on the stimulus, but it is eventually followed by the next event, slowing of the circulation.

Arterial hyperemia under the influence of a number of factors in inflammatory area is replaced by ***venous hyperemia***. The occurrence of venous hyperemia is due to:

1. *Blood factors* — marginal location of leukocytes, swelling of erythrocytes, output of blood liquid into the inflamed tissue and blood clots, the formation of microthrombi due to the activation of Hageman Factor and reduction of heparin.

2. *Factors of the vascular wall* — the swelling of endothelium, resulting in the narrowing of the small blood vessels lumen.

3. *Factors of surrounding tissues* — changed venules lose their elasticity and become more flexible to the compressing action of the exudate. Finally, the tissue action is that the edematous tissue compresses the veins and lymphatic vessels and contributes to the development of venous hyperemia. With the development of the prestatic condition the pendulum movement of blood is observed — during the systole it moves from the arteries to the veins, during the diastole — in the opposite direction. Finally, the blood flow may stop completely and stasis is developing, the result of which may be irreversible changes in the blood cells and tissues.

The output of the liquid part of the blood into the interstitium of the inflammation — actually ***exudation***, occurs due to a sharp increase of permeability of histohematogenous barrier and, consequently, enhance of the filtering process and microvesicular transport (fig. 3).

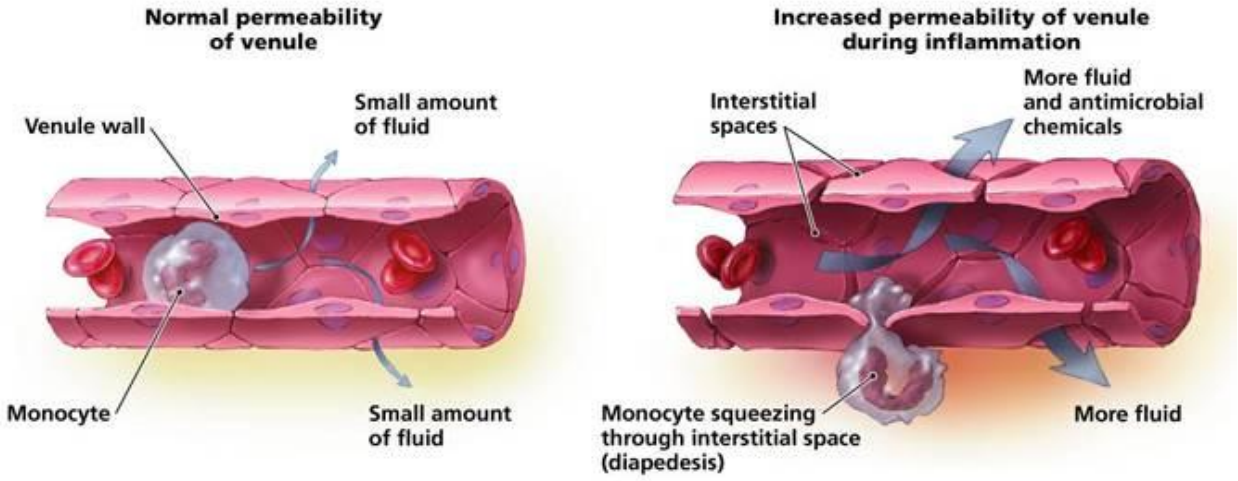

Fig. 3. Changes of permeability of blood vessels at inflammation

Output of fluid and soluble substances occur in the places of contact of endothelial cells. Gaps between them can be increased on the vessel expansion as well as contraction of contractile structures and rounding of endothelial cells. Additionally, endothelial cells can «swallow» the smallest liquid droplets (*micropinocytosis*), pass them on the opposite side and throw them out in a nearby environment (*extrusion*).

Transport of fluid into the tissues also depends on the physicochemical changes occurring on both sides of the vascular wall. Due to the output of the protein from the vascular stream, its quantity outside of vessels is increased, contributing to the increase of the oncotic pressure in the tissues.

In the inflammatory focus the protein and other large molecules split into smaller ones under the influence of lysosomal hydrolase. Hyperonkiya and hyperosmia in the damage focus create the inflow of fluid into the inflamed tissue. The increase of the intravascular hydrostatic pressure due to the changes in the blood flow in the area of inflammation contributes to it.

The result of exudation is a filling of the interstitial spaces and the focus of inflammation by exudate.

Exudate is a fluid passing from microvessels containing a large amount of protein (at least 2–3 %) and cellular elements and accumulating in the tissues and/or body cavities during the inflammation.

It is distinguished *serous, hemorrhagic, purulent, saprogenic, fibrinous and mixed* types of exudates depending on the presence of cells in the exudate and their type as well as the chemical composition of exudate.

Serous exudate is composed of translucent liquid-rich protein (more than 2–3 %) and a small number of cells, including blood cells.

Hemorrhagic exudate contains large amounts of protein and red blood cells and cellular elements.

Purulent exudate is a turbid viscous liquid, containing up to 6–8 % protein and a large number of different forms of leukocytes, microorganisms, dead cells of a damaged tissue.

Saprogenic exudate. Any type of exudate can obtain a saprogenic (ichorpus) character if a suprogenic micloflora invades into the inflammatory area.

Fibrinous exudate contains large amounts of fibrinogen and fibrin.

Mixed forms of exudate can be very variable (e. g., serous-fibrinous, purulent-fibrinous, purulent and hemorrhagic, etc.).

Exudate must be distinguished from transudate.

Transudate is extravascular fluid with low protein content and a low specific gravity. It has low nucleated cell counts (less than 500 to 1000/microlit). For instance, an ultrafiltrate of blood plasma is transudate. It results from increased fluid pressures in vessels or diminished colloid oncotic forces in the plasma of blood (fig. 4).

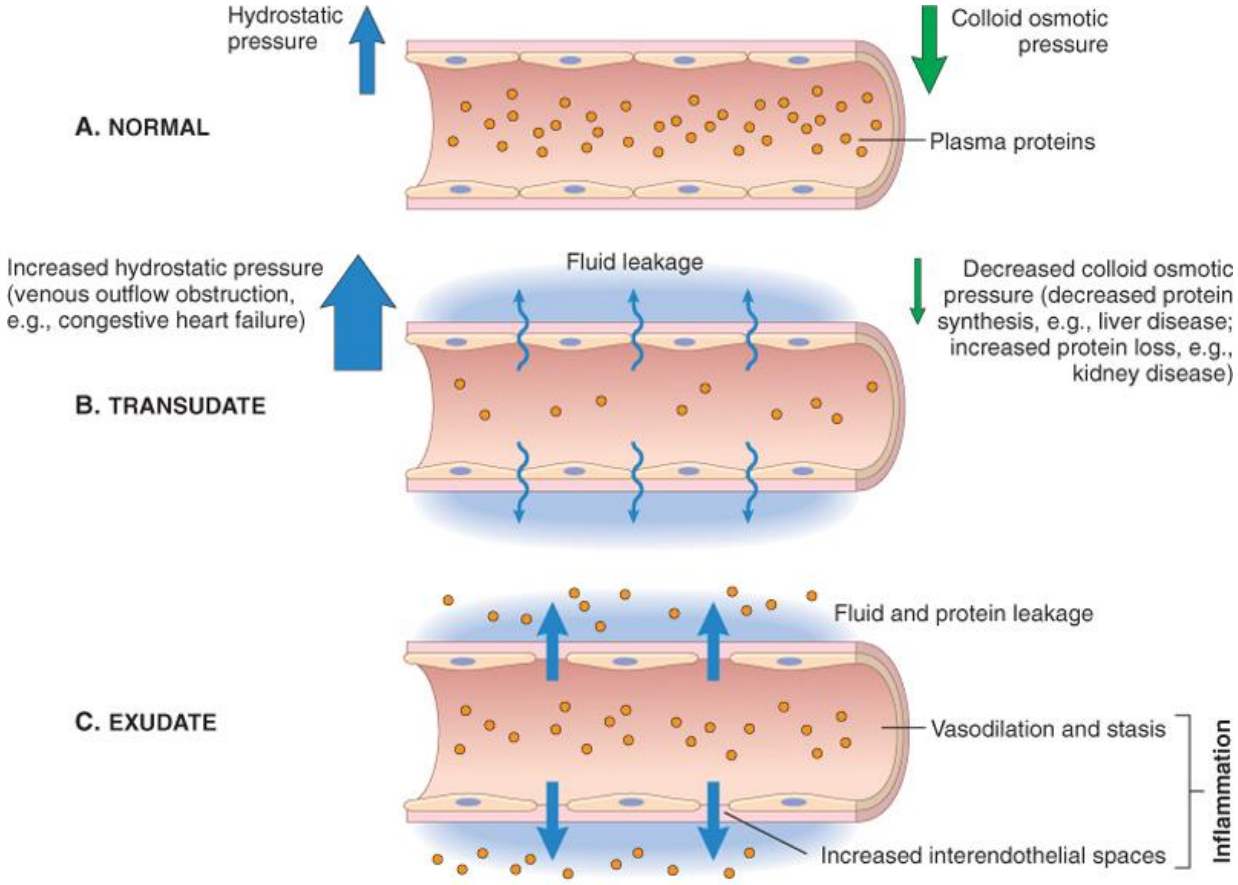

Fig. 4. The difference between of transudate exudate

Early increasing of vascular permeability is determined by the action of histamine, PGE_2, leukotriene E4, serotonin, bradykinin and primarily arises in venules with a diameter not more than 100 microns. Capillary permeability is not changes. Damage of the endothelial cells and the basal membrane and wall of microvessels by white blood cells and extracellular biologically active substances leads to a long-term growth response of permeability. As a result of the etiological factors necrosis of endothelial cells occurs at the arterioles of a small diameter, capillaries and venules, which leads to a stable increase of their permeability.

Deferred and stable reaction of a growth permeability of microvessels develops in the inflammatory area after hours or days from its beginning. It is characteristic of inflammation caused by burns, radiation and deferred allergic reactions (delayed) type.

Biological sense of an exudation as a component of an inflammation consists in:

1) delimitation of the inflammatory focus through the compression of blood and lymphatic microvessels due to interstitial edema, as well as in the dilution of phlogogenic and cytolytic factors in the inflammatory area to prevent excessive secondary alteration;

2) transport of immunoglobulins and other agents contributing to the eliminating of microorganisms, damaged cells and cell structures of tissues;

Vascular reactions and changes of blood circulation in the inflammatory area accompanying by a change of vascular wall permeability also result in emigration of leukocytes and other cellular elements outside the microvessels in the interstitial space. Particular significance in the development of the inflammatory response is the emigration of leukocytes.

THE EMIGRATION OF LEUKOCYTES

The emigration of leukocytes (leukodiapedesis) is the output of leukocytes from the vascular lumen through the vessel wall into the surrounding tissue. This process takes place normally, but in case of the inflammation acquires a much larger scale. Sense emigration is to accumulate a sufficient number of cells that play a role in inflammation (phagocytosis, etc.).

At present, the mechanism and a process of emigration is well studied. The sequence of emigration process includes:

1) *the stages of the marginal state of leukocytes*;

2) *their adhesion to the endothelium and penetration through the vascular wall*;

3) *the directional movement of leukocytes in the inflammatory area*.

At ***the stage of margination or regional standing of leukocytes*** two consecutive phases are conditionally selected.

1. *The exit of leukocytes from the axial cylinder of a blood stream and their approach to the wall of a microvessel* that is turned towards the center of an inflammation. The reason of this process is the high concentration of chemoattractants at a wall of the microvessel located in the center of an inflammation and retardation of a blood current, especially in venules.

2. *Slow movement or rolling (swing)* of leukocytess along a microvessel wall on a surface of endothelium cells (fig. 5). The reasons are: the high contents of «inflammation mediators» in the center of damage and allocation of the *selectines* (cell adhesion molecules) and *integrines* (transmembrane receptors that are the bridges for cell-cell and cell-extracellular matrix interactions) by the endothelium cells and thrombocytes.

In the subsequent there is the *adhesion* (receptor-mediated attachment) of the leukocytes to membranes of endothelial cells of the microvessels walls, caused by linking of CD15-leukocytes with E-selectin from an endothelium. This reaction brings to bracing of polymorphonuclears.

The exit of leukocytes from a lumen of vessels through a vascular wall in the inflammation center, their penetration through a wall of a vessel is realized through layer of endothelium cells, an intercellular matrix of a wall of vessels and a basal membrane of an endothelium (it makes about 3–6 min to do this).

At the time of leukocytes passing between cells of an endothelium there is an interaction of expressed molecules on their surface integrines to adhesion molecules. Various types of leukocytes (neutrophils, monocytes, eosinophils, lymphocytes) use a different range of adhesion molecules during an extravazation. Passing of leukocytes through a basal membrane of microvessels is accompanied

by releasing of hydrolytic enzymes by leukocytes (for example, collagenases and elastases). It provides hydrolysis of fibers and the main substance of a basal membrane that promotes an exit of leukocytes from a vascular channel.

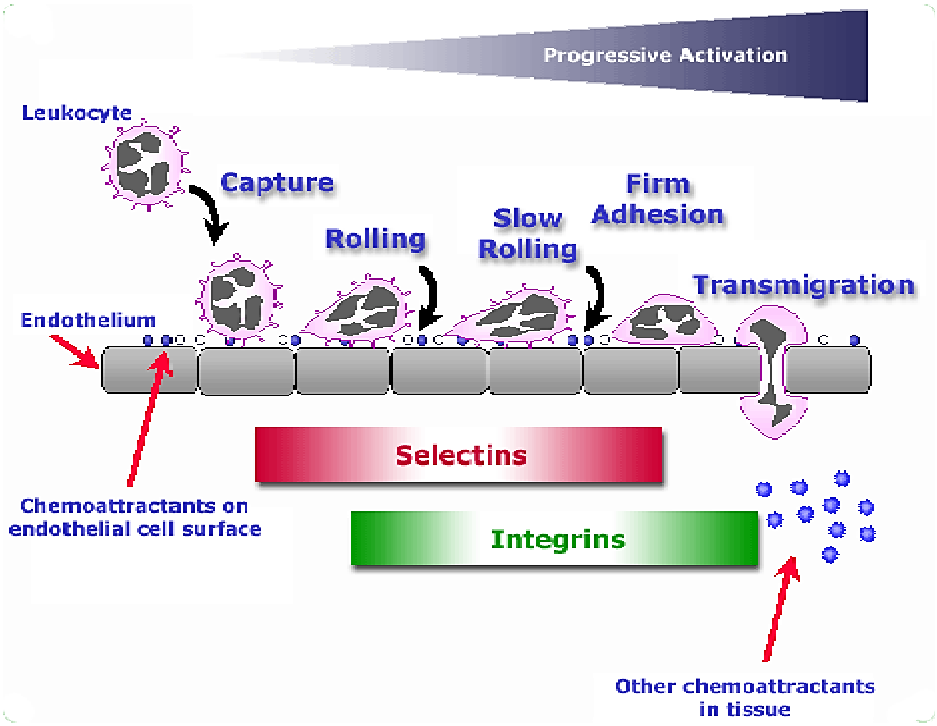

Fig. 5. The emigration of leukocytes

It is considered that granulocytes (through interendothelial clefts) and agranulocytes (through cytopemphisis — transendothelial transfer) pass through a vascular wall and move ahead to object of phagocytosis.

Granulocytes go beyond a vessel, on a joint between endothelial cells. It becomes possible after rounding of endotheliocytes and augmentation of intervals between them. After an exit of leukocytes contacts between endothelial cells become restored. Ameboid movement of leukocytes is possible due to reversible changes of a condition of their cytoplasma (gel mutually transition in sol — tiksotropy) and a surface intention of membranes, reversible «polymerization» of contractive proteins — an actin and a myosin and to use of energy of ATF from an anaerobic glycolysis. The referred movement of leukocytess is explained by accumulation in the inflammation center exo- and endogenic chemoattractants — the substances inducing a chemotaxis, temperature increase (thermotaxis), and also development of conditions for galvano- and hydrotaxis (fig. 6).

Function of endogenic chemoattractants is carried out by fractions of a complement system, in particular the S5a component. Properties of chemoattractants are possessed by kinins and Hageman's activated factor. Exogenous chemoattractants are peptides of a bacterial origin.

At substantial increase of permeability of vessels' walls erythrocytes and thrombocytes go passively in a tissue of the inflammation center. This process is

often observed at infection development with appreciable intoxication of an organism (at anthrax, plague), at a lesion of tissues with ionizing radiation.

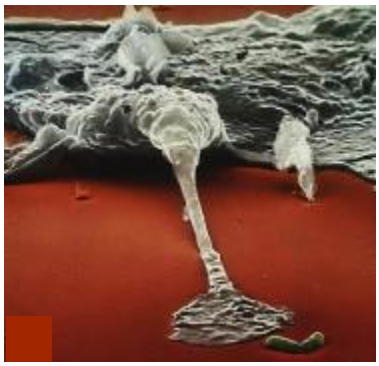

Fig. 6. Attraction — the phagocyte isattracted to the microbe

Outside a wall of a microvessel the referred (focused) movement of leukocytes to a lesion zone (chemo- and electrotaxis) begins. The focused movement of cells and organisms under the influence of chemical stimuli — ***chemoattractants*** (according to gradients of their concentration) is called ***chemotaxis***. In chemotaxis of leukocytes the system of a complement and first of all the components C3a and C5a has a great value. Leukotaksically active components of complement system C3a and C5a are formed in the inflammation center under the influence of various enzymes: trypsin, plasmin the level of which in the conditions of alteration increases.

Under the influence of leukotaksic substances there is a clump of chemoreceptors (kepping) on the side of a leukocyte turned to the region of the greatest concentration of chemoattractants. This pole («head») of a leukocyte becomes the leader, and the caudal one is conducted. Further the colloidal state of a leukocyte cytosole changes (transition from a condition of gel in sol). Actomyosin constriction of a leukocyte «caudal pole» and respectively referred movement of a leukocyte to object of a phagocytosis according to gradients of concentration of chemoattractants is made. For process of emigration of leukocytes it is very important value has an electrotaxis. ***Electrotaxis*** is a movement of leukocytes (carrying a negative charge on the surface) in the direction to epicenter of the center of an inflammation (where the damaged and lost cells, H^+, K^+ are collected forming a positive charge).

Emigration of leukocytes in the center of an inflammation is characterized by a certain sequence: at first neutrophils and monocytes and finally lymphocytes migrate. More later penetration of monocytes is explained by their lower hemotaxic sensitivity. In the course of completion of inflammation in the inflammatory focus gradual disappearance of blood cells is observed. At first a neutrophils then monocytes and lymphocytes are eliminate.

The sequence of an exit of different types of leukocytes from a vascular bed in the center of an inflammation is caused by the stages of a chemotaxis and adhesion factors emergence. These factors are: factor of system of complement C5a, lymphokines and others.

Having got into the inflammation center, phagocytes carry out the main phagocytic function.

PHAGOCYTOSIS

Phagocytosis and the release of enzymes by neutrophils and macrophages constitute two of the major benefits derived from the accumulation of leukocytes at the inflammatory focus. Phagocytosis involves three distinct but interrelated steps (fig. 7):

1) ***recognition and attachment of the particle to be ingested by the leukocyte***;
2) ***its engulfment, with subsequent formation of a phagocytic vacuole***;
3) ***killing or degradation of the ingested material***.

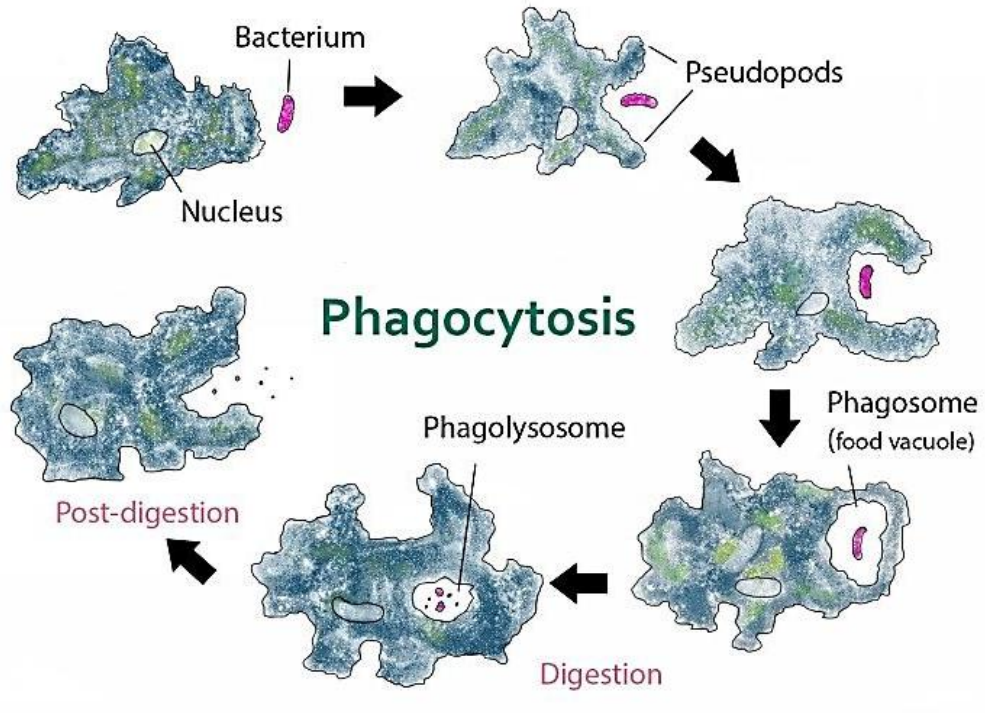

Fig. 7. Stages of phagocytosis

Recognition and Attachment. On occasion, neutrophils and macrophages recognize and engulf bacteria or extraneous matter (e. g., latex beads) in the absence of serum. Most microorganisms, however, are not recognized until they are coated by naturally occurring factors called *opsonins*, which bind to specific receptors on the leukocytes (fig. 8). Opsonization of particles such as bacteria markedly enhances the efficiency of phagocytosis.

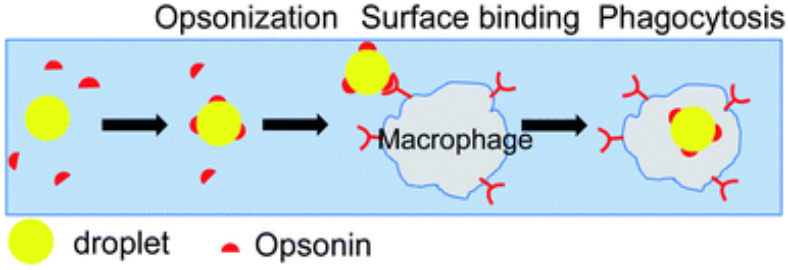

Fig. 8. Scheme of the process of opsonization

The major opsonins are: 1) *the Fc fragment of immunoglobulin G (IgG)*, apparently naturally occurring; 2) *C3b or opsonic fragment of C3*, generated by activation of complement by immune or nonimmune mechanisms; 3) *carbohydrate-binding proteins (lectins) of plasma called collectins*, which bind to microbial cell walls and are involved in innate immunity.

The corresponding receptors on leukocytes are FcgammaR, which recognize the Fc fragment of IgG; complement receptors 1, 2, and 3 (CR1, 2, 3), which interact with C3b and C3bi; and C1q receptors, which bind to the collectins; 26a CR3, which recognizes C3bi, is a particularly important receptor; it is identical with the beta 2 integrin-Mac-1 (CD11b), which is involved in adhesion to endothelium. It binds certain bacteria by recognizing bacterial lipopolysaccharides, without the intervention of antibody or complement, accounting for so-called nonopsonic phagocytosis. CR3/Mac-1 also binds the extracellular matrix components fibronectin and laminin. In addition to engaging the ligand, signals from the FcgammaRs are involved in metabolic activation of the phagocytes, increasing subsequent intracellular degradation of ingested material, as well as the release of proteases by these cells.

Engulfment. Binding of the opsonized particle to the FcgammaR is sufficient to trigger engulfment, which is markedly enhanced in the presence of complement receptors. Binding to the C3 receptors alone, however, is not followed by engulfment, unless such receptors are activated either by simultaneous binding to extracellular fibronectin and laminin or by certain cytokines. During engulfment, extensions of the cytoplasm (pseudopods) flow around the object to be engul fed, eventually resulting in complete enclosure of the particle within a phagosome created by the cytoplasmic membrane of the cell. The limiting membrane of this phagocytic vacuole then fuses with the limiting membrane of a lysosomal granule, resulting in discharge of the granule's contents into the *phagolysosome*. In the course of this action, the neutrophil and the monocyte become progressively degranulated.

Killing or Degradation. The ultimate step in phagocytosis of bacteria is killing and degradation. Bacterial killing is accomplished largely by *oxygen-dependent mechanisms*. Phagocytosis stimulates a burst in oxygen consumption, glycogenolysis, increased glucose oxidation via the hexose-monophosphate shunt, and production of reactive oxygen metabolites.

The generation of oxygen metabolites is due to the rapid activation of an oxidase (NADPH oxidase), which oxidizes NADPH (reduced nicotinamide-adenine dinucleotide phosphate) and, in the process, reduces oxygen to superoxide anion (O_2^-). Superoxide is then converted into H_2O_2.

The NADPH oxidase is a multiprotein enzyme complex consisting of at least seven proteins. In resting neutrophils, these NADPH oxidase protein components are separated into plasma membrane and cytoplasmic compartments. During assembly and activation of the oxidase, the cytosolic protein components translocate to the plasma membrane or phagosomal membrane, where they assemble to form the functional enzyme complex. Thus, the hydrogen peroxide is

produced within the lysosome. By segregating the oxidase components into different cellular locations, phagocytes are able to prevent inappropriate activation of the oxidase system and control the timing of the respiratory burst. The phagocyte NADPH oxidase complex is an essential component of the immune response and is also involved in nonspecific tissue damage associated with many inflammatory diseases, as shown subsequently.

The quantities of H_2O_2 produced in the phagolysosome are insufficient to induce effective killing of bacteria. However, the azurophilic granules of neutrophils contain the enzyme myeloperoxidase (MPO) which, in the presence of a halide such as Cl^-, converts H_2O_2 to HOCl. The latter is an antimicrobial agent that destroys bacteria by halogenation (in which the halide is bound covalently to cellular constituents) or by oxidation of proteins and lipids (lipid peroxidation). The H_2O_2-MPO-halide system is the most efficient bactericidal system in neutrophils. A similar mechanism is also effective against fungi, viruses, protozoa, and helminths. Most of the H_2O_2 is eventually broken down by catalase into H_2O and O_2, and some is destroyed by the action of glutathione oxidase. The dead microorganisms are then degraded by the action of lysosomal hydrolases.

Bacterial killing can also occur by *oxygen-independent mechanisms*, through the action of substances in leukocyte granules. These include *bactericidal permeability increasing protein* (BPI), a highly cationic granule-associated protein that causes phospholipase activation, phospholipid degradation, and increased permeability in the outer membrane of the microorganisms; *lysozyme*, which hydrolyzes the muramic acid-N-acetyl-glucosamine bond, found in the glycopeptide coat of all bacteria; *lactoferrin* , an iron-binding protein present in specific granules; *major basic protein*, a cationic protein of eosinophils, which has limited bactericidal activity but is cytotoxic to many parasites; and *defensins*, cationic arginine-rich granule peptides that are cytotoxic to microbes (and certain mammalian cells).

After killing, acid hydrolases found in azurophil granules degrade the bacteria within phagolysosomes. The pH of the phagolysosome drops to between 4 and 5 after phagocytosis, this being the optimal pH for the action of these enzymes.

Release of leukocyte products and leukocyte-induced tissue injury. The metabolic and membrane perturbations that occur in leukocytes during chemotaxis, activation, and phagocytosis result in the release of products not only within the phagolysosome, but also potentially into the extracellular space. The most important of these substances in neutrophils are: 1) lysosomal enzymes, present in the granules; 2) oxygen-derived active metabolites; 3) products of arachidonic acid metabolism, including prostaglandins and leukotrienes. These products are powerful mediators of endothelial injury and tissue damage and amplify the effects of the initial inflammatory stimulus. Products of monocytes/macrophages and other leukocyte types have additional potentially harmful products.

The ways by which lysosomal granules and enzymes are secreted are diverse. Release may occur if the phagocytic vacuole remains transiently open to the outside before complete closure of the phagolysosome. Lysosomal hydrolases may also be released during surface phagocytosis. There is some evidence that certain granules, particularly the specific (secondary) granules of neutrophils, may be directly secreted by exocytosis. After phagocytosis, neutrophils rapidly undergo apoptotic cell death and are either ingested by macrophages or are cleared by lymphatics.

DEFECTS IN LEUKOCYTE FUNCTION

Evidently that leukocytes play a cardinal role in host defense. Not surprisingly, therefore, defects in leukocyte function both genetic and acquired, lead to increased vulnerability to infections. Impairments of virtually every phase of leukocyte function - from adherence to vascular endothelium to microbicidal activity - have been identified, and the existence of clinical genetic deficiencies in each of the critical steps in the process has been described. These include the following:

1. *Defects in leukocyte adhesion.* In this cases recurrent bacterial infections and impaired wound healing are characteristic. In patients, there is a deficiency of beta integrins (CD18), which results in abnormal neutrophil adhesion, spreading, phagocytosis, and generation of the oxidative burst. The disorder results from an absence of a carbohydrate (sialyl-Lewis X), the ligand on neutrophils that is required for binding to the selectins expressed by cytokine-activated endothelium. The defect is attributed to mutations in the fucosyltransferase that makes the carbohydrate moiety.

2. *Defects in phagocytosis.* One such disorder is *Chediak–Higashi syndrome*, an autosomal recessive condition characterized by neutropenia (decreased numbers of neutrophils), defective degranulation, and delayed microbial killing. The neutrophils (and other leukocytes) have giant granules (fig. 9), which are the result from aberrant organelle fusion. In this syndrome, there is reduced transfer of lysosomal enzymes to phagocytic vacuoles (causing susceptibility to infections), melanocytes (leading to albinism), cells of the nervous system (associated with nerve defects), and platelets (generating bleeding disorders). The identification of a candidate gene suggests that the defect in the disorder is in a membrane-associated protein, which is involved in organelle membrane docking and fusion. This explains the inability to secrete lysosomal components into phagosomes or outside the cell.

3. *Defects in microbicidal activity.* It is revealed the existence of a group of congenital disorders in bacterial killing called *chronic granulomatous disease*. These patients are susceptible to recurrent bacterial infection. Chronic granulomatous disease results from inherited defects in the genes encoding several components of NADPH oxidase, which generates superoxide.

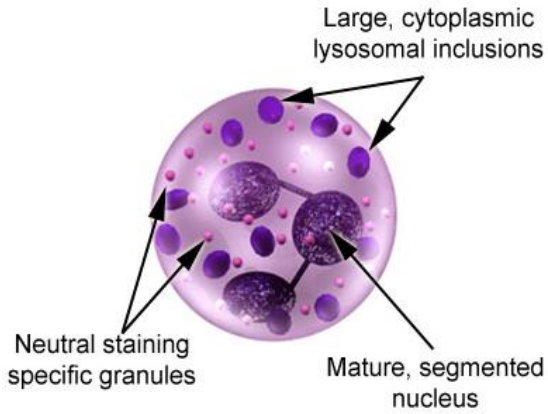

Fig. 9. Chediak–Higashi neutrophil

STAGE OF PROLIFERATION AND REPAIR

The inflammation always begins with damage and death of cells. But at a certain stage when processes of elimination of damage, purifications from all dead, alien to an organism come into force, infiltration, a pyesis and the related processes of a proteolysis and a necrosis stop and restoration processes act on the foreground. According to it the cellular composition of an inflammatory infiltrate changes also. Polymorphonuclear leukocytes gradually disappear (perish), and mononuclears (monocytes and lymphocytes) become dominating. The role of monocytes is that they, as well as macrophages absorb and digest the lost cells, and also the products of disintegration arising at alteration. Lymphocytes provide humoral immunity.

In process of purification of the center of an inflammation there comes ***a proliferation*** (from lat. proliferatio — reproduction) — a component of inflammatory process and a stage finishing it — being characterized by augmentation of number stromal and, as a rule, parenchymatous cells, and also formation of intercellular substance in the inflammation center. These processes are referred on neogenesis of the alterated and/or replacement of the blasted tissue elements. At this stage of an inflammation the various biologically active agents in particular stimulating a proliferation of cells have essential value.

Productive or proliferative stage of an inflammation is sometimes called a reparation stage. The proliferation is finished by a cicatrix involution that is destruction and elimination of excess collagenic structures. The main cellular effectors of a proliferation are the activated mononuclear phagocytes, fibroblasts and immunocompetent cells. Fibroblasts in the center of an inflammation form and release a collagen and the enzyme a collagenase responsible for formation of collagenic structures of a connecting tissue stroma. Besides they allocate a fibronectin defining migration, a proliferation and adhesion of fibroblasts. Mononuklears and lymphocytes cosecrete cytokines both stimulating, and overwhelming these functions of fibroblasts. Neutrophils as cellular effectors of an inflammation influence a proliferation, cosecreting the tissue-specific inhibitors interacting by the principle of feedback.

Regulation of Proliferation Stage. At the same time with process of a proliferation and even advancing it a little, there is a process of active suppression of inflammatory process that is shown by an ingibition of enzymes, deactivation of «inflammation mediators», detoxicating and removing of toxic products. Production of «inflammation mediators» is slowed down by different mechanisms. As for inhibitors of hydrolyzing enzymes, in this regard the major role plays α2-macroglobulin, α1-antihimotripsin, an antithrombin III and α-antiplasmin. They are the main inhibitors of kinin-productive enzymes of blood and thus eliminate their influence: expansion and rising of permeability of vessels. Besides, they are the main inhibitors of coagulation system, a fibrinolysis and a complement, inhibit elastase and a collagenase of leukocytess and by that protect from destruction elements of a connecting tissue. The antiinflammatory effect is rendered also by antioxidants (for example: hepatocuprein, peroxidases, superoxide-dismutase).

In the inflammatory center the relationship between cells changes. They cease to develop one mediator and start synthesizing others. Now on the same mediator the cell can give absolutely other answer because on its surface there are absolutely other receptors, and former plunge in its (internalization). Histamine is a typical «inflammation mediator», but its effect in a closing stage of an inflammation can become absolutely other, than in the beginning process. It appeared that it depends on what receptors are «exposed» on effector cells (for example, on endotheliocytes) at present. If it is H1, action will be pro-inflammatory, and if H2, — antiinflammatory.

In regulations of process of an inflammation, and a proliferation in particular, except local factors, a larger role play as well the general factors, including endocrine. Hormones of a cortex of adrenals — glucocorticoids — slow down synthesis of vasoactive substances in cells, cause a lymphopenia, and reduce number of basophiles and eosinocytes. Besides, they stabilize membranes of lysosomes, oppress development IL-1β. As for phagocytic activity, it to the end of an inflammation increases. Thanks to it the zone of an inflammation is exempted from the necrotized cells, alien and toxic substances.

Thus, at the end of an inflammation the crucial role is played by two cells: *fibroblast and endotheliocyte*. Two processes are made during this period: *zone settling by fibroblasts and neoangiogenesis*, i. e. formation of new blood and lymphatic vessels.

OUTCOMES OF ACUTE INFLAMMATION

The outcome of an inflammation depends on a type, force and action duration of phlohogene, reactivity of an organism, its current, localization and prevalence. In general, acute inflammation may have one of the four outcomes (fig. 10):

1. ***Complete resolution.*** In a perfect world, all inflammatory reactions, once they have succeeded in neutralizing the injurious stimulus, should end with restoration of the site of acute inflammation to normal. This is called resolution and is the usual outcome when the injury is limited or short-lived or when there

has been little tissue destruction and the damaged parenchymal cells can regenerate. Resolution involves neutralization or spontaneous decay of the chemical mediators, with subsequent return of normal vascular permeability, cessation of leukocytic infiltration; death (largely by apoptosis) of neutrophils; and finally removal of edema fluid and protein, leukocytes, foreign agents, and necrotic debris from the site. Lymphocytes and phagocytes play a role in these events, as shown subsequently.

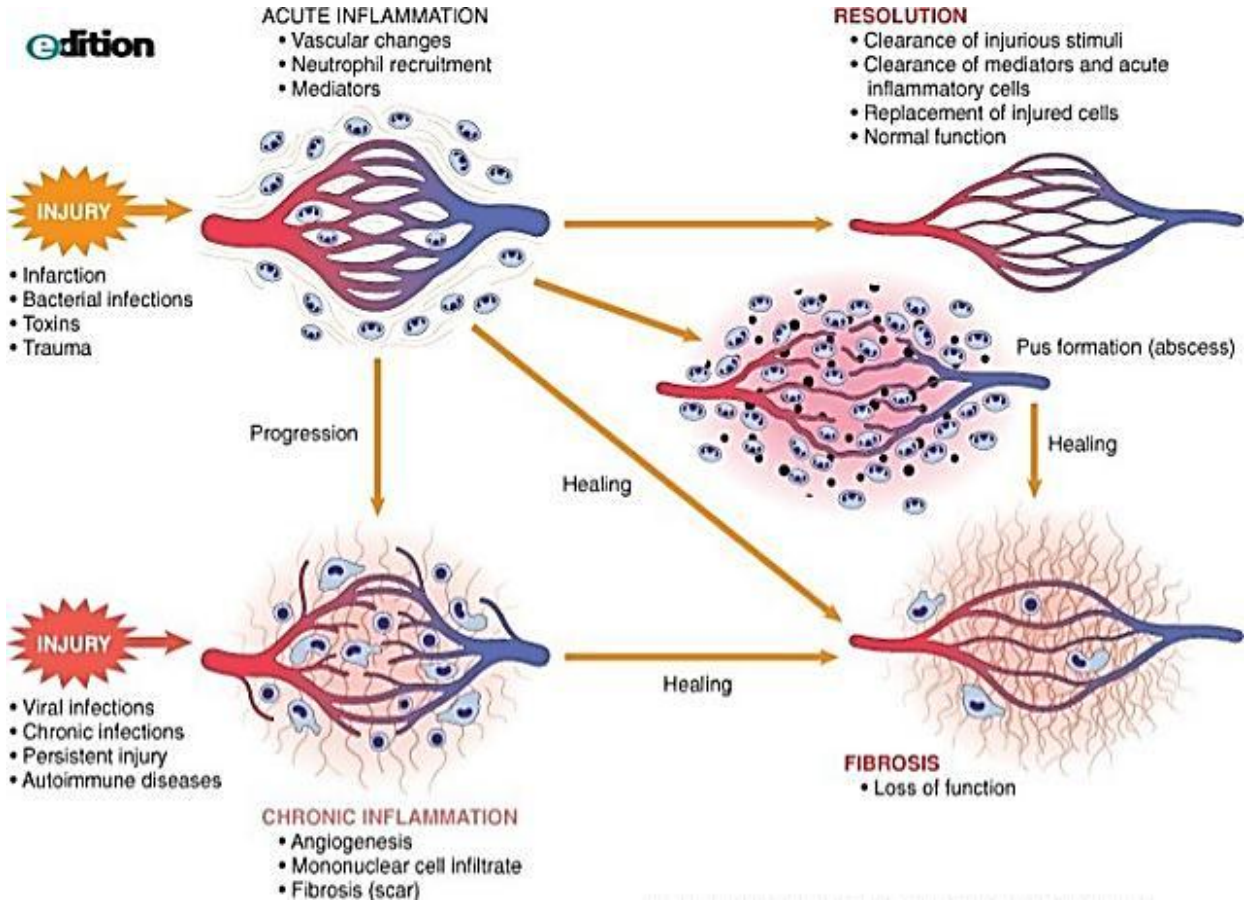

Fig. 10. Outcomes of Acute Inflammation

2. ***Abscess formation.*** This occurs particularly in infections with pyogenic organisms.

3. ***Healing or connective tissue replacement (fibrosis).*** This occurs after substantial tissue destruction, when the inflammatory injury occurs in tissues that do not regenerate, or when there is abundant fibrin exudation. When the fibrinous exudate in tissue or serous cavities (pleura, peritoneum) cannot be adequately resorbed, connective tissue grows into the area of exudate, converting it into a mass of fibrous tissue — a process also called *organization*.

4. ***Progression of the tissue response to chronic inflammation.*** This may follow acute inflammation, or the response may be chronic almost from the onset. Acute-to-chronic transition occurs when the acute inflammatory response cannot be resolved, owing either to the persistence of the injurious agent or to some interference in the normal process of healing. For example, bacterial infection of

the lung may begin as a focus of acute inflammation (pneumonia), but its failure to resolve may lead to extensive tissue destruction and formation of a cavity in which the inflammation continues to smolder, leading eventually to a chronic lung abscess. Another example of chronic inflammation with a persisting stimulus is peptic ulcer of the duodenum or stomach. Peptic ulcers may persist for months or years and, as seen subsequently, are manifested by both acute and chronic inflammatory reactions.

INFLAMMATION AND IMMUNE REACTIVITY OF AN ORGANISM

Between expression of the main processes of an inflammation and force of a stimulus there is certain dependence: with rising of aggression of a phlohogenic factor the answer amplifies also. However, it is known that such dependence is observed not always. The same stimulus can cause absolutely different reaction in different people. So, for example, from children who have caught diphtheria from the same source, one perishes from serious intoxication, and at others illness is shown by rather weak inflammatory changes. In this regard there was a representation that the inflammation depends not only by nature etiological factor, but also on organism's reactivity. If reaction of an organism doesn't go beyond observed most often, such inflammation is called *normergic*. If the inflammatory agent causes only weak lingering reaction with prevalence of alteration, the inflammation is *hypoergic*. It is observed, for example, at starvation. However in certain cases the inflammation proceeds so roughly that there is a disharmony between stimulus and response force (local and the general) an organism. Such inflammation is called *hyperergic*. Its feature is that it develops on «an immune (allergic) basis».

ACUTE AND CHRONIC INFLAMMATION

The current of an inflammation is defined by organism's reactivity, a look, force and action duration of phlohogene. Distinguish an acute, subacute and chronic inflammation.

The acute inflammation is characterized by intensive current and rather small (usually 1–2, about 4–6 weeks) duration (depending on the damaged organ or a tissue, degree and scale of their alteration, organism reactivity, etc.); moderately expressed alteration and destruction of tissues, exudation and proliferation in the damage center at normergic character of an inflammation. At its hyperergic current in the center of an inflammation alteration and destruction of tissues dominate.

The chronic inflammation is characterized by:

 long and flaccid current. Such inflammation lasts for many years and even all life of the patient (for example, at patients with leprosy, tuberculosis, a toxoplasmosis, chronic forms of pneumonia, a glomerulonephritis, hepatitis, a pseudorheumatism, etc.) proceeds;

 formation of granulomas (for example, at a tubercular, brucellous or syphilitic inflammation);

 formation of a fibrous capsule (for example, in the presence in a tissue of a foreign matter or adjournment of salts of a calcium);

 frequent development of a necrosis in the center of the center of a chronic inflammation.

The chronic inflammation can be primary and secondary.

If the inflammation current after the acute period gains lingering character, it is designated as «secondary and chronic» and when the inflammation initially has persistent — flaccid and long — a current, it call «primary and chronic».

Reasons of a Chronic Inflammation:

 various forms of a phagocytic failure;

 long stress and other conditions, being accompanied the increased concentration in a blood of catecholamins and glucocorticoids. The specified groups of hormones suppress proliferation processes, maturing and activity of phagocytes, exponentiate their destruction;

 repeated damage of a tissue or the organ, being accompanied formation of foreign antigens and development of immunopathologic reactions;

 persistent infection and/or intoxication;

 pathogenic action of factors of an immune autoaggression.

Character of a current of a chronic inflammation is defined by:

 local factors (cellular structure, inflammation mediators, character, degree and scale of damage of a tissue, etc.);

 the general, systemic factors to which carry: hormones (adrenaline, glucocorticoids, somatotropic hormone, thyroid hormones, glucagon, etc.) and opioid peptides (endorphines and enkephalins).

TYPES OF INFLAMMATION

Depending on nature of dominating local process (alteration, an exudation or a proliferation) three types of an inflammation are distinguished: ***alterative***; ***exudative*** and ***proliferative***.

In case of prevalence of alterative processes, a dystrophia, a necrosis, the ***alterative*** (necrotic) inflammation develops. It is observed most often in parenchymatous organs, at the infectious diseases proceeding with expressed intoxication (curdled disintegration of lungs or adrenals at tuberculosis).

The exudative inflammation is characterized by the expressed disturbance of a circulation with the phenomena of an exudation and emigration of leukocytess. On character of an exsudate distinguish the ***serous, purulent, hemorrhagic, fibrinous*** and ***mixed inflammation***. Besides, when involving in inflammatory process of mucosas when to an exsudate slime is added, speak about a ***catarrhal inflammation*** which is usually combined with an exudative inflammation of other types (serous — catarrhal, purulent — catarrhal, etc.).

The proliferative and productive inflammation is characterized by dominating reproduction of cells of a hematogenic and hystiogenic parentage. In a zone of an inflammation there are cellular infiltrates which depending on character of the accumulated cells are sectioned on round-cellular (lymphocytes, hystiocytes), plasmo-cellular, eozinofil-cellular, epitelioid-cellular, macrophagal infiltrates. At a cell inflammation with the finished cycle of development (mature) perish; mesenchymal cells undergo transformation and differentiation as a result of which the young connecting tissue is formed. It passes all stages of maturing owing to what the organ or part it is penetrated connective tissue that at late stages of an inflammation can lead to cirrhosis.

ROLE OF NERVOUS AND ENDOCRINE SYSTEMS IN AN INFLAMMATION PATHOGENESIS

Inflammatory reaction of an organism appeared at early stages of evolutionary development and further was improved in process of its complicating with education and development of nervous and endocrine systems. Researches show that inflammatory reaction with existence of all signs of an inflammation is established on 4–5 month of fetal human life.

Influence of nervous system on inflammatory process is confirmed by numerous experiences, and also clinical observations. It is known that at disturbance of a peripheric innervation, the inflammation gains flaccid, lingering character. For example, the trophic ulcers of extremities arising at wounds of a spinal cord or a sciatic nerve, heal is very long. Damage by a foreign matter of area of a gray hillock of a brain leads to extensive inflammatory changes of a skin and a mucosa that is explained by change of a trophicity of tissues, and together with this depression of their fastness to action of damaging agents (A. D. Speransky). At last, cases when obvious signs of an inflammation were observed at people in whom under hypnosis inspired are known that the heated subject was put to a skin.

Character of an inflammation can influence both nervous and humoral factors. Very great value for inflammatory reaction some hormones of hypothalamic-pituitary-adrenal (HPA) axis, mainly, have hormones of a cortex of adrenals and a pituitary body that is convincingly shown in experiment and in clinic. It is established that the somatotropic hormone of a pituitary gland and aldosterone are capable to increase inflammatory «potential» of an organism, i. e. to strengthen an inflammation though in itself can’t cause it. Mineralocorticoids (aldosterone, cortexone) raising permeability of a wall of vessels, enlarging an exudation and changing electrolytic structure of tissues, have pro-inflammatory effect.

Along with it glucocorticoids (hidrocortizone, etc.), adrenocorticotropic hormone (AKTH), without possessing bactericidal properties, have anti-inflammatory effect, reducing inflammatory reaction. Glucocorticoids, detaining development of the most precursory symptoms of an inflammation (a hyperemia,

an exudation, emigration of cells), interferes with edema emergence, this property of glucocorticoids widely use in applied medicine. Such action of glucocorticoids is explained by that they reduce number of tissue basophiles, reduce activity of histidine decarboxylase and at the same time enlarge activity of a histaminase — the enzyme blasting histamine. Formation of a serotonin decreases also. Recently it is established that glucocorticoids induce synthesis of specific proteins (lypomoduline, macrocortine) which work as inhibitors of phospholypase with A2, i. e. block process of formation of derivatives of arachidonic acid (prostaglandins and leucothryenes).

Besides, it is noticed that the inflammation proceeds at a hyperthyroidism more intensively and differs a current flaccidity at a myxedema.

INFLAMMATION THEORIES

The doctrine about an inflammation on a scientific basis began to develop from the middle of the XIX century — the first half of the XX century, in connection with development of biochemical, biophysical, histochemical methods and methods of electron and microscopical studying of tissues.

R. Virkhrov (1859), having paid attention to damage of a parenchyma of organs (dystrophic changes of cells) at an inflammation, also created the so-called *nutritive («nutritious») theory* of an inflammation.

The vascular theory of Y. Kongeym (1887). According to this theory the reaction of the small blood vessels and microcirculation disturbance has fundamental importance in the pathogenesis of inflammation. He considered that expansion of bringing vessels and inflow of an arterial blood in the center of an inflammation cause emergence of fever and reddening of tissues, augmentation of permeability of capillaries — a tumescence, formation of an infiltrate — pressing of nerves and pain emergence, and all together — function disturbance. Kongeym's vascular theory thanks to the clarity and simplicity was widely adopted. Modern electron and biomicroscopical researches give new confirmation to a series of provisions of this theory.

Further *I. I. Mechnikov (1892) the biological theory* of an inflammation was nominated. In its treatment the inflammation is surveyed as reaction of the adaptation and protection of an organism against harmful factors. I. I. Mechnikov developed the doctrine about a phagocytosis and attached it great value in the mechanism of fight of a macroorganism with «aggressor». All precursors of I. I. Mechnikov surveyed an inflammation as local process. I. I. Mechnikov characterized an inflammation as the process developing at all levels of the organization of an organism: cellular (phagocytosis), systemic (immune system), organismal (inflammation evolution in onto- and phylogenesis).

In 1923 H. Schabad put forward the physical and chemical theory of an inflammation. In his opinion a basis of an inflammation is the tissue acidosis, a hypoxia, a hyperoxia and a hypertonia in the damage center by which all set of changes is defined further at an inflammation.

Rikker (C. Ricker, 1924), surveying inflammation phenomena as implications of neurovascular disorders, offered *the neurovascular theory* of an inflammation.

However, all these theories, it is theories of the center of an inflammation, its separate parties. Now the pathogenesis of an inflammation is surveyed much more widely. Attempts to generalize the saved-up data on this question and to build the modern theory of an inflammation are made. However, still the uniform generalizing theory of an inflammation isn't present.

VALUE OF AN INFLAMMATION FOR AN ORGANISM

As well as any pathological process, an inflammation on the essence process inconsistent. In it, as well as at other sample pathological processes the harmful and useful is combined in indissoluble communication. In it mobilization of protective forces of an organism and the damage phenomenon is combined also. Having arisen in phylogenesis as the phenomenon adaptive, the inflammation kept this property and at the highest animals. The organism is protected from influence of factors alien and harmful to it by separating of the inflammatory center from all organism by formation round the center of an inflammation of a peculiar barrier with unilateral permeability. Localization of the center of an inflammation interferes with infection diffusion. At the expense of an exudation concentration of toxic substances in the center of an inflammation decreases. The inflamed zone not only fixes, but also absorbs toxic substances, provides their detoxication. In the center of an inflammation are created as well adverse conditions for life of microorganisms. However all stated reflects only one (positive) party of an inflammation above. The second, opposite is that an inflammation being evolutionarily developed protective process, at the same time has damaging impact on an organism, always carries in itself a destruction element. Fight against «aggressor» in a zone of an inflammation is inevitably combined with death of own cells, as carrying out specific protective function in an organism, and parenchymatous cells appeared in a zone of the center of an inflammation. In certain cases alteration that leads to death of a tissue or the whole organ starts prevailing. Besides, the exudation can cause disturbance of a delivery of a tissue, its enzymatic fusion, a hypoxia and the general intoxication. I. I. Mechnikov noticed that «the salutary force of nature, which main element makes inflammatory reaction, there is no adaptation at all still reached perfection».

In the all-biological relation the inflammation is a way of emergency protection of an organism, a way of conservation of the whole organism at the price of damage of its part.

The assessment of each concrete inflammatory process has to proceed from the analysis of many factors: reasons of emergence of an inflammation, its localization, intensity of process, initial condition of an organism, etc. As a whole, the measure of adequacy of inflammatory process, on the one hand, has to be established to character and intensity of a pathogenic stimulus, and on the other hand — needs of an organism for protection against action of this phlohogenic

factor. Depending on such assessment inflammatory process needs to be stimulated in one cases, and in others — to suppress. Such is the general scheme of approach to the inflammation analysis in its concrete expressions.

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