IMMANUEL KANT BALTIC FEDERAL UNIVERSITY

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TYPICAL PATHOLOGICAL PROCESSES

Part 1

Educational and methodological manual

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The educational manual systematizes basic knowledge in the field of pathophysiology in accordance with the academic program of the discipline. The manual presents 2 topics of classes dealing with issues of general pathology (pathological physiology): immunity and pathology of the immune response and inflammation. On the topic of each lesson, the goal, questions for self-control, tests and situational tasks for controlling knowledge during self-training are formulated in a concise form. Reference materials are of particular value in the practical work section, allowing the student to conduct a comparative analysis of the data obtained during the experimental/clinical work and make a reasonable conclusion.

The educational manual was developed in accordance with the working program of the discipline "Pathophysiology, Clinical Pathophysiology" and is intended for students of medical universities and students of FPK, graduate students, residents, research doctors and students of biological faculties.

This educational and methodological manual was prepared based on the results obtained within the framework of the Russian Science Foundation project (№23-15-00061) and the State assignment (№FZWM-2024-0012).

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CONTENT

INTRODUCTION

Pathological process — a combination (complex) of pathological-logical and protective-adaptive reactions in injured tissues, organs or organism, manifesting in the form of morphological, metabolic and functional disorders.

Permanent combinations or combinations of various pathological processes and individual pathological re-actions of cells and tissues formed and fixed in the process of evolution are called typical pathological processes. These include inflammation, fever, hypoxia, edema, tumor growth, etc.

The pathological process underlies the disease, but is not.

Differences in the pathological process from the disease:

1. The disease always has one main cause (special, producing etiological factor), the pathological process is always polyetiological. For example, inflammation (pathological process) can be caused by the action of various mechanical, chemical, physical and biological factors, and malaria cannot be caused without the action of malaria plasmodium.

2. The same pathological process can catch different pictures of the disease depending on the localization, in other words, the location of the pathological process determines the clinic of the disease (pneumonia, inflammation of the brain membranes — meningitis, inflammation of the heart muscle — myocarditis, etc.).

3. The disease is usually a combination of several pathological processes. For example, in croupous pneumonia, there is a combination (in the relationship) of such pathological processes as inflammation, fever, hypoxia, acidosis, etc.

4. The pathological process may not be accompanied by a decrease in the body's adaptability and disability (warts, lipoma, atheroma, etc.).

Topic 1

IMMUNITY AND PATHOLOGY OF THE IMMUNE RESPONSE

Training objectives:

To form modern ideas about the etiology and pathogenesis of immunodeficiencies, autoimmune diseases, allergic reactions, about methods of experimental modeling of allergic reactions. Develop students' ability to reason and argue, apply the scientific method in assessing the condition of a patient with a pathology of the immune system. To introduce students to the principles of problem learning in the knowledge of the basics of the pathophysiology of the immune system.

It is necessary:

• have an idea of the structure and function of organs, cells and molecules of the immune system, types of immunological resistance, types of immune response and mechanisms of its regulation; on methods for experimentally simulating an allergic reaction;

• know the etiology, pathogenesis and clinical manifestations of immunodeficiencies, autoimmune diseases, types and stages of hypersensitivity reactions and the main manifestations of allergic diseases;

• be able to solve standard situational tasks and test tasks on the topic of the lesson;

• to have the skill to determine the type of immunological reactivity disorder, as well as to assume possible methods of etiotropic and pathogenetic therapy of immunological disorders based on the medical history, the totality of available clinical signs and laboratory test results.

The immune system is able to destroy pathogenic organisms such as bacteria, fungi, viruses and parasites through various mechanisms. The organs involved in the immune response are divided into:

1. **Primary lymphoid organs** (thymus and bone marrow), where T- and B-cells express antigen receptors and become functionally mature.

2. **Secondary lymphoid organs** (spleen, tonsils, lymph nodes, cutaneous and mucosal immune systems) — it is here that B- and T-cells recognize foreign antigens and an immune response develops.

Antigen-specific adaptive immune response and innate immune response, also called natural, which recognizes Pathogen-Associated Molecular Patterns (PAMPs) are isolated. PAMPs are recognized by recognition receptors (PRR — Pattern recognition receptor), mainly expressed in innate immunity cells. PRRs can also recognize host molecules containing damage-associated molecular patterns (DAMPs) — molecules that are often released from necrotic cells damaged by pathogens.

The innate immune system consists mainly of physical barriers (skin and mucous membranes), chemical barriers through the action of antimicrobial peptides and reactive oxygen species, innate immune cells, and soluble mediators (the complement system, innate antibodies, and associated cytokines).

Non-specific immunity tasks:

1. Prevent the penetration of pathogens into the body through physical and chemical barriers;

2. Avoid the spread of infections due to the complement system and other humoral factors;

3. Remove pathogens by phagocytosis and cytotoxicity;

4. Activate the adaptive immune system through cytokine synthesis and antigen presentation to T- and B-cells;

Cells of nonspecific (innate) immunity

Cells of the innate immune system perform several functions necessary to protect against pathogens. Some cells form physical barriers that prevent infections. Some cell types express different receptors — PRRs, which recognize PAMP and DAMP.

Non-myeloid cells — epithelial cells, fibroblasts, which mainly form a barrier between the internal and external environment.

These cells produce antimicrobial substances — antimicrobial peptides (AMP — defensins (α and β), cathelicidins, statins), which prevent the penetration of pathogens, and contribute to the formation of the first line of defense against infections.

Myeloid cells — monocytes, macrophages, dendritic cells (DC), neutrophils, eosinophils, basophils, mast cells and platelets. All these cells perform specialized functions to protect against invading pathogens.

Monocytes are cells that develop in the bone marrow, are released into the bloodstream to circulate for 72 hours, and then emigrate to various tissues where they differentiate into macrophages or DCs. In humans, monocytes are divided into classical and non-classical depending on their surface expression of the cluster of differentiation of CD14 and CD16. *Classical monocytes* with the $CD14^{+}CD16^{-}$ phenotype are considered inflammatory cells (more than 92% of the total number of monocytes). *Non-classical monocytes* with the $CD14^{+}$ $CD16^{+}$ phenotype produce small amounts of pro-inflammatory cytokines and high levels of anti-inflammatory factors. During the development of inflammation, classic monocytes first appear, and after a few days non-classical ones appear. Among the main functions of monocytes is their participation in the innate immune response against pathogens and in inflammation, when they migrate to the focus of infection, mature into macrophages or DCs to participate in phagocytosis of pathogens or cellular debris. In addition, monocytes are antigen-presenting cells (APCs) known for their involvement in antigen presentation via major histocompatibility complex (MHC II) molecules to T-cells and involvement in activation of the adaptive immune response.

Macrophages, a heterogeneous cell population, act as effector cells of the innate immune system. In general, macrophages can be divided into two populations: resident and inflammatory. Resident macrophages are found in almost all tissues and regulate cell differentiation, repair, and immunological supervision. Inflammatory macrophages originate from circulating monocytes and rapidly invade affected tissues. In response to several signals from the microenvironment, macrophages can be activated and perform vari-

ous functions: *M1 macrophages* (classically activated macrophages) and *M2 macrophages* (alternatively activated macrophages). Proinflammatory macrophages are M1 involved in host defense against pathogens and tumor cells and contribute to the development of the Th1 immune response. In contrast, M2 macrophages are associated with tissue remodeling, tumor progression, and have an immunoregulatory effect. M2 macrophages express interleukin (IL)-10, an IL-1 receptor antagonist, chemokines (for example, CCL22 and CCL17), transforming growth factor (TGF)-β, mannose and galactose receptors and have effective phagocytic activity. M2 macrophages are thought to promote the Th 2 immune response and limit the inflammatory response.

Macrophages have a wide range of surface receptors, among which Toll-like receptors (TLRs) and NOD-like receptors play an important role, which recognize PAMP, DAMP, foreign substances, apoptotic or damaged cells. Proinflammatory macrophages produce inflammatory mediators — TNF-α, IL-1, IL-6 and INF-γ, which are involved in the activation of microbicidal mechanisms, contributing to the elimination of the pathogen.

The involvement of macrophages in inflammation involves four stages:

1. Recognition of an infectious agent through PRR;
2. Attracting and proliferating macrophages *in situ* into infected tissue;
3. Elimination of an infectious agent;
4. Conversion to M2 macrophages to repair damaged tissue.

Dendritic cells (DC). Monocytes can differentiate into inflammatory DCs in inflammation. Dendritic cell PRRs, including the TLR family, are able to recognize PAMPs on the surface of bacteria, viruses, fungi, and parasites. DCs represent an important association between innate and adaptive immunity. DCs are able to capture, process and present antigens to T-cells, but they differ in origin, localization, migration pattern and functional properties.

There are two subtypes of DC: ***classical and plasmacytoid***.

Classical DCs are cells specializing in antigen processing and presentation, with high phagocytic activity and the ability to pro-

duce cytokines. These are rapidly migrating cells that can move from tissues to the T- and B-cell zones of lymphoid organs. *Plasmacytoid DCs* are present in the bone marrow and in all peripheral organs and specialize in the response against viral infection, producing type I interferons (IFNs). However, they can also act as antigen-presenting ones.

Neutrophils play an important role in the fight against microbial infections. After the entry of pathogens through epithelial barriers, neutrophils are **the first cell line of defense for the innate immune response**, which are recruited from the bloodstream to the focus of infection, due to chemotactic factors and cytokines. Neutrophils reach the focus of infection and initiate the phagocytosis process through recognition of PAMP by TLR receptors. Neutrophils exert their antimicrobial effects by releasing reactive oxygen species and cytotoxic components. Neutrophils using the extracellular trap (NET) mechanism (consisting of DNA strands that are formed and released into the extracellular space) are used by the innate immune system to destroy and eliminate pathogens. Neutrophils can regulate the adaptive immune response as they mediate suppression of T-cell proliferation as well as their activity, while being able to stimulate and activate spleen B-cells.

Eosinophils are multifunctional white blood cells involved in the pathogenesis of numerous inflammatory processes and allergic diseases. The movement of eosinophils into the focus of inflammation is facilitated by the cytokines IL-4, IL-5 and IL-13, adhesion molecules (for example, integrins β1, β2 and β7) and chemokines (eotaxin). Once in the focus of inflammation, eosinophils can have a proinflammatory effect, stimulating adhesion, increased vascular permeability, mucus secretion and smooth muscle contraction, due to the secretion of proinflammatory mediators IL-2, IL-6, IL-8, TGF-α/β, GM-CSF, TNF-α INF-γ, as well as chemokines and eicosanoids — platelet-activation factor (PAF) and leukotriene (LT)-C4. In addition, eosinophils can serve as effector cells that can induce tissue damage by releasing various cationic proteins, major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophilic peroxidase (EPO) from their granules. These proteins are very im-

portant as they are directly related to the effector functions of eosinophils. For example, ECP is involved in suppressing proliferative T-cell responses and immunoglobulin synthesis by B-cells, causing mast cell degranulation and stimulation of airway mucus secretion, as well as glycosaminoglycan production by human fibroblasts. In addition to the multiple effector actions of eosinophils, these cells can initiate antigen-specific immune responses by acting as antigen-presenting cells (APCs) and presenting various bacterial, viral, and parasitic antigens. Eosinophils are known to be classical effector cells in host defense against helminthic invasion.

Basophils are cells derived from myeloid hematopoietic progenitors in the bone marrow; phenotypically and functionally, basophils differ from other white blood cells, including mast cells, as mast cells are in tissues and basophils are in the bloodstream and can be recruited into tissues. Basophils **have the ability to bind innate and adaptive immunity**, including the ability to induce **Th2-type immune responses**. Basophils are important in all allergic diseases, including anaphylaxis, allergic rhinitis, asthma, urticaria, and food allergies. Basophils rapidly release histamine and synthesize LTC4 after immunoglobulin (Ig)-E binds to their FcεR I receptor. Subsequently, Th2 produces cytokines — IL-4 and IL-13, causing clinical symptoms of immediate-type hypersensitivity, as well as contributing to the development of delayed-type hypersensitivity reactions. The role of basophils in protective immunity against helminths is well established, however basophils have recently been shown to stimulate an immune response against bacterial respiratory infection.

Mast cells are granular resident cells derived from $CD34^+$ hematopoietic progenitor cells. Mast cells circulate as immature cells and migrate to vascularized tissues where they complete their differentiation. Mast cells, together with dendritic cells, are the first immune cells to interact with environmental antigens, pathogens and toxins, which allows them to be classified as "guards" of the innate system.

Mast cell activation is accompanied by the release of a wide range of mediators, both pre-existing and newly formed. Some of

these mediators (e. g., histamine, TNF-α, vascular endothelial growth factor, VEGF) promote local vascular permeability and development of edema at the site of inflammation, while chemokines (eg, IL-8/CXCL8, eotaxin) induce recruitment of other immune cells, such as neutrophils, natural killer (NK) cells, and eosinophils. Importantly, mast cells may also be involved in defense against pathogens through phagocytosis, release of antimicrobial peptides, or production of extracellular traps. Mast cells detect pathogens by TLR.

Mast cells express the high-affinity IgE receptor (FcεRI). Cross-linking of FcεRI with complexes of IgE antigens and/or allergens induces mast cell activation and rapid degranulation with release of pro-inflammatory mediators. Due to this property, along with circulating basophils, mast cells are known as effector cells for IgE-mediated (Th2-like) responses against helminthiasis and as primary effector cells in hypersensitivity reactions. Mast cells are able to modulate both the innate and adaptive immune response by acting as immunomodulatory cells.

Platelets are fragments of cytoplasm (diameter from 1 to 4 μm) formed as a result of fragmentation of megakaryocytes, which are bone marrow cells. Platelets are non-nuclear organelles that possess the functional characteristics of a complete cell, as they possess the cytoskeleton, mitochondria, Golgi residues, and endoplasmic reticulum involved in enzyme synthesis, calcium ion storage, as well as spare granules. These storage granules are δ-granules, α-granules and lysosomal granules, which play an important role in homeostasis, inflammation, wound healing and cell-matrix interaction. During the inflammatory response, platelets can be activated through their receptors, which act as adhesion molecules and interact with the damaged endothelium, other platelets and white blood cells, playing an important role in the coagulation process to repair the damaged blood vessel and restore its integrity.

Lymphoid cells include NK cells, natural killer T-cells (NKTs), and innate lymphoid cells (ILCs). ILCs have a protective role in innate immunity against infectious microorganisms.

Innate lymphoid cells (ILCs) are an innate version of helper and cytotoxic T cells as part of the innate immune system that play an important role in the early immune response. All members of the ILC family are characterized by classical lymphoid cell morphology and expression of IL-7Ra (CD127) and CD161, but lack expression of T- and B-cell like antigenic receptors.

ILCs can be classified based on their phenotypic and functional characteristics:

Group 1 (ILC1) includes cells that have the ability to produce IFN-γ as a major effector cytokine and express T-bet transcription factor. The prototype cell of this group is the NK cell.

Group 2 (ILC2) are cells that require IL-17 for their development. These cells are characterized by cytokine production associated with the Th2 immune response.

Group 3 (ILC3) includes subtypes of cells that produce IL-17 and/or IL-22 and IFN-γ.

Recent studies have identified different functions of ILC cells: ILC 1 promotes host defense against infections and regulates interaction with the microbiota; ILC 2 stimulates wound healing and tissue repair; ILC 3 is involved in the development of inflammation and tumor progression. ILC cells are poorly represented in lymphoid tissues, but they are important in parenchymal tissues, especially on the surface of mucous membranes. Thus, **ILC subtypes play an important role in the innate immune response to viruses, bacteria, fungi, as well as intracellular and extracellular parasites and have rapid activation in response to the production of cytokines and growth factors.**

Natural killer cells. NK cells are derived from cellular lymphoid progenitors. However, they do not mediate the usual adaptive immune response, since they lack antigen-specific receptors, as in T- and B-cells. Studies have shown that NK cells also develop in secondary lymphoid organs. NK cells are important effector lymphoid cells of the innate immune system as they represent a key element in the rapid recognition and death of both infected and oncogenic cells that can cause host tissue integrity impairment (absence of MHC I) (Fig. 1 and 2).

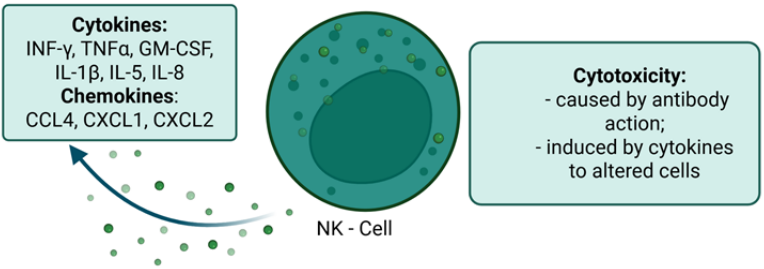

Fig. 1. Characteristics and functions of NK cells

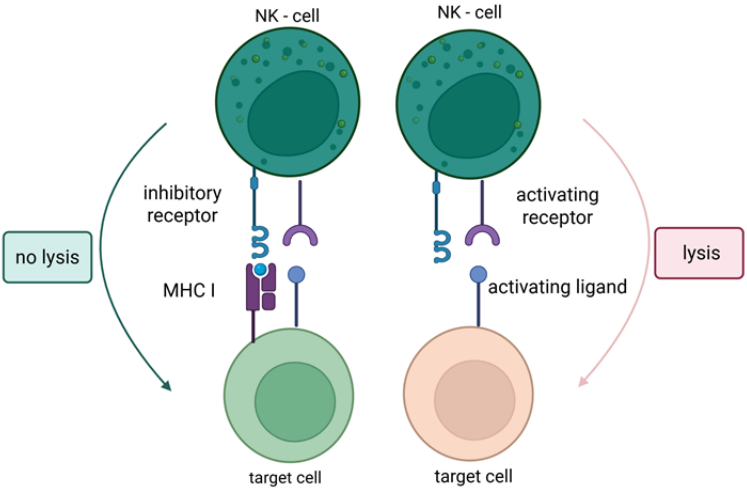

Fig. 2. Hypothesis of recognition of the presence and absence of its

NK cells identify target cells (cells having some damage) through complex combinations of signals from receptor activation or inhibition (Fig. 3). In addition, NK cell activation is regulated by dendritic cells, which allows NK cells to acquire potent cytotoxic activity, the ability to produce cytokines such as IFN-γ, and activate the T-cell adaptive immune response.

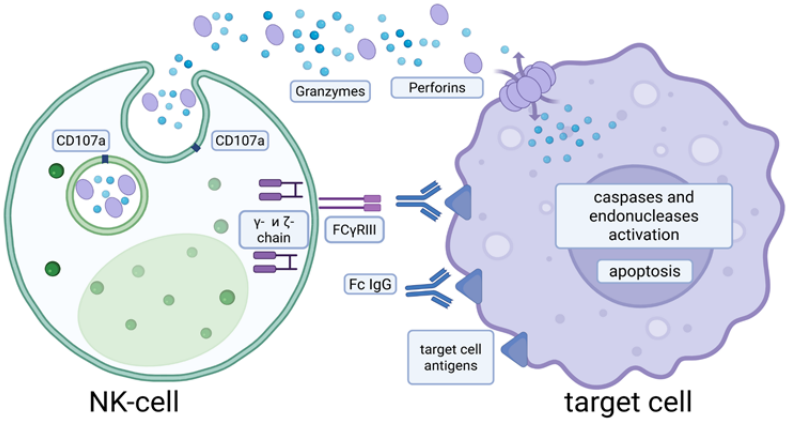

Fig. 3. Mechanism of cytotoxic action of NK cells

Natural T hitmen (NKT) make up a small subpopulation of lymphocytes, which are characterized by the expression of markers of NK cells and αβ T-cell receptors. NKT cells develop in the thymus and have the same lymphoid progenitors as conventional T-cells, but they have phenotypic and functional characteristics distinct from T-cells. Four subpopulations of $CD4^+$, $CD8\alpha\beta^+$, $CD8\alpha\alpha^+$ and double negative ($CD4^-CD8^-$) NKT cells have been identified in human peripheral blood.

The fastest host defense is provided by the innate immune system, which has the ability to recognize invading pathogens, and thereby effectively eliminate them so that they do not cause damage to «the host cells».

Pathogen recognition occurs through cells involved in the innate immunity response by non-specific molecules that are typically common to most pathogens, called pathogen-associated molecular patterns (PAMPs). PAMPs are highly conserved products and are produced by numerous microorganisms. PAMPs do not have specific structures with antigenic variation, and «host cells» do not share the same molecular patterns with pathogens, leading to im-

mune system recognition of these molecules. PAMPs include lipopolysaccharide (LPS), peptidoglycan (PGN), lipoteichoic acid, unmethylated cytosine phosphorus-guanine nucleic acids, double-stranded RNA virus, and a yeast cell wall component called mannan. LPS represents the major component of Gram-negative bacteria, whereas PGN of Gram-positive bacteria. However, pathogens are not the only cause of cell and tissue damage. Trauma, vascular pathology are the causes of intracellular protein release — damage-associated molecular patterns (DAMPs). DAMPs include any endogenous component associated with tissue damage. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are recognized by pattern recognition receptors (PRRs), primarily belonging to the TLR receptor family, which are abundant on the phagocyte membrane.

Soluble mediators of innate immunity

Innate immunity involves a large number of soluble mediators such as cytokines, chemokines, and the complement system. All these mediators provide protection in the initial phase of contact with pathogens and are responsible for preventing potentially dangerous infections.

Complement system. The complement system is seen as an effector response of the innate immune system, capable of killing a wide variety of pathogens, including bacteria, viruses and parasites. The complement system consists of plasma proteins that are present as inactive proteins. After activation, components of the complement system attract cells of the immune system to the site of injury to eliminate the pathogen by opsonization or direct destruction. Activation of the complement system occurs in three ways (Fig. 4):

1) classical antigen-antibody complex pathway;

2) alternate pathway through spontaneous C3 hydrolysis;

3) a lectin pathway in which mannose is recognized on the surface of bacteria by lectin.

During activation, a lytic C5a-C9 complex is formed to form a membrane attack complex, which is a lytic pore embedded in the pathogen membrane. In addition, the complement system is responsible for the elimination of apoptotic cells by opsonization with C3b molecules, which facilitates the phagocytosis process (Fig. 4).

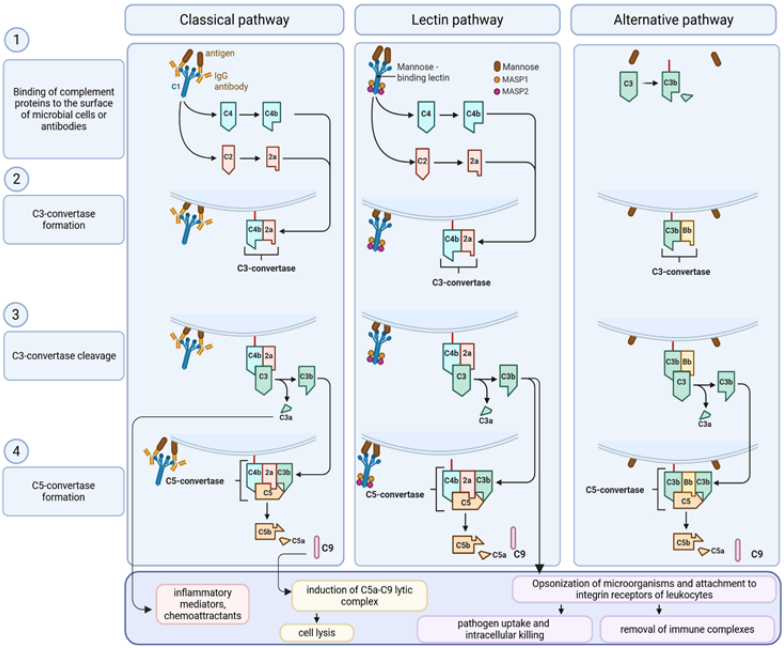

Fig. 4. Compliment activation paths

Cytokines. Cytokines are synthesized and released by various cell types in response to damage or recognition of specific pathogen structures by receptors (PRR and TLR). Cytokines regulate the activity of the immune system or perform an effector function not only locally, but also systemically (Fig. 5).

Cytokines are divided into five groups:

1) I type — cytokines include IL-2 to IL-7 cytokines;

2) II type — interferons and cytokines of the IL-10 family;

3) III type — TNF family;

4) IV type — IL-1 family such as IL-1, IL-18, IL-36, IL-37 and IL-38;

5) V type — IL-17 family (IL-17E).

The amount of cytokines in the blood increases with acute and chronic inflammation. Cytokines activate leukocytes, the production of adhesion molecules on endothelial cells, reactive oxygen species, histamine, serotonin, as well as arachidonic acid derivatives, which, on the other hand, regulate the release of cytokines.

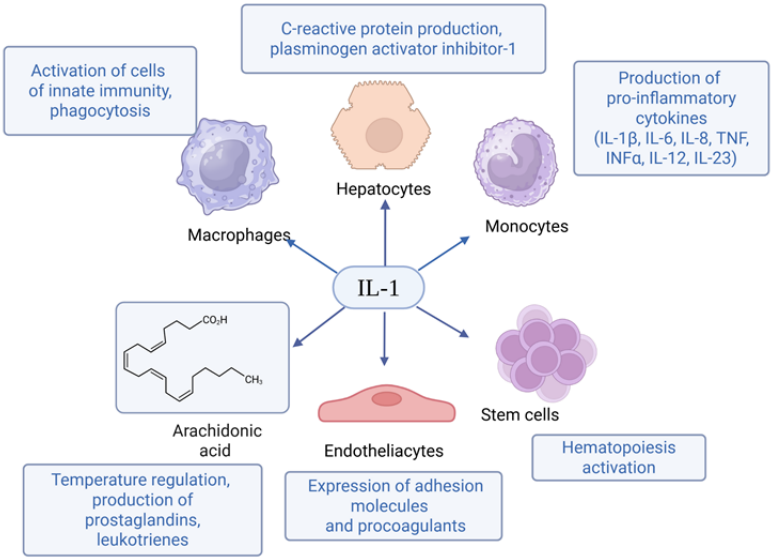

Fig. 5. Biological effects of IL-1

Chemokines. Chemokines or chemotactic cytokines are small molecules that make up a large family of peptides (60—100 amino acids) structurally related to cytokines. Their main function is to stimulate the migration of white blood cells. They are secreted in response to exposure to proinflammatory factors and selectively attract monocytes, neutrophils, and lymphocytes (Fig. 5—8).

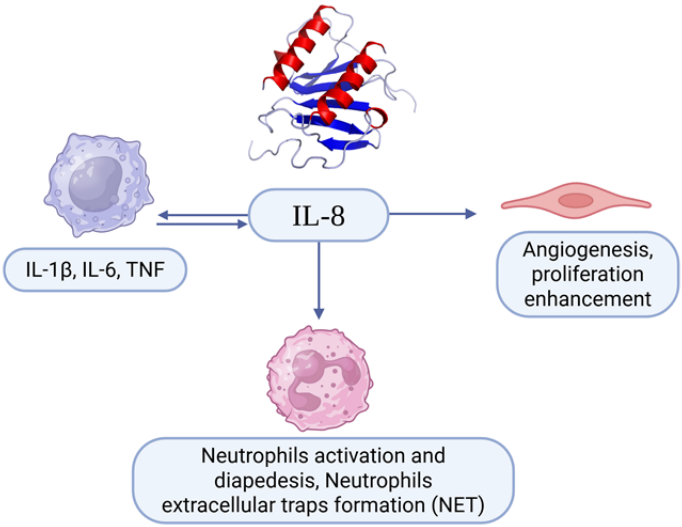

Fig. 6. Biological effects of IL-8

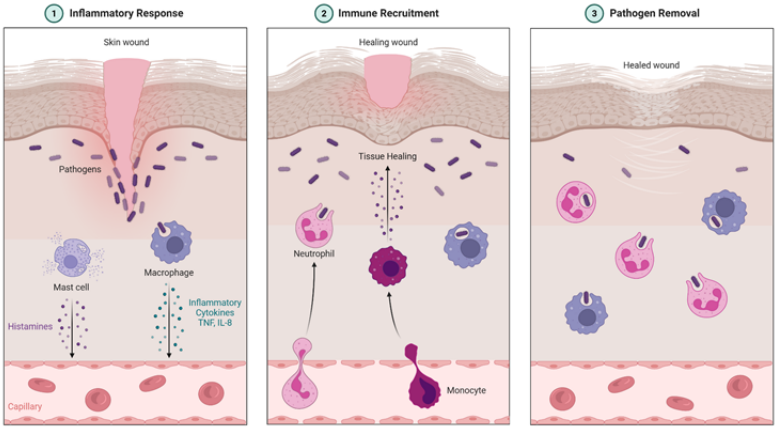

Fig. 7. Mechanism of innate response

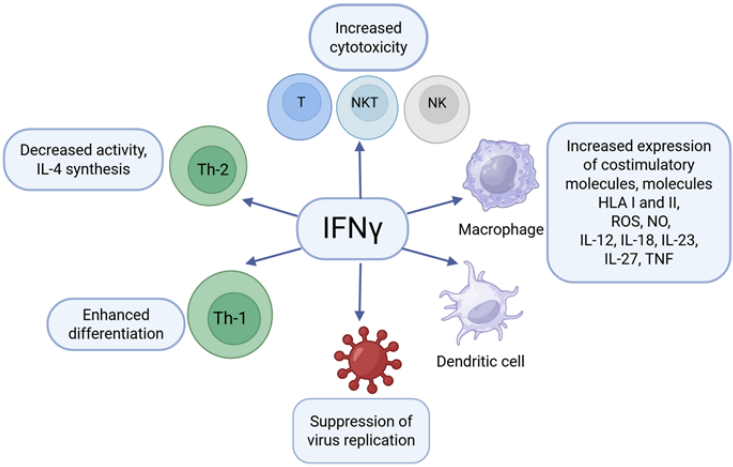

Fig. 8. Biological effects of IFN γ

Effectiveness of innate immunity

• ***Immune response against bacteria***

The main mechanism of the innate immune response to kill bacteria is activation of the complement system, HC (Fig. 7).

The complement system is involved in the opsonization of bacteria and potentiates their phagocytosis. Activation of TLR is required for phagocytosis. Activation of these receptors leads to inflammation by attracting white blood cells to the focus of infection. In the case of infection of cells with bacteria, microbes have the ability to survive and multiply inside phagocytic cells, which makes circulating antibodies inaccessible to intracellular bacteria.

The innate immune response against these bacteria is mediated primarily by phagocytes and NK cells. Phagocytic cells include neutrophils and macrophages. However, these pathogens are resistant to degradation, but their products are recognized by TLR and NLR receptors, which are responsible for activating more phagocytes. NK cells are also activated in this type of infection and are

involved in stimulating the production of the cytokine IL-12 DC (dendritic cells) and macrophages. NK cells also produce IFN-γ, which contributes to the death of phagocytosed intracellular bacteria. But usually this immune response is ineffective against infection (Fig. 8).

In contrast, the adaptive immune response against intracellular bacterial infections is mediated by $CD4^+$ T-cells, which help recruit and activate phagocytes that destroy/eliminate the pathogen, and the response of cytotoxic $CD8^+$ T-cells that destroy infected cells.

Both T cell subpopulations are responsible for antigen presentation by MHC type I and II receptors.

• Immune response against fungi

Most fungi are present in the environment, so animals, including humans, are exposed to them. Mechanisms of defense against fungi include both innate and adaptive immune responses. TLRs recognize fungal PAMPs.

Immunity against fungi is realized by activation of phagocytosis, production of pro-inflammatory cytokines and chemokines. The interaction of fungi with TLR4 or TLR2 generates an adaptive immune response via the Th1 or Th2 pathway, respectively.

• Immune response against viruses

In the infectious process, the most common host reaction is the inflammatory process. Viruses, in the absence of cytopathological damage in the early stages of infection, suppress the induction of an acute-phase protein response, since early monocytes are not activated. In contrast, the participation of NK cells against the virus plays an important role in host defense, they recognize cells infected with viruses in an antigen-independent manner, exhibit cytotoxic activity and rapidly produce large amounts of IFN-γ, which is involved in the activation of the adaptive immune cell. Type I interferons are the main cytokines responsible for protecting the human host from viral infections. Interferons have not been shown to exhibit their direct antiviral effects, but they promote gene activation, leading to the production of antiviral proteins that inhibit viral replication.

• Immune response against parasites

Due to the wide variety of parasites and the fact that each of their life cycles is very complex, in this section we will focus on the immune response against helminth parasites. This is because more than 1 billion people worldwide are currently infected with helminthiasis, making them one of the most common infectious agents responsible for many diseases in both animals and humans. The first protective barrier when infected with intestinal helminthiasis is a layer of mucus secreted by the host intestines either at the larval stage at the beginning of the infectious process or as adult parasites during the reproductive phase of infection. Thus helminth parasites will interact with the mucus layer and in many cases will have to cross it to reach and multiply within the epithelial layer.

Adaptive immune response

Benefits of adaptive immune response. The specificity of the adaptive immune response lies in its ability to specifically recognize a wide range of pathogens with their further neutralization. Antigens (small chemical molecules of pathogens) are recognized by immunocompetent cells. The adaptive immune response to these antigens is so universal that it can respond to almost any pathogen. Lymphocytes have a unique ability to synthesize up to 10^{11} different receptors capable of recognizing almost all pathogens.

The first exposure of the pathogen to the immune system leads to the development of *a primary adaptive response*. Symptoms of primary disease are always relatively severe because it takes time for the initial adaptive immune response to the pathogen to become effective. Upon repeated contact with the same pathogen, a secondary adaptive immune response occurs that is stronger and faster than the primary. A secondary adaptive response often eliminates the pathogen before it can cause significant tissue damage and the appearance of any symptom. Without symptoms, there is no dis-

ease, and a person does not even suspect infection. This secondary reaction is mediated by the phenomenon of *immunological memory*, which protects the macroorganism from being repeatedly infected with the same pathogen. Thanks to this mechanism, the exposure of pathogens to humans at an early age saves a person from these diseases later in life. A third important feature of the adaptive immune response is its ability to distinguish between self antigens, which are normally present in the body, and foreign antigens of a potential pathogen. As T and B cells mature, mechanisms are at work that prevent them from recognizing their own antigen, preventing a damaging immune response against the body. However, these mechanisms are not 100 % effective, and their violation leads to the development of autoimmune diseases.

Pathogen antigens are usually large and complex and consist of many antigenic determinants. *An antigenic determinant* (epitope) is one of the small regions within an antigen to which a receptor can bind, and antigenic determinants are limited by the size of the receptor itself.

Antigen processing and presentation. The mechanism by which T-cells recognize the antigen is highly complex. T-cells recognize antigen only on the surface of specialized cells called antigen-presenting cells (Fig. 9, 10, Table 1).

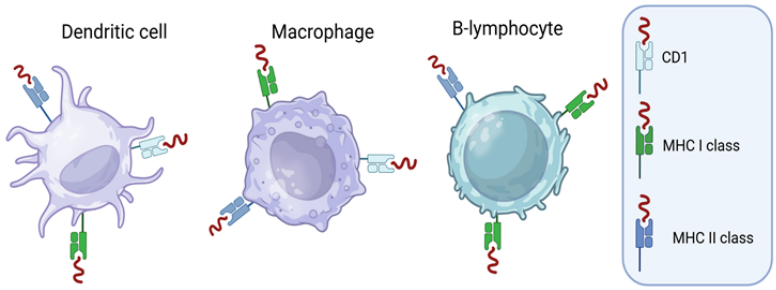

Fig. 9. Antigen presenting cell types

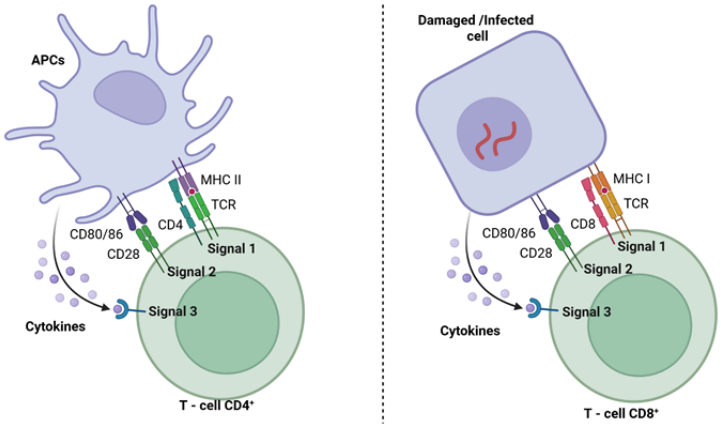

Fig. 10. Interaction of antigen-specific cells (APCs) with T cells

Table 1

Antigen presenting cell classes

Type of MHC	Type of cell	The presence of phagocytic properties	Function
Class I	All nucleated cells	No	Stimulates cytotoxic T-cell immune response
Class II	Macrophage	Yes	Stimulates phagocytosis and presentation at the site of primary infection
Class II	Dendritic	Yes, in tissues	Delivers antigens to regional lymph nodes
Class II	B-cell	Yes, internalizes surface Ig and antigen	Stimulates the secretion of antibodies by B-cells

Antigens are phagocytosed by these cells; further antigen processing begins, which is the enzymatic cleavage of the antigen into smaller parts. Antigen fragments are carried onto the cell surface and bind within the cell to a specialized type of antigen-presenting protein known as the *major histocompatibility complex (MHC)*. The association of antigen fragments with the MHC molecule on the cell surface is known as antigen presentation and leads to antigen recognition by the T-cell. MHC molecules are capable of presenting multiple antigens, depending on the amino acid sequence, in their peptide binding slots.

It is the combination of the MHC molecule and a fragment of the parent peptide or carbohydrate that is physically recognized by the T cell receptor (Fig. 9).

There are two different types of MHC molecules: MHC class I and MHC class II, which play a role in antigen presentation. Antigens of different pathogen classes use their MHC class to get to the surface for presentation. Extracellular antigens, characteristic of many bacteria, parasites and fungi, not multiplying inside the cytoplasm of the cell, enter the endomembrane system of the cell by receptor-mediated endocytosis. The formed vesicles fuse with the vesicles of the Golgi complex, which contain preformed MHC class II molecules. After the fusion of these two vesicles, an association of antigen and MHC molecule is formed, appearing on the cell surface.

The process of eliminating T-cells that can attack cells in one's own body is called tolerance. Although thymocytes are found in the cortex of the thymus, they are called «double negatives»: meaning they do not carry CD4 or CD8 molecules, which are markers of their differentiation. In the cortex of the thymus gland, they undergo positive selection — twice negative thymocytes bind to the MHC molecules of the thymic epithelium (MHC molecules of their «own»). This mechanism promotes the disposal of many thymocytes during T-cell differentiation. In fact, only 2% of thymocytes entering the thymus leave it as mature functional T-cells.

Later, the cells become twice positive, express both CD4 and CD8 markers, and move from the cortex to the zone between the cortex and the medulla. This is where negative selection occurs. In negative selection, autoantigens are introduced into the thymus from other parts of the body by professional antigen-presenting cells.

T-cells that bind to these autoantigens die as a result of apoptosis. Thus, the only remaining T-cells are those that can bind to body MHC molecules with foreign antigens, preventing attack on the body's own tissues. However, tolerance may be impaired by the development of an autoimmune response.

Cells leaving the thymus become singly positive, expressing either CD4 or CD8, but not both. $CD4^+$ T-cells bind to MHC class II and $CD8^+$ T-cells bind to MHC class I. The following discussion explains the functions of these molecules and how they can be used to differentiate different functional types of T-cells.

Mechanism of immune responses

Mature T-cells are activated after recognizing the processed foreign antigen in association with their own MHC molecule and begin to divide rapidly, called clonal expansion, which is essential for an effective immune response. How is clonal selection performed? This is the process of antigen binding only to those T-cells that have receptors specific for this antigen.

Clonal selection and expansion

Clonal selection theory was proposed by Frank Burnet in the 1950s. However, the term «clonal selection» is not a complete description of the theory, as clonal expansion develops parallel to the selection process. The basic principle of the theory is that a typical person has many (10^{11}) different types of T-cell clones that differ from each other in receptors. In this case, the clone is a group of lymphocytes that share the same antigen receptor. Each clone is

necessarily present in the body in small quantities. Otherwise, there would be no room in the body for lymphocytes with so many specific features.

Only lymphocyte clones whose receptors are activated by the antigen are stimulated to proliferate. Most antigens have multiple antigenic determinants, so the T-cell response to a typical antigen involves a polyclonal response. The polyclonal response is the stimulation of multiple T-cell clones. After activation, the selected clones increase in number and create many copies of each cell type, each clone with its own unique receptor. By the time this process is complete, the body will have a large number of specific lymphocytes available to fight infection.

Cellular basis of immunological memory

During the primary adaptive immune response, both memory and effector T-cells are generated. Memory T-cells are long-lived and can even persist throughout life. Memory cells are ready to act quickly. Thus, any subsequent exposure to the pathogen will trigger a very rapid T-cell response. This rapid secondary adaptive response generates large numbers of effector T-cells so rapidly that the pathogen is often suppressed before it can cause any disease symptoms. Similar immune responses develop in the case of a B-cell immune response.

T-cell types and functions

As previously mentioned, mature T-cells express either the CD4 marker or the CD8 marker, but not both. These markers are cell adhesion molecules that keep the T-cell in close contact with the antigen-presenting cell, by direct binding to the MHC molecule. Thus, T-cells and antigen-presenting cells are held together in two ways: by attachment of CD4 or CD8 to MHC and by binding of the T-cell receptor to the antigen (Fig. 11).

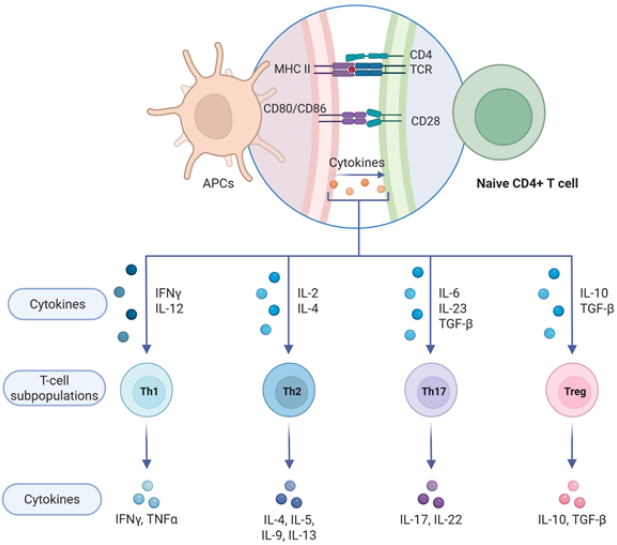

Fig. 11. Activation of T cells and their subpopulations

Helper T-cells and their cytokines

Helper/helper (Th) T-cells carrying the CD4 molecule function through cytokine secretion and enhance other immune responses. There are two classes of Th cells; they act on different components of the immune response. These cells differ not in their surface molecules, but in the characteristic set of cytokines secreted by them (Table 2).

Table 2

Functions of T-cell types and their cytokines

T-cell	The main goal	Function	Pathogen	Surface marker	MCH	Cytokines and mediators
Cytotoxic T lymphocyte (Tc)	Infected cells	Cytotoxicity	Intracellular	CD8	Class I	Perforin, granzymes and fas ligand
Th1	Macrophage	Auxiliary inductor	Extracellular	CD4	Class II	IFN-γ and TGF-β

End of the Table 2

T-cell	The main goal	Function	Pathogen	Surface marker	MCH	Cytokines and mediators
Th2	B-cell	Auxiliary inductor	Extracellular	CD4	Class II	IL-4, IL-6, IL-10 and all
Th17	Neutrophil	Auxiliary inductor	Extracellular bacteria and fungi	CD4	Class II	IL-17 IL-22
Tfh	B-cell	Antibody production	Extracellular	CD4	Class II	IL-21 (IL-4 and IFN-γ)
Treg	Th cell	Regulation	—	CD4, CD25	?	TGF-β and IL-10

Th1 cells are a type of helper T-cell that secrete cytokines and regulate cytotoxic T-cells (Tc) differentiation.

Th2 cells secrete cytokines that stimulate B-cell differentiation into antibody-producing plasma cells.

Th17 cells are involved in the recruitment of monocytes and neutrophils, promoting local inflammation. The Th1 immune response is induced, which promotes activation of macrophages with sufficient phagocytic capacity and the production of cytokines such as IFN-γ (Fig. 12).

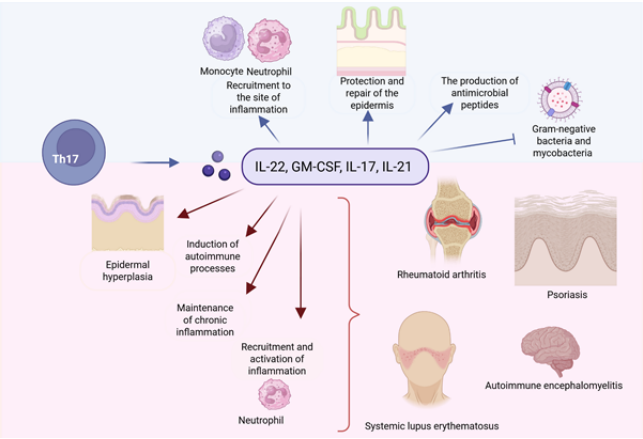

Fig. 12. Role of Th17 in hemostasis and immune damage

T follicular helper (Tfh) cells are a subpopulation of $CD4^+$ T-cell affecting B-cell. Tfh are necessary for the formation of germinal centers in the follicles of peripheral lymphoid organs and the stimulation of events that occur there: switching immunoglobulin isotypes, maturation of antibody affinity, formation of memory B-cells and long-lived plasmocytes.

Cytotoxic T-cells (Tcs) are $CD8^+$ T-cells that destroy target cells by inducing apoptosis using the same mechanism as NK cells. They either express a Fas ligand that binds to the fas molecule on the target cell, or act with perforins and granzymes contained in their cytoplasmic granules. As previously discussed, killing a virus-infected cell before the virus can complete its replication cycle does not produce infectious particles. Because more Tc develop during the immune response, they suppress the ability of the virus to cause disease. In addition, each Tc can kill more than one target cell, making them particularly effective. Tcs are so important in the antiviral immune response that some suggest this was the main reason why the adaptive immune response developed in the first place.

In the case of a long-lasting infection in the body, the pathogen is located mainly inside giant and epithelioid cells (incomplete phagocytosis). Both of these cell types are derived from macrophages (giant multinucleated cells — fused Mf). In the peripheral part of the granuloma, activated Mf and T-cells (mainly Th1 cells) are located, forming an external cell shaft. T-cells in the granuloma are constantly moving. They produce cytokines that activate macrophages with captured bacteria — IFN-γ, IL-1, TNF. Bacteria, remaining alive, are not able to multiply. Granuloma can exist in the body for decades (Fig. 13).

Regulatory T-cells (Treg), or suppressor T-cells, are the most recently discovered of the types listed herein. In addition to CD4, they carry CD25 and FOXP3 molecules. Exactly how they function is still being investigated, but they are known to suppress other T-cell immune responses. This is an important feature of the immune response because if clonal expansion during immune responses continues unchecked, these responses can lead to autoimmune diseases and other medical problems.

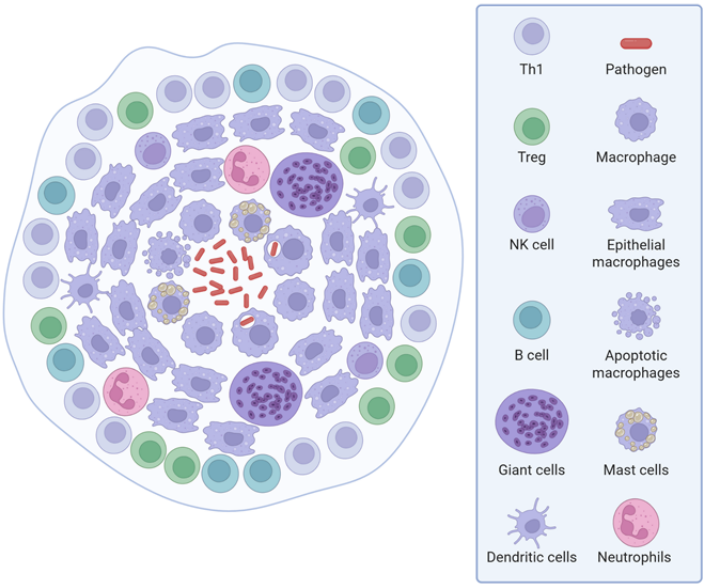

Fig. 13. Cell composition of granuloma

T-cells not only directly destroy pathogens, but also regulate almost all other types of adaptive immune response, as evidenced by the functions of T-cells, their surface markers; the cells they work with and the types of pathogens.

Humoral immune response: B-cells

B-cells interact with antigens present in the body and cause the production of specific antibodies that circulate throughout the body and bind to the antigen whenever it occurs. During the maturation of B-cells, a set of highly specific B-cells is formed, each of which has antigenic receptor molecules in its membrane. Each B-cell has only one type of antigen receptor, which makes each B-cell unique (Fig. 14).

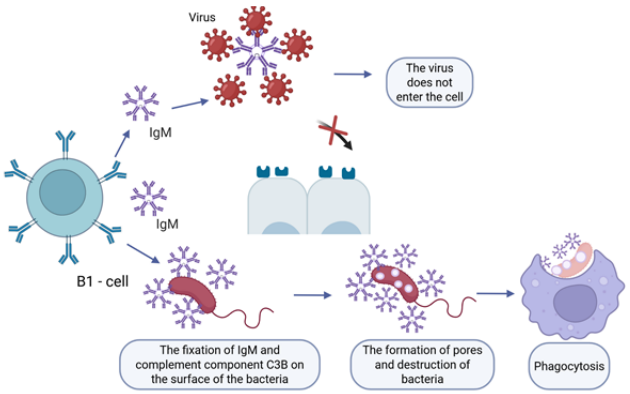

Fig. 14. Role of B cells and antibodies in the first line of defense against pathogens

Once B-cells mature in the bone marrow, they migrate to the lymph nodes or other lymph organs, where they wait to encounter potential antigens. When a B-cell encounters an antigen that binds to its receptor, the antigen molecule enters the cell, where, after processing, it reappears on the surface of the cell bound to the B-cell protein. When this process is complete, the B-cell is considered activated. Activation induces B-cells to rapidly divide and form thousands of identical (clonal) cells. These cells become either plasma or memory B-cells (Fig. 15).

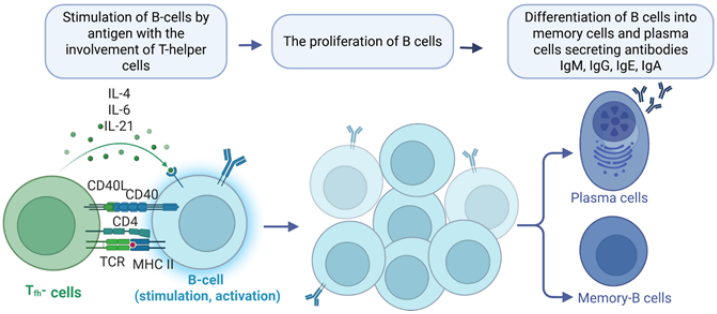

Fig. 15. Stages of humoral response

Memory B-cells remain inactive at this point until the next encounter with the antigen, caused by reinfection by the same bacterium or virus, causes them to divide and form a plasma cell clone. Plasma cells, on the other hand, produce and secrete a large number, up to 100 million molecules per hour, of antibody molecules. An antibody (immunoglobulin (Ig)), is a protein that is produced by plasma cells after stimulation with an antigen. Antibodies are found in the blood, in gastric and mucous secretions, in breast milk. Antibodies in these biological fluids can bind pathogens and label them to be killed by phagocytes before they can infect cells. B1-cells are self-renewing long-lived cells producing low-affinity polyreactive IgM antibodies, known as «natural, or normal» antibodies. These antibodies play an important role in the first line of defense of the body against encapsulated bacteria. B1-cells are also responsible for the synthesis of «natural» autoantibodies involved in the clearance of apoptosis and cell breakdown products. Thus, B1-cells serve as a link between the innate and acquired immune response. 48 hours after encountering the pathogen, B1-cells begin to produce specific AT — IgM.

The activated B-cell receives additional stimuli from Th2 cells and undergoes 7—8 mitoses.

Antibodies can bind to viruses or bacteria and prevent their pathogenic effect on body cells. The antigen-antibody complex stimulates the previously described complement system by destroying the antigen-bearing cell. Phagocytic cells of the innate immune system are attracted by antigen-antibody complexes, and in the presence of complexes, phagocytosis is enhanced. Finally, antibodies stimulate inflammation (Fig. 14).

Antibody production by plasma cells in response to an antigen is called active immunity and describes the active response of the host immune system to infection or vaccination. There is also a passive immune response, where antibodies come from an external source rather than from a person's own plasma cells and are injected into «the host». For example, antibodies circulating in a pregnant woman's body cross the placenta into the developing fetus. Antibodies are also passed to the baby with breast milk. The baby benefits from the presence of these antibodies for several months

after birth. In addition, a passive immune response is possible by administering antibodies to humans as an antidote to snakebite toxin or antibodies in serum to combat hepatitis infection. This provides immediate protection, as the body does not need the time it takes to prepare its own response.

Pathology of immune response:

1. **Transplant rejection** is an immune-mediated response that constitutes an obstacle to transplantation.

2. **Autoimmune diseases.** The etiology of many autoimmune diseases is unclear — the reality is that the prevalence of these diseases is increasing and manifests itself more aggressively.

3. **Allergy.**

4. **Immunodeficiency.**

Autoimmunity and hypersensitivity are manifestations of immune response disorders. Autoimmunity is a term that is used when the immune system attacks its own tissues. Most autoimmune reactions occur in the II (cytotoxic) and III (immunocomplex) types of hypersensitivity. For example, myasthenia gravis is both an autoimmune disease and a type II hypersensitivity reaction; immunocomplex glomerulonephritis — autoimmune disease and type III hypersensitivity reaction. When hypersensitivity reactions occur in response to foreign antigens, (bee venom), they are not autoimmune. The causes of the aggressive reaction of the immune system are poorly understood. Autoimmune pathology and allergy can be attributed to multifactorial diseases, when genetic and environmental factors play an important role.

Autoimmune disorders occur when the immune system mistakenly responds to «own» tissues. These disorders are considered polygenic and multifactorial. The main pathogenetic factors for the development of autoimmune diseases:

• The theory of antigenic mimicry suggests the possibility of antigens of viruses or bacteria to look like «their own», which causes auto-aggression.

• The theory of release of sequestered antigens suggests that antigens that do not come into direct contact with lymphocytes during intrauterine development can cause autoimmune reactions if, due to damage to the membranes, they meet with immune-competent cells.

• Inhibition of T-suppressor production and development of abnormal B-cells not sensitive to T-suppressors.

• Hereditary predisposition to autoimmune disorders (female sex and HLA-associated genes).

• Autoimmune reactions occur, as a rule, in the type of type II and III hypersensitivity. Examples: ankylosing spondyloarthritis, rheumatoid arthritis, Graves` disease, type I diabetes, systemic lupus erythematosus, narcolepsy, multiple sclerosis, Crohn's disease, psoriasis, myasthenia gravis, hemolytic anemia, etc.

• chronic viral, prion and other infections;

• hereditary or acquired molecular abnormalities of the structure of the most important structural and regulatory molecules of the immune system (including molecules involved in the control of apoptosis);

• older age.

Thus, an autoimmune process is an immune inflammation directed against normal (unchanged) antigens of their own tissues and due to the formation of autoantibodies and autoreactive lymphocytes (i. e., autosensitization).

Conventionally, the pathogenesis of autoimmune disorders can be divided into two stages: inductive and effector.

The inductive stage is closely related to the disruption of any mechanism of immunological self-tolerance (Fig. 16).

Type of tolerance	Mechanism	Where they act
Central tolerance	Clonal deletion or receptor editing	Bone marrow, thymus
Antigen segregation	Physical separation of autoantigen from the lymphoid system	Immunoprivileged and some other organs
Peripheral anergy	Inactivation of cells by signaling in the absence of costimulation	Secondary lymphoid organs
Regulatory T cells (Tregs)	Suppression by cytokines and intracellular signaling	Secondary lymphoid organs and inflammation sites, malignant tumors
Functional deviation	Differentiation into regulatory cells	
Cell death induced by activation	Apoptosis	

Fig. 16. Mechanisms of self-tolerance

The effector stage of any autoimmune process proceeds according to one or more (II, III, IV or V) types of hypersensitivity according to P. G. H. Gell and P. R. A. Coombs (1969).

Tolerance to the body's own antigens is a natural condition in which the destructive activity of the immune system is directed only to external antigens. The aging processes of the body from an immunological point of view are due to the slow cancellation of such tolerance.

Allergy

Hypersensitivity is an immune response that has a damaging effect on the body. The main mechanism causing hypersensitivity is a specific antigen-antibody reaction or a specific antigen-lymphocyte interaction. According to P. G. H. Gell and P. R. A. Coombs (1969), four types of allergic reactions are distinguished. Type I, II and III hypersensitivity are mediated by antibodies produced by B-cells. Type IV hypersensitivity — T-cells.

General pathogenesis of allergic reactions.

In the development of allergic reactions distinguished 3 aspects:

- immunological;
- pathochemical;
- pathophysiological.

Type I hypersensitivity

Type I hypersensitivity has 2 subspecies: reagin and anaphylactic.

Etiology of anaphylaxis:

Medicines — penicillin, analogues of penicillin and other antibiotics, radiographic contrast agents, aspirin, indomethacin and other analgesics, allergenic extracts.

Biological agents — serum proteins including γ -globulin, insulin and other hormones, vaccine, local anesthetics, hymenopteran (stinging) insects — wasps, honey bees, fire ants, hornets.

Food — nuts, seafood (especially shellfish), eggs, fruits (citrus and strawberries), tartrazine (yellow dye).

Inorganic chemicals — nickel, aluminium, zinc.

Pathogenesis of type I allergic reactions (Fig. 17).

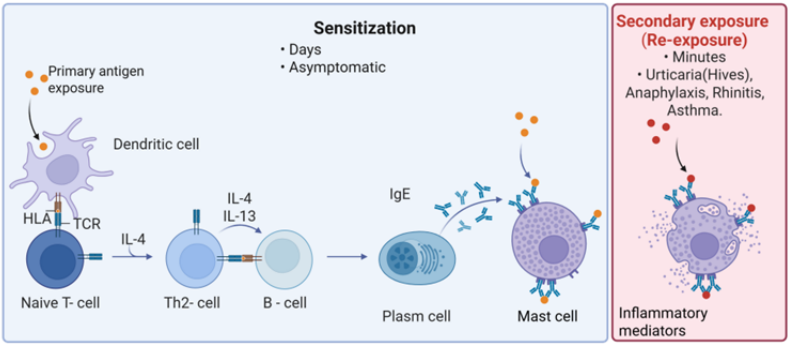

Fig. 17. Pathogenesis of type I allergic reactions

Classification of type I mediators

Pre-existing mediators include:

• Neutrophil and eosinophil chemotaxis factors — NCF, ECF;

• Histamine — reduces smooth muscles, dilates vessels, increases their permeability.

• Heparin — prevents the formation of fibrin (anticoagulant).

Newly synthesized mediators include:

• Serotonin — reduces smooth muscle, increases vascular permeability;

• Platelet-activation factor (FAT) — causes smooth muscle spasm, causes platelet aggregation and release of serotonin and histamine from them.

• Arachidonic acid derivatives (eicosanoids). There are two pathways for the metabolism of arachidonic acid in the cell (after the enzymes that break it down): cycloxygenase (using cycloxygenase) and lipoxygenase (using lipoxygenase).

Clinical manifestations. Manifestations of an immediate hypersensitivity reaction vary in severity and intensity.

For a type I hypersensitivity reaction, such as urticaria, seasonal allergic rhinitis, may manifest itself by the development of eczema or atopic bronchial asthma.

In other patients, symptoms are more severe, including a choking feeling in the throat, localized swelling, wheezing, and tachycardia, suggesting angioedema or severe airway damage. In a very small number of people, the type I hypersensitivity reaction can be expressed in the form of a life-threatening — anaphylactic shock.

Type II hypersensitivity

Peculiarity of allergic reactions of type II — develop in the absence of repeated admission of allergen.

Etiology:

The antigens to which the immune response is triggered are located on the surface of specific cells or tissue (Table 3).

Table 3

Types of antigen causing type I allergy

Disease	Antigen localization
Type 1 diabetes	Islet cells
Insulin-resistant diabetic conditions	Insulin receptor
Myasthenia Gravis	Acetylcholine receptor
Addison's disease	Adrenal epithelial cells
Autoimmune hemolytic anemia	Red blood cell membrane
Immune thrombocytopenic purpura	Platelet membrane
Autoimmune neutropenia	Neutrophil antigens
Pernicious anemia	Castle's intrinsic factor, parietal cells
Lymphocytic thyroiditis	Thyroglobulin
Graves' disease	TSH receptor
Pemphigus vulgaris	Desmosomes
Hyperacute transplant rejection	Donor antigen

The pathogenesis of the cytotoxic allergic reaction is presented on the example of hemolytic disease of newborns and myasthenia gravis (Fig. 18).

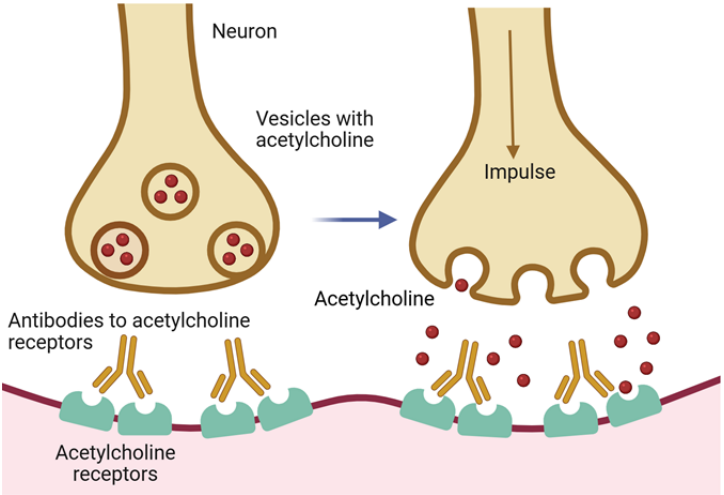

Fig. 18. Pathogenesis of myasthenia gravis

Pathogenesis of myasthenia Gravis

Myasthenia Gravis is an autoimmune disease of the neuromuscular synapse. In this case, antibodies are formed mainly to the acetylcholine receptor (AChR) and less often to the muscle-specific kinase (MuSK) or protein on the muscle membrane. When an antigen-antibody complex forms at the receptor site, ***complement is activated***, which destroys the muscle cell membrane. Effector cells are not thought to be involved in this type II hypersensitivity reaction. The formation of AT to acetylcholine receptors occurs in the thymus. Loss of acetylcholine stimulation of the motor endplate causes the development of muscle weakness. The main symptoms of myasthenia gravis are ptosis, diplopia, and muscle weakness after exertion that resolves at rest (Fig. 18).

Type III hypersensitivity

Features of type III reactions:

• Allergens (endo- and exoallergens) in this case are dissolved in plasma, lymph, tissue fluid (Table 4).

• Damage is done by circulating immune complexes (CICs) allergen + antibody.

Table 4

Types of allergic reaction type III antigens

Disease	Antigen
Immune complex glomerulonephritis	Glomerular basement membrane antigens, exogenous antigens, drugs
Systemic lupus erythematosus	Double-stranded DNA, DNA-histone complex, Sm (Smith) — U1-,U2-, U4- Ribonucleoproteins antibodies, RNP, Ro:SSA, La:SSB, centromere
SLE-associated glomerulonephritis	Double-stranded DNA, DNA-histone complex, Sm (Smith) — U1-,U2-, U4- Ribonucleoproteins antibodies, RNP, Ro:SSA, La:SSB
Hypersensitivity pneumonitis/ extrinsic allergic alveolitis	Various fungal spores in damp rooms
Farmer's lung disease	Thermophilic actinomycetes from contaminated hay or grain
Chemist's lung	Isocyanates
Post-infectious arthritis	RANA(rheumatoid arthritis associated nuclear antigen)
Rheumatoid arthritis (RA)	RANA
Serum sickness	Lymphocytes or thymocytes from heterologous serum
Henoch-Schönlein purpura	Upper respiratory tract viruses, drugs (antibiotics and thiazides), foods (milk, eggs, rice, nuts, beans)

End of the Table 4

Disease	Antigen
Drug-induced vasculitis	Medicines (antibiotics and thiazides)
Polyarteritis nodosa	Antineutrophil cytoplasmic antigen
Wegener's granulomatosis	Antineutrophil cytoplasmic antigen
Goodpasture syndromea	Glomerular basement membrane antigens (GBM)

The main mediators are:

1. Complement, under conditions of activation, various complement components have a cytotoxic effect. The leading role is played by the formation of S3, S4, S5 that enhance certain links of inflammation (C3b enhances the immune adhesion of immune complexes to phagocytes, C3a is anaphylatoxin, like C4a, etc.).

2. Lysosomal enzymes, the release of which during phagocytosis enhances damage to the basement membranes, connective tissue.

3. Kinins, in particular bradykinin. With the damaging effect of immune complexes, Hageman factor is activated, as a result, bradykinin is formed from blood α-globulins under the influence of kallikrein.

4. Histamine and serotonin play a large role in type III allergic reactions. Their source is mast cells, blood basophils and platelets. They are activated by the C3a- and C5a-components of complement.

5. Superoxide radical anion.

Type IV hypersensitivity, cell-mediated reactions

Type IV hypersensitivity is a T-cell mediated immunological reaction manifested by inflammation at the site of allergen ingestion.

Type IV hypersensitivity forms the basis for the development of certain autoimmune diseases and antitumor protection, develops in bacterial and viral infections, in transplant rejection reactions (Table 5).

Table 5

Examples of pathogens that cause delayed hypersensitivity reactions

Disease	Bacteria
Tuberculosis	Mycobacterium tuberculosis
Leprosy	Mycobacterium leprae
Histoplasmosis	Histoplasma capsulatum
Coccidioidomycosis	Coccidioides immitis
Brucellosis	Brucella abortus Brucella suis (less often) Brucella melitensis (less often)
Tularemia	Francisella (Pasteurella) tularensis

There are several types of delayed hypersensitivity reactions, including skin basophil hypersensitivity (Jones-Mote sensitivity), contact hypersensitivity, tuberculin hypersensitivity and granulomatous hypersensitivity.

Basophilic skin hypersensitivity

The fastest type of delayed hypersensitivity. This basophil response is mediated by lymphocytes. Soluble antigen injected intradermally or antigens injected into the skin trigger T-cell activation, cytokine release followed by activation of basophils that infiltrate the area. The reaction peaks with swelling of the skin after 24 hours and can last from 7 to 10 days. An example of this type of hypersensitivity is skin graft rejection reactions.

Contact hypersensitivity

Contact hypersensitivity is the most well-known type IV hypersensitivity. It is an immune or inflammatory response that develops when the skin is exposed to a wide variety of plants, oils, chemicals, ointments, clothing, cosmetics, dyes and adhesives. Contact hypersensitivity is an epidermal phenomenon. Clinical symptoms appear after 48—72 hours. The reaction is slow, because the anti-

gen penetrating the skin is very small and is an incomplete fat-soluble antigen — hapten. The hapten must first enter the epidermis, where it binds to the body's normal protein called the carrier. Further, the formed complete antigen is processed by dermal dendritic cells located in the suprabasal epidermis. Dermal dendritic cells travel to the local lymph channel, from where they migrate to regional lymph nodes. In the lymph node, dermal dendritic cells present the treated complete antigen to $CD4^+$ cells in the paracortex. Antigen-sensitized $CD4^+$ cells then secrete lymphokines that initiate an inflammatory response and attract other effector cells. The main lymphokines are IL-2, IL-3, interferon, TNF and macrophage stimulating factors.

Skin symptoms resulting from contact dermatitis include: redness (erythema), swelling, itching, and blisters. Hypersensitive individuals may also experience respiratory symptoms upon contact with an aerosolized hapten. Delayed type IV hypersensitivity caused by exposure to latex glove compounds poses an occupational risk to surgeons and nurses working in operating rooms.

Tuberculin-type hypersensitivity (Type IV hypersensitivity)

Tuberculin-type hypersensitivity occurs when a previously infected tuberculosis patient is exposed to tuberculin antigen while performing a tuberculin test. Erythema peaks after 48—72 hours. Inflammation develops at the site of intradermal injection. Sometimes people may experience tissue necrosis at the injection site.

Granulomatous hypersensitivity

The type IV granulomatous hypersensitivity reaction is the primary defense against intracellular infection. This is a protective reaction that eventually causes tissue destruction due to antigen persistence. In this case, the antigen is not destroyed in macrophages either due to disruption of the fusion of the lysosome with the phagosome, as in tuberculosis and leprosy, or due to the resistance of various materials to lysosomal enzymes, as in the case of the remaining suture or talc in the operating wound. Lymphocytes and macrophages, protecting the body, cause tissue damage,

releasing cytokines and stimulating the development of the inflammatory process. Active macrophages contribute to the development of granuloma, consisting of lymphocytes, tissue histiocytes, eosinophils, plasma cells, giant and epithelioid cells. The main cell in the granuloma is the macrophage. Epithelioid cells arise from macrophages and are large cells with large amounts of endoplasmic reticulum. When epithelioid cells merge, multinucleated giant cells form. This nucleus is surrounded by lymphocytes. Gradually, fibroblastic activity and increased collagen synthesis lead to the fact that granuloma causes the development of a connective tissue scar. Often there is a central necrosis inside the granuloma, which is called caseous or curd necrosis.

Immunodeficiencies

A deficient immune response results from a functional decline in one or more components of the immune system. These disorders can affect lymphocyte activity, antibody formation, phagocyte activity, and complement system components. There are two types of immunodeficiency: primary and secondary.

Primary immunodeficiencies are congenital immunodeficiencies. Examples of primary immunodeficiency disorders are severe combined immunodeficiency syndrome (SCID), DiGiorgi syndrome, selective IgA deficiency, and AIDS. Individuals with primary immunodeficiency may be predisposed to multiple deficits, as in agammaglobulinemia or SCID, IL-12 chain abnormalities, interferon-γ (IFN-γ) (Table 6).

Table 6

Examples of primary immune deficiencies

Types of disorders	Pathogenesis
X-linked agammaglobulinemia (XLA), or Bruton agammaglobulinemia	B-cell; antibody
Hypogammaglobulinemia and common variable immune deficiency	B-cell; antibody

End of the Table 6

Types of disorders	Pathogenesis
Selective IgA deficiency	B-cell; antibody IgA
Secretory component deficiency — chronic mucocutaneous candidiasis	B-cell, IgA antibody secretion
Selective IgG deficiency	IgG
Selective IgM deficiency	IgM
Transient hypogammaglobulinemia of infancy	Low antibody levels
X-linked lymphoproliferative disease or Duncan's syndrome	Epstein-Barr virus antigen antibody
DiGeorge syndrome (congenital thymic hypoplasia or aplasia)	Primed T-cells
Autosomal recessive SCID	T-cell, antibody
X-linked recessive T-B+ SCID	T-cell, antibody
T-B- SCID (reticular dysgenesis)	T-cell, antibody
Deficiency of MHC class II expression	T-cell, antibody
Wiskott-Aldrich syndrome (immunodeficiency with eczema and thrombocytopenia)	Antibody, T-cell
Chediak-Higashi syndrome	Natural killers, phagocytic cells, granulocytes, platelets
Chronic granulomatous disease in pediatric patients	Phagocytic cells (neutrophils)

Secondary immunodeficiencies are a consequence of the development of a disease not initially associated with a disorder of the immune system, or treatment that has affected the state of the immune response. Examples of secondary disorders develop with hyperlipidemia or malnutrition, drug treatment (cancer chemotherapy — cytostatics; with generalized immunosuppression — methotrexate) or psychosocial stress. For example, an excessive neuroendocrine stress response with increased corticosteroid secretion in-

creases a person's susceptibility to infectious agents and tumors, but increases resistance to autoimmune diseases. On the other hand, a defective neuroendocrine response to stress with low levels of corticosteroids increases the severity of autoimmune diseases.

Acute illness, like surgery, is a stressor that affects the state of the immune system. After surgery, the number of T- and B-cells decreases within 1 month, which is most likely the result of stress. Spleen removal reduces serum IgM levels and antibody responses to encapsulated bacteria (e. g., S. pneumoniae, H. inluenzae, S. aureus). Many diseases — diabetes, cirrhosis of the liver caused by drugs or alcohol, severe burns, injuries, sickle cell anemia, malignant neoplasms and severe infections are associated with secondary immunodeficiencies.

Anesthetics (e. g., halothane, cyclopropane, nitrous oxide, ether), alcohol, antibiotics, antithyroids, anticonvulsants, antihistamines, and steroids reduce cellular or humoral immunity by various methods.

The role of nutrition on the state of the immune system is shown. Inadequate nutrition can lead to protein depletion, carbohydrate, lipid, vitamin and mineral deficiencies. Antibodies consist of proteins that are also low in protein fasting. Low levels of zinc, folate and vitamin B6, A, D and E can lead to T- and B-cell dysfunction. Hyperlipidemia can lead to dysfunction of lymphocytes and granulocytes. In the elderly, the function of the immune system is altered. Response to antigenic stimulation is variable. Older adults respond less well to «novel» antigenic stimuli. Cells of the immune system in old age are not able to proliferate as effectively as in young people. Although the total number of T cells remains the same, their function is reduced. T-cells are less capable of proliferation/clonal expansion, their cytotoxicity decreases. Antibody production is also reduced. There is an increase in the production of autoantibodies, which can affect the exacerbation of autoimmune diseases in the elderly.

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Topic 2

INFLAMMATION

Training objectives: to form modern ideas about etiology and pathogenesis, cardinal signs of inflammation.

As a result of studying the topic, students should:

— be aware of the principles of pathogenetic therapy of inflammation;

— know the etiology and pathogenesis of inflammation, alteration and disorder of microcirculation in the focus of inflammation, the role of mediators, exudation and emigration of leukocytes to the focus of inflammation, types of exudates;

— be able to substantiate the pathogenesis of common manifestations in inflammation, assess the dynamics of the inflammatory process according to clinical and laboratory data, solve typical situational tasks and test tasks.

Inflammation is one of the most common pathological processes that occurs when the body is exposed to various factors of exogenous and endogenous nature. Inflammation is the basis of the pathogenesis of many diseases, and its localization in a particular organ often determines the specifics of the disease and its nosological form. Currently, inflammation is understood as a complex of complex changing reactions to tissue damage caused by infectious or non-infectious agents of the external and internal environment of the body. Some of these reactions may be adequate, in the process of wound healing and infection control, or inadequate, as in many chronic conditions. Inflammation is the **«second line»** of defense against infectious agents. Inflammation-induced responses are the cornerstone of pathology. Diseases in which inflammation plays a dominant pathological role have the suffix "it". Both cell-mediated and humoral responses of the immune system play a cen-

tral role in inflammation. **Inflammation is an important aspect of innate immunity, which involves localizing harmful agents and moving phagocytic cells to this area.**

Depending on the reactivity of the body, the following are distinguished:

— *normergic form* of inflammation (occurs "mildly," with well-defined local signs and general manifestations);

— *hyperergic form* (proceeds "violently," with pronounced manifestations of alteration and exudation, "necrotic" inflammation such as the Arthus phenomenon can develop);

— *hypoergic form* (inflammation with mild local and general manifestations). Positive hyperergic inflammation develops in the body with high resistance. Negative hyperergic inflammation (flows for a long time and sluggishly) is formed in a weakened body (old age, when fasting).

If the inflammatory process is accompanied by severe stress, redistributive lymphocytopenia develops as a result of the release of lymphocytes from the blood into the tissues under the influence of glucocorticoids, as well as true lymphocytopenia as a result of cell death by apoptosis in the lymphopoietic organs.

Acute or chronic inflammation

Acute inflammation has a rapid onset within minutes or hours and usually resolves in a few days, has classic signs and symptoms, is accompanied by the formation of a cellular infiltrate consisting mainly of neutrophils. Erythema seen in acute inflammation is explained by vasodilation and increased blood flow to the affected area. Chronic inflammation is characterized by a slow onset over several days, lasting several years, less pronounced classical signs and symptoms, a cellular infiltrate mainly consisting of monocytes/macrophages and lymphocytes. Chronic forms of inflammation are accompanied by significant hypoproteinemia due to massive protein losses with exudate.

Inflammatory mediators and biomarkers

The discovery of cellular and molecular mediators of inflammation and the development of sensitive biomarkers have expanded our understanding of inflammation and its role in pathology.

Classification of inflammatory mediators:

• *Humoral* — complement components, kinins, blood coagulation system factors;

• *Cellular* — pre-existing (vasoactive amines, lysosomal enzymes, neuropeptides and neurotransmitters) and newly formed (arachidonic acid derivatives, phospholipids, cytokines, reactive oxygen and nitrogen species);

Biomarkers of inflammation characterizing inflammation activity and of diagnostic significance:

1. Active oxygen and active forms of nitric oxide (ROS and RNS);
2. Formation of DNA adducts;
3. Cytokines (e. g. IL-6 and TNF-alpha) and chemokines;
4. Acute phase proteins (eg, C-reactive protein (CRP));
5. Prostaglandins;
6. Arachidonic acid metabolites associated with cyclooxygenase (COX) activation — prostaglandins, thromboxane;
7. Inflammation-related growth factors and transcription factors (eg, NF-kappa B);
8. Major immune cell types.

The population of immune cells and the activity of mediators depend on the phlogogen (etiological factor) and the duration of the injury.

Three cytokines of macrophage origin — IL-1, IL-6, and TNF-α — are responsible for most systemic effects in inflammation. TNF-α and IL-1 act on the center of thermoregulation, increasing body temperature, inducing sleep and appetite suppression. Cytokines

provide heat retention through vasoconstriction and muscle tremors. It is believed that an increase in body temperature contributes to an increase in immunity. IL-1 stimulates and induces the development of neutrophilia by stimulating the release of neutrophils from the bone marrow. All three cytokines enhance protein catabolism in muscle tissue and provide substrate (amino acids) for antibody synthesis by plasma cells.

The liver is an important target for IL-1, IL-6 and TNF-α. These cytokines promote the synthesis of acute phase proteins in the liver, which include complement components, clotting factors and protease inhibitors. The most important acute phase proteins are CRP and serum amyloid A. CRP is the most popular of all acute phase proteins, but the interpretation of the titers of this protein is complex, since its amount may not reflect the intensity of the inflammatory process. Normally, its concentration is from 0.1 to 8.0 mg/l. CRP levels peak on days 2—3 of the inflammatory process and gradually return to baseline on days 12—15. With prolonged and chronic inflammation, the content of CRP remains elevated. CRP binds to phospholipids on bacterial cell membranes and acts as an opsonin, facilitating phagocytosis. Acute phase proteins also include fibrinogen, the level of which in serum increases with the development of acute inflammation. Fibrinogen covers the erythrocyte membrane and reduces their charge, which leads to the formation of sweets and an increase in ESR values. With inflammation, dysproteinemia forms: there is an absolute decrease in the amount of albumin in the blood plasma and an absolute or relative increase in globulins, which leads to an acceleration of ESR. The development of dysproteinemia is primarily associated with a change in liver function, which occurs as a result of the action on hepatocytes IL-6 and the entry of albumin into the focus of inflammation during plasma extravasation.

Serum CRP activity and ESR is used as a non-specific indicator of inflammation (Fig. 19).

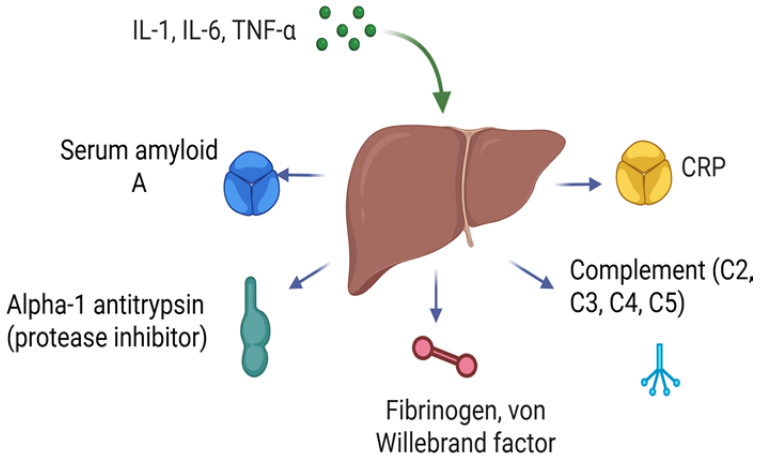

Fig. 19. Inflammatory mediators

CRP is a widely used clinical biomarker of inflammation present in two forms with different functions. One form is a homopentamer called native CRP (nCRP) and the other is a monomer (mCRP). High-sensitivity (hs) CRP is often used to assess increased risk of cardiovascular disease (CVD). Elevated plasma hs-CRP and cholesterol are a risk factor for cardiovascular disease.

Key clinical signs of inflammation

Clinically, acute inflammation is characterized by **five main features:** rubor (redness), calor (increased fever), tumor (swelling), dolor (pain), and functio laesa (impaired function). The first four were described by Celsus (c. 30 BC — 38 AD e.); the fifth was added later by R. Virkhov in the XIX century. Redness and fever occur due to increased blood flow to the inflamed area; edema occurs due to the accumulation of fluid (exudate) in the focus of inflammation; pain arises from the release of chemicals that stimulate nerve endings; loss of function is due to a combination of fac-

tors. These signs appear with acute inflammation on the surface of the body, but not all of them appear with acute inflammation of the internal organs. Pain occurs only if there are appropriate sensory nerve endings at the site of inflammation. For example, acute inflammation of the lung (pneumonia) does not cause pain, unless the inflammation affects the parietal pleura, where there are pain-sensitive nerve endings. An increase in the temperature of inflamed skin occurs due to the flow of a large amount of blood of internal body temperature into usually colder skin. When inflammation occurs internally, where the tissue typically has an internal body temperature, there is no increase in temperature.

Morphological and functional changes in inflammation

Morphological and functional changes in acute inflammation were described in the late nineteenth century by Congheim, who demonstrated vascular changes in frog tongue vascular damage. **The two main components of the acute inflammatory response are the microvasculature and cellular response.**

Microcirculatory response

Vasodilation and stasis. The first change in microcirculation is transient and minor vasoconstriction, followed by marked active dilatation of the arterioles, capillaries, and venules. Vasodilation leads to increased blood flow in this area (flushing). Subsequently, when fluid from the vessel enters the tissue during the formation of exudate, blood viscosity increases and stasis develops. Postcapillary venules expand due to impaired blood outflow, while the endothelial cells of the vascular wall swell, which contributes to the formation of red blood cells, marginal standing and emigration of white blood cells.

Increased permeability. Capillary and venule permeability depends on intercellular contacts between vascular endothelial cells. The resulting pores usually allow small molecules to pass (molecular weight < 40,000 g/mol). With acute inflammation, there is an

immediate (but reversible) pronounced increase in the permeability of venules and capillaries due to the active contraction of actin filaments in endothelial cells.

Exudate formation. An increase in fluid output from microvasculature vessels due to increased vascular wall permeability is called exudation. Exudate composition approaches plasma composition — it is rich in plasma proteins, including immunoglobulins, complement components, and fibrinogen. Fibrinogen in acute inflammatory exudate is rapidly converted to fibrin with the participation of tissue thromboplastin.

Exudation helps to fight the pathogen, the concentration of which is reduced due to filling the focus of inflammation with plasma containing numerous protective proteins (immunoglobulins and complement), and increased lymphatic flow. Enhanced lymphatic drainage carries harmful agents to the draining lymph nodes, thereby promoting the development of a protective immune response. Sometimes, in the presence of virulent organisms, lymphatic vessels can inadvertently contribute to the spread of infection, which is accompanied by inflammation of the lymphatic vessels (lymphangitis) and lymph nodes (lymphadenitis).

Cellular response

Acute inflammation is characterized by the active emigration of inflammatory cells from the blood to the injury zone. Neutrophils (polymorphonuclear leukocytes) predominate in the early phase of inflammation (first 24 hours). After the first 24—48 hours, phagocytic cells of the macrophage (reticuloendothelial) system and immunologically active cells, such as lymphocytes and plasma cells, enter the focus of inflammation. However, neutrophils remain the predominant cellular elements for several days.

Neutrophil marginalization (WBC margin). With acute inflammation, the speed of blood flow decreases, sludges are formed and favorable conditions are created for the adhesion of leukocytes to the vascular wall. In inflammation, as a result of the increased ex-

pression of various cell adhesion molecules (CAMs) on both leukocytes and endothelial cells, optimal conditions are created for the adhesion of leukocytes to the vascular wall.

Neutrophil emigration. Adhesive neutrophils actively leave the postcapillary venules through the intercellular junctions and pass through the basement membrane, reaching the interstitial space (emigration). Active emigration of neutrophils and the direction in which they move are regulated by chemotactic factors.

Complement factors C3a and C5a (collectively known as anaphylatoxins) are potent chemotactic agents for neutrophils and macrophages, as is leukotriene B4 (LTB4). The interaction between neutrophil surface receptors and these chemotaxins increases neutrophil motility (through Ca^{2+} ion influx, which stimulates actin contraction) and promotes degranulation.

Red blood cells enter the focus of inflammation passively, in contrast to the active process of emigration of white blood cells. Erythrocytes are expelled from the vessel by hydrostatic pressure through expanded intercellular junctions following emigrating leukocytes (diapedesis). In severe injuries associated with impaired microcirculation, a large number of red blood cells enter the focus of inflammation (hemorrhagic inflammation).

Phagocytosis

The first step in phagocytosis is recognition of the damaging agent by the phagocytic cell either directly (as occurs with large inert particles) or after coating the phlogogen with Ig immunoglobulin or complement factor 3b (C3b) (opsonization). Opsonin-mediated phagocytosis is a mechanism acting in immune phagocytosis of microorganisms. *IgG and C3b are effective opsonins*. Immunoglobulin, which specifically binds to the damaging agent antigens (specific antibody), is the most effective opsonin. At the onset of acute inflammation — before an immune response has developed — non-immune phagocytosis dominates, but as immunity develops, immune phagocytosis becomes more effective.

Pathogenetic factors of phagocytosis:

1. The hydrogen peroxide (H_2O_2) — myeloperoxidase-halide system is the most important microbicidal mechanism in neutrophils whose cytoplasmic granules contain myeloperoxidase. Superoxide ions are formed by oxidase in the plasma membrane. Superoxide spontaneously transforms into bactericidal H_2O_2 in lysosomes. In addition, myeloperoxidase in combination with a halide ion (usually chloride) potentiates the microbicidal effect of H_2O_2, probably due to the formation of highly toxic ions such as Acidum hypochlorum (HOCl).

2. Toxic oxygen-based radicals (superoxide (O_2^-), hydroxyl (OH), and singlet oxygen (O_2)) are produced in all phagocytic cells. The elimination of microbes as a result of the action of these oxygen-based radicals can be direct or mediated by ferric ions. The reaction of superoxide with a ferric ion produces a ferrous ion which reacts with hydrogen peroxide to form hydroxyl radicals. Hydroxyl radicals react with phospholipids of the bacterial cell wall, causing disruption of the integrity of the bacterial cell membrane (lipid peroxidation).

3. Bactericidal agents (hydrolases, proteases (cathepsin G), lactoferrin and lysozyme) are released by neutrophil granules. Lysozyme was first discovered in a tear secret by A. Fleming, who called it an «antiseptic for tears». Lysozyme attacks muramic acid in bacterial cell walls.

4. Macrophage activation factor — lymphokine released by sensitized T lymphocytes contribute to the destruction of microbes by macrophages.

Pathogenetic features of acute inflammation

Mediators of acute inflammation:

Vasoactive amines. Histamine and serotonin are released from mast cells and platelets and can be identified in the early stages of acute inflammation. Histamine is more important to humans than serotonin, which acts primarily on venules having H1-histamine receptors. Both amines cause vasodilation and increased permea-

bility and are likely the main agents responsible for the immediate phase of the acute inflammatory response. Histamine levels decrease rapidly within an hour of the onset of inflammation.

Kinin system. Bradykinin, the final product of the kinin system, is formed by the action of kallikrein on the plasma precursor protein (high molecular weight kininogen). Kallikrein is present in the inactive form of prekallikrein in plasma and is activated by the XII factor (Hageman factor) of the coagulation system. Bradykinin causes increased vascular permeability and stimulates pain receptors.

Folding system. Activation of coagulative hemostasis leading to fibrin formation is initiated by Hageman factor (activated factor XII). Fibrinopeptides produced by fibrin catabolism (fibrinolysis) also cause increased vascular permeability and are chemotactic to neutrophils.

Complement system. Components of the C5a and C3a complement system (anaphylatoxins) cause increased vascular permeability by stimulating histamine release from mast cells. C5a is a potent chemotactic agent for neutrophils and macrophages. C3b is an important opsonin. C5a activates the lipoxygenase pathway of arachidonic acid metabolism.

Arachidonic acid metabolites. Arachidonic acid is a 20-carbon unsaturated fatty acid found in the phospholipids of cell membranes of neutrophils, mast cells, monocytes and other cells. The release of arachidonic acid by phospholipases initiates a number of complex reactions culminating in the formation of prostaglandins, leukotrienes, and other inflammatory mediators.

Neutrophil factors. Proteases and reactive oxygen species (oxygen-based free radicals) generated by neutrophils are thought to cause endothelial damage and lead to increased vascular permeability.

Other mediators and inhibitors. Negative feedback (inhibition) of inflammation also occurs, but it is not well understood; possible inhibitory factors include C1-esterase inhibitor (inhibits complement cascade) and α 1-antitrypsin (inhibits proteases).

Systemic clinical signs

Acute inflammation may be accompanied by systemic signs in addition to local cardinal signs described previously.

High temperature. Fever can result from the formation of secondary pyrogens and prostaglandins, which enter the bloodstream and affect the center of thermoregulation.

Leukocytosis. An increase in the total number of neutrophils (neutrophil leukocytosis) is observed in peripheral blood. Initially, the leukocyte reaction is associated with an accelerated release of neutrophils from the bone marrow depot. Later, there is an increase in bone marrow granulocytopoiesis. Regenerative forms of neutrophilic leukocytes, which often contain large cytoplasmic granules (toxogenic granularity), enter the peripheral blood. Viral infections usually cause neutropenia (a decrease in the number of neutrophils in the blood) and lymphocytosis (an excess of normal lymphocytes in the blood). *Thus, acute inflammation caused by viral infection is an exception, since microcirculatory changes and fluid exudation are accompanied by a lymphocytic rather than neutrophilic reaction.*

Changes in plasma protein levels. Levels of some plasma proteins usually increase with acute inflammation. These acute phase reagents include CRP, α 1-antitrypsin, fibrinogen, haptoglobin, and ceruloplasmin (a copper-containing ferroxidase involved in iron metabolism and in many redox reactions). An increase in these substances, in turn, leads to an increase in the rate of sedimentation of red blood cells, which is a simple (albeit non-specific) sign of the presence of inflammation.

The acute inflammatory response aims to neutralize or inactivate the agent causing the injury. Several outcomes of acute inflammation are possible.

Diagnosis of acute inflammation

Local cardinal signs of inflammation make it possible to diagnose acute inflammation when surface structures are involved in the process — skin, conjunctiva, oral cavity, etc. Acute inflamma-

tion of internal organs, such as the lungs and kidneys, can first manifest with systemic changes, such as fever and changes in the blood (number of white blood cells, proteins, etc.). Sometimes it is necessary to examine a liquid exudate or tissue sample (biopsy) to establish the presence of acute inflammation.

Clinical and laboratory diagnostics of acute inflammation

Systemic disorders:

• Fever (usually with acute onset and rapidly increasing);

• Changes in the number of white blood cells in peripheral blood;

— Left-shifted neutrophilic leukocytosis;

— Lymphocytosis and neutropenia in acute viral infections;

• Plasma protein changes;

— Elevated acute phase markers (eg, C-reactive protein, 1-antitrypsin α, haptoglobin);

— Increased erythrocyte sedimentation rate;

With inflammation, all types of metabolism are disturbed not only in the focus of inflammation, but also outside it. This is evidenced by: activation of glycolysis in many tissues, especially with exudative inflammation, an increase in blood intermediates of carbohydrate, protein and lipid metabolism. Hypoproteinemia develops with a relative increase in the content of globulins, especially gamma globulin (which is most closely related to the formation of antibodies) and fibrinogen (hyperfibrinosis).

Laboratory evaluation:

• Inflammatory exudate study;

— Characteristically high protein content and high specific gravity;

— Presence of acute inflammation cells (neutrophils; lymphocytes in viral infections);

• Biopsy and microscopic examination of tissues;

— Hyperemia;

— Edema;

— Neutrophils;

— Fibrin;

• Diagnostic tests;

— Microbiological (inoculation and Gram-stained smear);

— Immunological: serum antibody levels, complement levels, etc.

Chronic inflammation

Currently, two types of chronic inflammation are distinguished: ***mononuclear (primary, proliferative) and chronic purulent (secondary).***

Mononuclear inflammation. This type of inflammation was formed in the process of evolution as a reaction of nonspecific protection, aimed at eliminating intracellular bacteria, viruses, helminths, pathogenic fungi that entered the body. Phlogogenic factors that cause the development of primary chronic inflammation are phagocytosed by macrophages, but cannot be destroyed and remain for a long time inside cells (persistence). In this form of inflammation, macrophages, monocytes and lymphocytes are the first to react to the phlogogenic factor. Mononuclear inflammation is characterized by a wide variety of clinical manifestations, develops slowly — over several days, proceeds for a long time, is characterized by the presence of macrophages and lymphocytes in the focus and the predominance of the processes of proliferation of capillary endothelial cells, fibroblasts and connective tissue outgrowth. Unlike acute exudative-destructive inflammation, in which neutrophil leukocytes are the first to react to the pathogenic factor, in mononuclear inflammation, connective tissue mononuclear cells (macrophages and lymphocytes) react to the phlogogenic factor. In this case, persistent infiltrates are formed, which can be diffuse, or have the form of compact foci (granulomas), clearly limited from normal tissue.

Chronic purulent inflammation (secondary chronic inflammation). A similar course of the inflammatory process can be characteristic of osteomyelitis, pyelonephritis, cholecystitis, as well as other diseases based on acute exudative-destructive inflammation. The formation of chronic inflammation is primarily associated with

a violation of the body's resistance, which may be associated with intercurrent diseases (diseases of the cardiovascular system, diabetes mellitus, leukemia), as well as occupational hazards (xenobiotic intoxication), exogenous and endogenous types of starvation (hypovitaminosis), chronic hypoxia, alcohol intoxication, stress, etc.

It can be assumed that under the influence of the above factors, an acquired (secondary) immunodeficiency state (IDS) is formed in the body, i. e. a temporary or persistent change in the immune system, in which it inadequately reacts to foreign genetic information.

Prolonged inflammation can contribute to impaired healing and accumulation of macrophages, fibroblasts and collagen, leading to granuloma formation. Granulomas are usually found when examining tissue biopsies — an accumulation of macrophages surrounding particulate matter or resistant microbes such as Mycobacterium tuberculosis. The normal organ parenchyma is replaced by fibrous tissue.

Inflammation outcomes:

1. *Resolution:* With uncomplicated acute inflammation, tissues return to normal during the resolution process, in which exudate and cellular debris are liquefied and removed by macrophages and lymph flow.

2. *Repair:* If tissue necrosis occurred before the agent was neutralized, repair occurs and dead cells are either replaced by regeneration or repaired by scar formation.

3. *Suppuration:* with virulent bacterial infections, increased emigration of neutrophils with thinning necrosis (purulent inflammation) occurs. A thin mass of necrotized tissue and neutrophils is called pus.

4. *Chronic inflammation:* When a harmful agent is not neutralized by an acute inflammatory reaction, the body triggers an immune response, leading to the development of chronic inflammation.

5. *Regeneration:* Regeneration of damaged tissue into a preexisting tissue type requires survival of the basement membrane and tissue stem cells. Some cell types are able to constantly regenerate. Among these types are skin epithelial cells and mucous

membranes, bone marrow cells and lymphoid cells. Liver, pancreatic, endocrine gland and renal tubule cells are also able to regenerate when needed. However, some cell types, such as neurons and muscle cells, do not regenerate well. The regeneration process in this case can last 2 years or more. This process can be called wound remodeling by fibroblasts, macrophages, neutrophils and eosinophils. Wound remodeling is a process of collagen deposition and lysis with wound edge treatment. At this stage, the wound changes color from bright red to pink or whitish. While the wound is pink, the maturation phase is not complete. Healing is stimulated by growth factors released by platelets and immune cells that stimulate fibroblasts to divide and form extracellular matrix proteins. Endothelial cells respond to angiogenic growth factors by forming capillary networks, which improves blood supply and promotes regeneration.

SITUATIONAL TASKS

Clinical case No 1.

A girl at the age of 2 was admitted to the department for children with respiratory pathology on the 6th day of the disease. Complaints: fever to febrile digits within 5 days; dry cough of a seizure-like nature; anxiety; vomiting; stool liquefaction. She was treated at home by a district pediatrician with a diagnosis of acute respiratory viral infections, suspected left-sided pneumonia (asymmetry of percussion and auscultation sounds: weakening of respiratory noises (mainly on the left), shortening of percussion sound) — from the 2nd day of the disease she received azithromycin, lazolvan*; continued to cough, body temperature increased to 39.5 ° C; — delivered to the hospital on the 5th day of the disease due to the lack of effect of therapy.

Prehospital management comments:

In this case, there was an acute respiratory disease in a young child with signs of lower respiratory tract damage, and not an elementary acute respiratory viral infection (high fever for several days, intoxication syndrome, cough, asymmetry of physical data in

the lungs). Given the early age of the child, hospitalization was necessary, and in case of parental disagreement, the organization of an appropriate examination (radiological and laboratory) to clarify the diagnosis.

Comments on the patient's therapy in the prehospital stage:

If the doctor assumed that the child had ARVI, then it was not worth prescribing antibacterial therapy, if pneumonia, then the starting antibiotic from the point of view of both international recommendations and the protocol for the treatment of pneumonia in children was chosen incorrectly: macrolides are not the starting antibiotic for the treatment of pneumonia in young children. In this situation, it would be most appropriate to prescribe amoxicillin/clavulanate as the starting antibiotic.

In-hospital physical examination results:

Vital functions: body temperature — 39.2 °C; heart rate (HR) — 146 bpm; respiratory rate (RR) — 56 per minute; blood pressure (BP) — 100/65 mm Hg.

Objective data: dry obsessive paroxysmal cough; dyspnea of a mixed nature with the participation of auxiliary muscles; auscultation: weakened breathing in the lower parts, more on the left, there were also small bubble wet wheezing. Preliminary diagnosis after hospital examination: community-acquired left-sided pneumonia.

According to the American Academy of Family Medicine, strict predictors of pneumonia are fever and cyanosis, as well as more than one of the following signs of respiratory distress: tachypnea, cough, widening of the wings of the nose, retraction of chest areas, weakening of respiratory noises. Pneumonia should be assumed if tachypnea occurs in a patient younger than 2 years with a temperature above 38 °C. *In the absence of fever, the presence of pneumonia in children is doubtful.*

Assessing the clinical symptoms of the patient upon admission to the hospital, you can make the following comment on the interpretation of the diagnosis in the hospital. The child was rightly given a clinical diagnosis of community-acquired pneumonia, since when assessing the history, clinical picture and physical data, the clinical criteria for the diagnosis of pneumonia were correctly as-

sessed and considered. *At the same time, it should be noted that clinical data for the diagnosis of pneumonia is not enough, an obligatory component of the diagnostic process is X-ray and laboratory-diagnostic examination.*

Radiological and laboratory findings:

Laboratory data: complete blood count: leukocytes — 12.5×10^9/L, stab neutrophils — 20 %, segmented neutrophils — 56 %, lymphocytes — 19 %, platelets — 260×10^9/L, ESR — 50 mm/h. Returning to the analysis of this clinical case regarding the alleged etiology of pneumonia, the following comment can be made.

Comment: Analyzing the situation of this case (the child was healthy before the onset of the disease, fell ill at home), it can be assumed that the causative agents of pneumonia could be both viruses and bacteria, among which the most common in this age group are a group of respiratory viruses and bacteria (pneumococcus, hemophilic bacillus, moraxella, etc.). However, since the child is in the age group of 1—5 years and did not have serious aggravating premorbid risk factors, pneumonia occurred at home, severe leukocytosis, neutrophilia with a shift to the left, and accelerated ESR were observed in the blood test. It can be assumed that the child has community-acquired pneumonia caused by a bacterial group of pathogens, among which pneumococcus and hemophilic bacillus are the leaders.

Chest X-ray: first examination (at admission to hospital) — confluent infiltration of lung tissue with a more intense shadow on the left in the lower medial region; second study (after 2 days) — darkening increased — total left-sided pneumonia, cloak pleurisy.

Comment: The disease was interpreted as a large left-sided lobar pneumonia complicated by left-sided cloak-like pleurisy. Since lobar lung damage is most often associated with pneumococcal infection, even though the result is negative, the tank. blood culture, it can be assumed with a high degree of confidence that this pneumonia has a pneumococcal etiology. Pneumonia was complicated by cloak-like pleurisy, which indicates its severe course, but does not contradict the pneumococcal nature of pneumonia.

Treatment of the child in the hospital (etiotope, symptomatic and pathogenetic): amoxicillin + clavulanic acid intravenously 45 mg/kg every 6 hours; clarithromycin; intravenous immunoglobulin; oxygen therapy; infusion detoxification therapy; mucolytic, expectorant therapy.

Clinical case No 2.

Patient S., 25 years old, was taken to the emergency room of the hospital with complaints of weakness, spilled abdominal pain, nausea, and repeated vomiting. He fell ill acutely, two days ago, when he felt unwell, nausea, pain in the epigastric region. He did not go to the doctor, as he regarded his condition as food poisoning. The next day, abdominal pain increased and moved to the right iliac region, general well-being deteriorated markedly, there was repeated vomiting.

When examining the patient: wet skin, temperature 38.5 °C, pulse 105 beats/min, respiratory rate 25 per minute.

On palpation, the abdomen is tense, sharp soreness is noted in the right iliac region, signs of peritoneal irritation are unclear.

Complete blood count: white blood cell count — 15.9×10^9/L. Leukocyte formula: eosinophils — 0 %; basophils — 0 %; metamyelocytes — 4 %; band neutrophils — 13 %; segmented neutrophils — 63 %; lymphocytes — 12 %; monocytes — 8 %.

After examination, the patient was urgently hospitalized for emergency appendectomy. The vermiform process is phlegmonous, soldered to the surrounding tissues, the peritoneum is hyperemic, hemorrhagic exudate is found in the abdominal cavity.

Questions:

1. Name the local and general manifestations of inflammation in the patient.
2. Characterize changes in hematology parameters.
3. Give a pathophysiological assessment of the severity of the patient's condition and justify your conclusion.

Answer:

1. This patient has a typical pattern of acute inflammation, which is characterized by the presence of stages. You can follow the pa-

tient's history of the stage of alteration and the stage of exudation, when hemorrhagic exudate was already found in the abdominal cavity. Clinical signs of acute inflammation are noted: rubor (redness), calor (increased fever), tumor (swelling), dolor (pain) and functio laesa (impaired function).

2. In the complete blood count, neutrophilic leukocytosis with a shift of the leukocyte formula to the left, which indicates the presence of acute bacterial inflammation.

3. Hyperergic form of inflammation (proceeds «violently», with pronounced alteration and exudation, «necrotic» inflammation may develop). The variety of forms and stages of acute appendicitis makes us think about the polyetiology of the occurrence of this disease.

With the onset and development of acute appendicitis, events can proceed according to the following pathophysiological mechanisms:

1. Obstruction of the lumen of the appendix. The causes can be very diverse:

— hyperplasia of lymphatic (lymphoid tissue) follicles;

— coprolites (appendicoliths);

— lists;

— foreign bodies (seeds, seeds of vegetables and fruits, etc.);

— muscle spasm in the area of the mouth (controversial).

2. This leads to a violation of the outflow of the contents of the appendix. There is an increase in intraluminal pressure in the appendix, which is manifested by clinical signs in the form of visceral pain.

3. With a persisting high intraluminal pressure in the process, a change in the microcirculation of its vascular and lymphatic bed occurs (impaired blood and lymphatic flow). This leads to damage to the vascular endothelium, which, against the background of impaired tissue perfusion, leads to a violation of the integrity of the mucous membrane of the appendix.

4. Flora of various composition (bacteria and their toxins, viruses) present in the process lumen is introduced into the areas of

the damaged mucous membrane and a typical inflammatory process occurs, leading (against the background of vascular disorders in the tissues) to the destruction of the vermiform process — phlegmon, gangrene. At this stage, due to the involvement of the serous membrane (visceral) and the adjacent peritoneum (parietal) in the pathological process, peritoneal pain (constant, increasing in nature) occurs in the abdomen.

With continued impaired perfusion (blood supply) of the type of increasing thrombosis, a heart attack and necrosis occur, leading to perforation of the process wall and the occurrence of peritonitis.

Clinical case No 3.

Patient N., 19 years old, machine operator, 5 days after sexual contact with an accidental partner, complains of burning pain in the urethra when urinating, purulent discharge from the urethra.

An objective examination revealed: the external opening of the urethra is hyperemic, the surrounding tissues are edematous.

When pressed from the urethra, abundant purulent discharge appears. The inguinal lymph nodes are enlarged to the size of beans, painful when palpated, not soldered with the surrounding tissues.

Microscopic examination of urethral discharge; a large number of gonococci, polymorphonuclear leukocytes.

PCR also confirmed infection of the patient with Chlamydia trachomatis.

Questions:

1. What phlogogenic factors caused urethritis?

2. Explain the mechanisms of purulent discharge from the patient's urethra.

3. What is the pathogenesis of regional lymphadenitis in acute urethritis?

4. What are the possible outcomes of acute urethritis? Complete blood count: red blood cells — 5.0×10^{12}/L, hemoglobin — 145 g/L, white blood cells — 11.2×10^{9}/L, ESR — 25 mm/h.

5. Explain the mechanism of leukocytosis and fever in N. Body temperature N. — 37 °C.

After examining the patient, he was prescribed antibiotic therapy, but he did not purchase the necessary drugs. He did not contact the doctor for medical help further; repeatedly called for an appointment, but did not appear. After 7 years, N. and his wife turned to the district clinic to a gynecologist about the impossibility of having children. According to the spouses, 4 years are married. Despite an active sexual life without protection from pregnancy, pregnancy in wife N. does not occur. According to N., his wife is his second sexual partner. After a thorough examination of both spouses, it was established that N. suffers from chronic chlamydia urethritis, and his wife suffers from bilateral adnexitis with partial obstruction of the fallopian tubes.

Questions:

6. What explains the transition of acute inflammation in N. (acute urethritis) to chronic (chronic urethritis)?

7. What blood cells can be found in the focus of chronic inflammation and why?

8. Explain the mechanism of tubal obstruction in spouse N. as a result of a chronic inflammatory process.

Answer: These patients have chronic inflammation, which occurred against the background of the lack of adequate treatment during the development of acute inflammation. The formation of chronization is primarily associated with a violation of the body's resistance, that is, during acute inflammation, adequate treatment with antibacterial drugs has not been carried out. Initially, with primary infection, inflammation proceeded in the type of acute and if the patient had not ignored the doctor's prescriptions and used the entire arsenal of recommended etiological therapy, acute inflammation would have been eliminated and would not have passed into chronic mononuclear inflammation. which is characterized by a wide variety of clinical manifestations, develops slowly, proceeds for a long time, characterized by the presence of macrophages and lymphocytes in the focus and the predominance of processes of proliferation of endothelial cells of capillaries, fibroblasts and proliferation of connective tissue (the patient's wife developed bilateral adnexitis with partial obstruction of the fallopian tubes).

Clinical case No 4.

Patient N., 20 years old, went to an otolaryngologist with complaints of sore throat when swallowing, general weakness, malaise. The patient had complaints a week ago. From the anamnesis it is known that in recent years N. suffered from frequent sore throats (3—4 times a year). It is also known that since childhood he suffers from seasonal allergic rhinitis (sensitization to birch pollen was revealed).

The results of an objective examination: body temperature — 36.8 °C; the skin is dry, pale; BP — 90/60 mm Hg; pulse — 60 beats per minute. The thyroid gland is not enlarged. Submandibular lymph nodes enlarged to the size of a pea, painless. Nasal breathing is free, curvature of the nasal septum to the left. When examining the pharynx, the patient had an excessive gag reflex. Pharyngeal tonsils are hyperplastic, slightly hyperemic, dense. Lacunae are expanded, point foci of gray-white plaque are determined in them. No pathology was detected on the part of internal organs. Laboratory parameters without pathological changes. Chronic tonsillitis in the subcompensation stage was diagnosed. Conservative treatment was prescribed. After washing the tonsil lacunae with antiseptic solutions, the patient began to notice a deterioration in general condition — weakness, aches in the whole body, chills, body temperature increased to 37.3 °C and remained at this level for several hours.

Questions:

1. What are the causes and conditions that contributed to the development of chronic inflammatory disease in patient H.

2. Why did his pharyngeal tonsils become denser?

Answer:

1. In the pathogenesis of chronic tonsillitis, mutually related processes of formation of a chronic inflammatory focus in the area of the palatine tonsils and body reactions in the form of tonsillogenic disorders in distant organs and systems and changes in the functioning of the macroorganism as a whole are important. A chronic inflammatory process is the result of a long-term interaction of an infectious agent and a macroorganism with altered general reactivi-

ty and insufficiently formed immunity. The development of chronic inflammation in the palatal tonsils is facilitated by their anatomical and topographic features — narrow repeatedly branching crypts (lacunae), a deep location between the palatolingual and palatopharyngeal arches, high standing of the upper pole of the amygdala. Accumulation of pathological lacunar content has an adverse effect on the cellular structures of the amygdala tissue, perilacunar nerve plexuses, chemoreceptors of the subepithelial layer, which, against the background of a decrease in the general reactivity of the body, causes regional immunity reactions that are both specific (antibody formation) and non-specific (epithelial barrier, phagocytosis, enzymes, etc.) humoral and cellular factors. In the development of chronic inflammation of the tonsils, an important role is played by the functional failure of mononuclear cells — lymphocytes and, especially, macrophages, which leads to incomplete phagocytosis, intracellular (mainly in macrophages) persistence of pathogenic microorganisms, and the development of opportunistic infections. The primary link in the pathogenesis of chronic tonsillitis is the immunodeficiency state of the body.

2. The active functioning of the tonsils contributes to their hypertrophy, an increase in follicles in the parenchyma and a deterioration in the drainage function of lacunes. A change in the relationship of the palatal tonsils with the structures of the hypothalamus naturally leads to an aggravation of violations of immunological reactivity in chronic tonsillitis. Chronic focal infection in the palatal tonsils is accompanied by multidirectional changes in the synthesis of major proinflammatory cytokines. Immune antigen-antibody complexes formed in tonsil tissue, having chemotactic activity, increase the proteolytic ability of macrophage enzymes, which leads to lysis of tonsil tissue, denaturation of tissue proteins that acquire antigenic properties. The entry of autoantigens into the bloodstream causes the formation of autoantibodies, which, fixing on the cells, damage them. Palatal tonsils become the site of "permanent" delayed-type sensitization to antigens of microorganisms, most often vegetating in lacunae. General nonspecific sensitization exacerbates the course of chronic tonsillitis.

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Part 1

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