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«Гомельский государственный медицинский университет»

Кафедра патологической физиологии  
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Протокол №7 от 30.08.2017

**МЕТОДИЧЕСКАЯ РАЗРАБОТКА**  
Для проведения занятия со студентами  
3 курса ФПСЗС, обучающихся на английском языке  
по патологической физиологии

**Тема: Патофизиология системы лейкона. Изменения количественного и качественного состава лейкоцитов**

**Theme: Pathophysiology of leukon. Changes in quantitative and qualitative composition of white blood cells.**

Время 3 ак. часа

**1.Actuality of the theme.** Leucocytosis are considered as a reaction hematopoietic system due to action of physiological and pathological irritations. Leucocytosis is a pathological symptom of many diseases. In a basis of leucocytosis lay pathophysiological mechanisms connected with proliferation, maturation going out of leucocytes and their flow into vessels and redistribution. Different kinds of leucocytosis may be the additional criteri for establish the diagnosis. Eosinophilia, for example, is characterized for allergy reactions, neutrophile leucocytosis - for acute inflamation processes.

Leucopenia may depend upon oppressive influence of some toxines on the maturation and outflow of leucocytes from the bone-marrow. Often these phenomenas are observed during the infectious diseases. They have significanse for the differential diagnostic.

**Learning goals of the lesson:** to study etiology, pathogenesis, manifestations of disorders of leukocyte system; to study etiology and pathogenesis of leukemoid reactions.

**Educational goals of the lesson:** formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

**Objectives of the lesson:**

1. To know etiology and pathogenesis of leukocytosis and leukopenia.
2. To know etiology and pathogenesis of pathological changes in leukocytes.
3. To be able to analyze the changes in leukocytes in data of hemograms.
4. To know etiology and pathogenesis of leukemoid reactions.

**To repeat the following questions from related disciplines to ensure absolute mastery of the material:**

1. Scheme of leukopoiesis (histology, cytology, embryology disciplines).
2. Leucocytes formula of blood (normal physiology discipline).

**Control questions of the lesson:**

1. Violation of structure and function of certain types of leukocytes, their role in pathological processes.
2. Leukocytosis: types, causes and mechanisms of development, changes in leukocyte formula of peripheral blood. Value of leukocytosis.
3. Leukopenia: types, causes, mechanisms of development, manifestations. Value of leukopenia.
4. Leukemoid reactions: types, etiology, pathogenesis, changes in organs of hematopoiesis and peripheral blood.
5. Differences in leukemoid reactions from leukemia, value for the body. Infectious mononucleosis.
6. Agranulocytosis: classification, types, causes, mechanisms of development, clinical manifestations. Picture of peripheral blood in agranulocytosis. Panmyelophthisis.
7. Leukocyte formula, its analysis. Index of nuclear shift.

**Calculation of study time**

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

## **Additional materials:**

### **LEUKOPOIESIS**

#### **Neutrophils**

The process of formation the mature neutrophil from the myeloblasts carried out in BM within 10-13 days. Can be represented schematically: myeloblast → promyelocyte → myelocyte → metamyelocyte → band cell → segmented neutrophil. At elevated body's needs, this process can be considerably accelerated. After maturation band and segmented neutrophils do not leave BM immediately, and stored in the sinuses for 4-5 days before entering the bloodstream. These cells make up the so-called bone marrow granulocyte reserve, which is the number of almost 30 times exceeds the number of circulating leukocytes. Cells of bone marrow reserve every 3-5 days updated. From the usefulness of bone marrow reserve the outcome of the disease often depends. The total time of circulating mature neutrophils is 6-12 hours, after which the cells were transferred into tissue, where they live 4-5 days. Neutrophils, past the endothelial barrier between blood and tissues, do not return to the circulation. Within 2-4 days, they die by apoptosis, while in case of inflammation – by necrosis.

#### **Eosinophils**

Duration of eosinophils maturation is approximately 3-4 days. After this period they are stay in BM 2-5 days, and then go into the bloodstream, where circulate 10-18 h, then migrate into tissues and accumulate in the largest amount in the skin, lungs, gastrointestinal tract. Their tissues lifetime is up to 6 days. It is believed that tissue eosinophils can be returned to the bloodstream, which explains the length of eosinophilic reactions.

#### **Basophils**

Differentiation of basophils in BM lasts up to 5 days. Basophils found in the bloodstream approximately 10h, then arrive in tissues where after 1-2 days after realization of basic effector function they die.

#### **Monocytes**

In the process of monocytes differentiation and take place following stages: pluripotent hematopoietic stem cells → pluripotent hematopoietic progenitor myelopoiesis cells → unipotent progenitor granulo-monocytopoiesis cells → monocyte progenitor cells → monoblasts → pro-monocytes → monocytes.

The maturation process of monoblasts in monocytes occurs in BM approximately 5 days, after which the cells out in the bloodstream unlike granulocytes without forming bone marrow reserve. Monocytes are located in peripheral blood from 36 to 104 hours, and then they penetrate into tissue, where transformed into macrophages. Extravascular pool of monocytes is approximately 25 times greater than intravascular. Lifespan tissue macrophages – up to several months. They can be returned to the bloodstream. In these cases, blood smears can be found original monocytoid cells – histiocytes. Single histiocytes are in the blood of healthy people and in larger amounts (2-3%), they appear in severe intoxication, protracted septic endocarditis.

#### **Lymphocytes**

Lymphocytes with myeloid elements have common pluripotent hematopoietic stem cells, but then they get an independent lineage. In this case, cells maturation undergo following steps: lymphoblast → pro lymphocyte → lymphocyte.

##### ***T-lymphocytes***

The early T-lymphocyte precursors formed in the BM. Precursors of T lymphocytes leave the bone marrow and migrate to the thymus. Under the influence of thymic epithelial cells and growth factors produced by them, T-lymphocyte pass a number of consecutive stages of maturation moving from the capsular zone in the cortical and then into the medullary.

Past intrathymic differentiation the T cells out of the thymus through the blood vessels and directed to the periphery. They occupy certain areas of peripheral lymphoid system.

##### ***B-lymphocytes***

Lymphopoiesis of B lymphocytes in the bone marrow involves five main stages: pluripotent hematopoietic stem cells → common lymphoid progenitors for T and B cells → committed progenitors of B lymphocyte (pro-B cell) → pre-B-cell → immature B cell (the final form of the B cells differentiation

in the bone marrow). «Naive» B lymphocytes migrate through the blood vessels in the peripheral lymphoid organs.

Described above stages of T and B lymphocyte maturation is called antigen-independent, as used for the acquisition the ability of cells to recognize antigen. The next step is antigen-dependent (immunogenesis). It occurs in the peripheral lymphoid organs after a meeting with an appropriate lymphocyte antigen.

Through the step of activated lymphocyte, T cells formed regulators and effectors of the immune response. At stimulation of B-lymphocytes there is their transformation into plasma cells (through the stages: activated lymphocyte → plasmoblast → proplasmocyte → plasma cell) and begins an active antibody synthesis.

### CHANGES IN THE WBC SYSTEM

Amount of leucocytes in unit of blood volume is  $4,0-9,0 \times 10^9/l$  in a norm. Changes in the WBC system may occur:

- 1) qualitatively (or functional);
- 2) quantitatively:
  - reactive (temporary) (leukocytosis, leukopenia, leukemoid reactions);
  - the nature of the tumor (leukemia, lymphoma);
- 3) in the character of leukocyte formula.

### QUALITATIVE CHANGES OF WBC

Qualitative defects of leukocyte can be formed not only with changes on the number of leukocytes but also carry autonomous character.

#### **Production of pathologic leukocytes may arise as a result of**

- tumorous transformation of leukopoietic tissue in leukemia;
- metabolic disturbances in leukocytes;
- genetically determined structural disturbances (dominant hereditary Pelger anomaly of granulocytes, deficiency of myeloperoxidase, glucose-6-phosphatedehydrogenase G-6-PDG).

Table 13. Characteristics of pathological changes of leukocytes

<b>Pathological changes of WBCs</b>	<b>Characteristics</b>
anisocytosis	decrease (microform) and increase in the size (macropolycytes - giant white blood cells)
<b>Pathology of the nucleus:</b>	
hypersegmentation	increasing the number of segments in the nuclei of neutrophils (more than 5 at norm 2-5) or eosinophils (more than 3 at norm 2-3) is a characteristic finding in megaloblastic anemia ( $B_{12}$ and folate deficiency), but can also be seen as an inherited autosomal dominant trait (hereditary hypersegmentation of neutrophils).
hyposegmentation	reducing the number of segments or a complete lack of segmentation (nucleus can be round, elliptical, in form of bean, peanut, gym weights, pince). Can be inherited (Pelger-Huët anomaly), or acquired (pseudo-Pelger-Huët cells) in patients with malignant myeloproliferative disorders and infections or tumors which have metastasized to the bone marrow.
pycnosis	compaction of chromatin
rrhexis	decay of a nucleus into separate parts, the disappearance of intersegmental "threads" in mature granulocytes
fragmentation	formation of fragments of nuclear chromatin (micronuclei)
lysis	dissolution of the nuclear membrane
chromatinolysis	liquefaction of chromatin
vacuolization	discolored spots ("holes") in the chromatin
bare nuclei of	lymphocytes without cytoplasm

Pathological changes of WBCs	Characteristics
lymphocytes	
Reed–Sternberg giant cell	giant multinucleated or binuclear cell with prominent eosinophilic inclusion-like nucleoli in patients with Hodgkin's disease
Botkin – Gumprecht shadows (basket cells)	crushed core of lymphocytes in patients with lymphoproliferative syndromes and particularly in CLL
<b>Pathology of the cytoplasm:</b>	
«Exhaustion» of granularity	deficiency or absence of specific granules
toxigenic granularity	small dark-blue or large rough basophilic granules of metamyelocytes, bands and segmented neutrophils during inflammatory states, burns, and trauma
azurophilic granularity	multiple, overlapping nuclei of cells or single large azurophilic granules in the cytoplasm of mature leukocytes
vacuolization	discolored spots ("holes") in the cytoplasm
Döhle bodies	round or oval amorphous blue inclusion appear in the neutrophils, bands, and metamyelocytes of patients with infection, burns, uncomplicated pregnancy, toxic states
Auer rods	cherry color needle- or rod-shaped structures (agglomerated azurophilic grain) occur in the cytoplasm of immature leukocytes (blasts) and more mature cells in some patients with AML
Alder-Reilly granules	large, coarse, dark purple, azurophilic granules, found in in patients with mucopolysaccharidoses
Chédiak-Higashi granules	very large red or blue granules that appear in the cytoplasm of granulocytes, lymphocytes, or monocytes in patients with the Chédiak-Steinbrinck-Higashi syndrome
May-Hegglin anomaly	neutrophils contain small basophilic cytoplasmic granules which represent aggregated ribosomes
atypical lymphocyte (Downey cells)	large lymphocytes that contain a greater amount of cytoplasm and bluish tinge of cytoplasm are found in viral illnesses such as infectious mononucleosis

### Functional defects in leukocyte

Violations of the functional properties of leukocytes can be hereditary or acquired. They are associated with defects in neutrophil granulocytes due to violation of their margination, adhesion, migration, and microbicidal properties.

#### **Violations of neutrophil function:**

- 1) Hereditary/congenital
  - Violation of adhesion
    - ✓ absence or reduction in the level expression of  $\beta_2$ -integrins on neutrophils
    - ✓ lack of E-selectin on neutrophils
    - ✓ actin dysfunction of neutrophil
  - Violation of chemotaxis:
    - ✓ hyperimmunoglobulinemia E
    - ✓ defects in the membrane of neutrophils (a syndrome of "lazy" leukocytes)
    - ✓ defects in the complement system
  - Violation of bactericidal activity:
    - ✓ deficit of specific granules in neutrophils
    - ✓ NADPH oxidase defect
    - ✓ myeloperoxidase deficit in neutrophils
    - ✓ lactase deficit in neutrophils
    - ✓ deficit of glutathione peroxidase, glutathione reductase, glutathione synthetase in neutrophils
    - ✓ glucose-6 phosphatase deficit in neutrophils
- 2) Acquired:

- Defects of margination, adhesion, chemotaxis, bactericidal activity of neutrophils
- Reduction of opsonic activity of plasma

### **Disorder of leukocyte maturation**

Disorder of leukocyte maturation is caused by the blockade of differentiation at different levels of cell development. Differentiation is provided by certain metabolites and genetic regulation. This disorder can be associated with a decrease of leukocyte production. The reasons of maturation disorders are:

- genetic defects;
- effect of exo- and endogenic factors (agents of purulent and viral infections, medicinal allergens and intoxication);
- tumorous hyperplasia and leukemoid reaction;
- disorder of the bone marrow barrier and its permeability (influence of CSF, glucocorticoids, interleukins, bacterial toxins), when immature leukocytes leave the bone marrow.

## **QUANTITATIVE CHANGES OF WBC**

### **Leukocytosis**

**Leukocytosis** is increase in total amount of WBC in a unit of blood above the upper limit of age norm ( $9 \times 10^9/l$ ).

#### ***Etiology***

There are physiological and pathological leukocytoses.

Physiological leukocytosis is characterized by a slight increase in the number of cells per unit volume, short-term and no change in leukocyte formula. Physiological leukocytosis can be due to digestive process, myogenic, emotional leukocytosis, leukocytosis during pregnancy and neonates, at water loss (sweating, etc.).

Causes of pathological leukocytosis are:

- physical – small doses of radiation, traumatic etc.;
- chemical – alcohol, certain medications, hypoxemia, acidosis;
- biological – viruses, bacteria, rickettsiae, parasites; antigen-antibody complexes; increase in BAS (leukopoietins, lymphokines, histamine, decay products of nucleic acids).

#### ***Mechanisms of leukocytosis***

Mechanisms of leukocytosis can be:

- ***increase in normal leucopoiesis***

It is reactive type of leukopoiesis activation. It is a proliferation of the leukopoietin-sensitive cells of the bone marrow, which results in leukocytosis. It can be caused by increased production of humoral activators (CSF, interleukins) or decreased production of their inhibitors (keilons, prostoglandins E, lactoferrin and isoferitin). The type of proliferated leukocytes depends on etiological factor)

- ***increase in formation of tumor transformed WBC***

It is the development of leukemia – leukocytosis is the result of increasing the number of dividing malignant and atypical modified cells and their release from the bone marrow into the bloodstream

- ***redistribution of WBC in vessels***

At muscular exercises (myogenic), shock (traumatic, blood transfusion, anaphylactic, etc.), stress, digestion, pregnancy, newborn.)

- ***hemoconcentration***

It is a consequence of hypohydration in various origins (diarrhea, repeated vomiting, polyuria, hyperventilation, etc.). In such cases, there is an increase in the number of WBC and other blood cells).

### **Increase in certain type of WBCs:**

#### ***Neutrophilia***

Neutrophilic leukocytosis (neutrophilia) - increase of over 70% of neutrophils in the hemogram. It can be observed at:

- physiological conditions (stress, physical load, overheating, undercooling, the last trimester of pregnancy);

- inflammation or tissue necrosis (surgery, burns, myocardial infarction, pneumonia, rheumatism, rheumatoid arthritis);
- infections caused by Gr<sup>+</sup> and Gr<sup>-</sup> microflora;
- hematologic disorders (acute bleeding, hemolysis, myelo-proliferative disease, myeloid leukemia);
- drugs and BAS (adrenalin, steroid hormones, histamine, heparin);
- metabolic disorders (diabetic ketoacidosis, eclampsia, gout, thyrotoxic crisis);
- tumor growth (in the liver, gastrointestinal tract, bone marrow).
- hereditary neutrophilia

Practical importance has determining the degree of nuclear shift in leukocyte formula. Nuclear shift index (NSI) is calculated as:

$$NSI = \frac{\text{promyelocytes(\%)} + \text{myelocytes(\%)} + \text{metamyelocytes(\%)} + \text{bandcells (\%)}}{\text{segmented cells(\%)}}$$

NSI in healthy man is equals 0,05 up to 0,10. Increase in index means nuclear shift to the left, decrease in index – shift to the right

On this basis distinguish six kinds of neutrophilic leukocytosis

- 1) ***without nuclear shift*** (in acute blood loss, stress reactions) – the increase in the total number of neutrophils (> 70%);
- 2) ***hyporegenerative nuclear shift to the left*** (in mild infections and inflammations) – the increase in the total number of neutrophils (> 70%) due to segmented (> 65%) and band cells (> 5%);
- 3) ***regenerative nuclear shift to the left*** (in purulent-septic processes) – the increase in the total number of neutrophils (> 70%) due to segmented (> 65%), band cells (> 5%) and metamyelocytes (> 0.5%);
- 4) ***hyperregenerative nuclear shift to the left*** (sign of an unfavorable course of infectious and septic diseases) – the increase in the total number of neutrophils (> 70%) due to segmented, band cells (> 5%), metamyelocytes (> 0.5%) and younger cells (myelocytes, promyelocytes, myeloblasts). Aneosinophilia
- 5) ***degenerative nuclear shift to the left*** (the indicator of functional activity showed the inhibition of bone marrow, can occur in severe infectious diseases, endogenous intoxication etc.) – the increase in the total number of neutrophils (> 70%) due to segmented (> 65%) and band cells (> 5%); the appearance of neutrophils with signs of degeneration (vacuolization of nucleus and cytoplasm, toxigenic granularity, karyorrhexis and others) in blood;
- 6) ***degenerative nuclear shift to the right*** (in radiation sickness, pernicious anemia) – the increase in the total number of neutrophils (> 70%) due to segmented cells (> 65%) with increasing of hypersegmented-nuclear neutrophils (more than 5 nuclear segments) in blood.

### ***Eosinophilia***

When eosinophilia the number of eosinophils in the peripheral blood above  $0,35 \times 10^9/l$  or more than 5% in relation numbers, and when hypereosinophilia their number  $1,5 \times 10^9/l$ . There are three degrees of eosinophilia:

- minor – the content of eosinophils in the blood ranges 15-20%;
- moderate – eosinophils is 20-50%;
- severe – cell content greater than 50%.

The causes of eosinophilia may be the following:

- allergic disorders (asthma, allergic rhinitis, eczema, occupational lung diseases, insect bites, urticaria, eosinophilic angioedema, drug intolerance);
- parasitic infestations (helminthiasis);;
- non-parasitic infection (aspergillosis, brucellosis, infectious mononucleosis, scarlet fever);
- malignant neoplasms (cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma);
- leukemias;

- syndromes of eosinophilic infiltrates in the lungs (volatile eosinophilic infiltration (Löffler's syndrome), chronic eosinophilic pneumonia, tropical pulmonary eosinophilia);
- skin lesions (exfoliative dermatitis, psoriasis, pemphigus);
- collagenoses, vasculitis (periarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus);
- immune disorders (reaction "graft-versus-host disease", congenital immunodeficiency syndrome);
- endocrine disorders;
- idiopathic hypereosinophilic syndrome;
- other (cirrhosis, radiation therapy).

### ***Basophilia***

Basophilia (more than 1% basophils in hemogram) - is rare form of leukocytosis. Main causes of basophilia are following:

- myeloproliferative diseases (CML, polycythemia vera, idiopathic myelofibrosis, essential thrombocythemia, basophilic leukemia);
- exposure of ionizing radiation;
- inflammatory diseases (ulcerative colitis);
- viral infections (measles, chicken pox);
- drugs (estrogens);
- hypersensitivity reactions;
- iron deficiency;
- hyperlipidemia.

### ***Monocytosis***

Main causes of monocytosis are:

- persistent bacterial and viral infections (tuberculosis, infectious mononucleosis, measles, rubella etc.);
- inflammatory diseases (ulcerative colitis, sprue, collagenoses etc.);
- recovery of infectious disease;
- systemic vasculitis;
- tetrachloroethane intoxication;
- hemoblastosis, malignant tumors (ovarian carcinoma, breast cancer);
- steroid hormone prolonged intake;
- after splenectomy.

### ***Lymphocytosis***

Lymphocytosis (more than 45 % lymphocytes in leukocyte formula) may be observed at:

- physiological lymphocytosis (children after 5 days to 5 years, vegetarians and after exercise (myogenic));
- infectious diseases (typhoid fever pertussis, malaria, infectious mononucleosis etc.);
- acute viral infection;
- chronic infectious (brucellosis, tuberculosis, syphilis, etc.);
- malnutrition;
- asthma;
- tumor growth (lympholeukemia, lymphosarcoma);
- endocrine disorders (eunuchoidism, myxedema, acromegaly).

## **Leukopenia**

**Leukopenia** is decrease in the number of WBC in a unite of blood volume less than lower limit of age norm ( $4 \times 10^9/l$ )

### ***Etiology***



By origin the leukopenia may be primary (congenital, hereditary) and secondary (acquired). The hereditary leukopenia (usually neutropenia) includes persistent hereditary neutropenia, neutropenia periodic hereditary, genetic monocytopenia (Chediak-Higashi syndrome). The causes of acquired leukopenia are:

- physical (ionizing radiation, X-ray radiation, excessive sun exposure, etc.);
- chemicals (industrial chemicals – benzene, insecticides etc.; drugs – cytostatics, sulfonamides, barbiturates, immunosuppressants; use of food crops affected by fungus; lack of vitamin B<sub>12</sub> and folic acid);
- biological (hard infections (typhus, virus of influenza, measles, rickettsia toxin, tuberculosis); immune (effect of antibodies against leukocytes); excess of BAS (catecholamines, leukotoxins etc.) in shock, stress; hormonal (stress, redistributive type of leukopenia).

***Mechanisms of leukopenia:***

1) Violation or suppression of the WBC formation as a result of:

- violation of proliferation and differentiation of hematopoietic stem cells:
- ✓ genetic defects of hematopoietic stem cells;
- ✓ lack of the components needed for leukopoiesis (eg., proteins, phospholipids, amino acids, hypovitaminosis - B<sub>12</sub>, folic acid, etc.);
- ✓ disorders of mechanisms of leukopoiesis humoral regulation (hypothyroidism, hypocorticism, reducing leukotrienes or sensitivity to them of the germ cells leukocyte hematopoiesis);
- ✓ loss of the ability of hematopoietic stem cells to differentiate;
- ✓ autoimmune mechanisms associated with the formation of anti CFU-GM antibodies and autoreactive T cells;
- damage of stem cells:
- ✓ cytolytic (due to ionizing radiation, cytostatic drugs, immune factors (antibodies);
- ✓ antimetabolic – action of agents interfered in the exchange of purine and pyrimidine bases (some antitumor drugs, levomycetin);
- ✓ idiosyncratic;
- pathology of hemopoiesis microenvironment, hyposecretion by these cells of growth factors (GM-CSF, G-CSF, IL-3, M-CSF, etc.);
- decreasing area of granulocytopoiesis as a result of substitution of hematopoietic tissue in bone marrow by tumor (leukemia and cancer metastasis to the bone marrow), fibrous, bone, adipose tissue.

2) Leukopenia due to increased destruction of WBC:

- under the influence of antibodies - leucoagglutinins that may be formed during blood transfusion, the action of certain medications haptens (sulfonamides, amidopyrine et al.), toxic factors of infectious origin (severe infectious diseases, extensive inflammation), diseases accompanied by an increase in the number of circulating immune complexes in the blood (autoimmune diseases, lymphomas, leukemias etc.);
- premature cell death due to cytogenetic abnormalities (tetraploidy) in some hereditary neutropenias;
- increased destruction of circulating WBCs in the spleen in cases with hypersplenism (collagenoses, cirrhosis, hemolytic anemia, and others.).

3) Leukopenia due to redistribution of leukocytes, are temporary in nature, found at:

- shock (anaphylactic, traumatic, posthemorrhagic, etc.);
- after heavy muscular work (increases WBCs in the capillaries of muscles, intestines, kidneys and lungs and decreases in other organs);
- during the phenomenon of regional state of leukocytes in large areas of vessels (diffuse peritonitis, pleurisy, phlegmon etc.)

4) Increased loss of WBCs in the presence of fistulas in lymphatic vessels and trunks, plasma- and lymphorrhea, burns, purulent processes.

5) Hemodilution leukopenia (rare) is a consequence resulting hypovolemia large volume plasma transfusion, plasma expanders, saline, liquid outlet from tissues into the bloodstream (under hyperaldosteronism, hyperglycemia, hyperalbuminemia)

### ***Neutropenia***

Neutropenia is a condition in which the absolute neutrophil count in blood less than  $2,0 \times 10^9/l$ . Neutropenias can be distinguished by the number of neutrophils and the risk of infection: mild –  $1,0-2,0 \times 10^9/l$ ; moderate severity –  $0,5-1,0 \times 10^9/l$ ; severe – less than  $0,5 \times 10^9/l$ . Severe acute neutropenia is a danger for life. The main reasons of neutropenia are:

- oppression of leucopoiesis in bone marrow (radiation, chemotherapy, leukemia, aplastic anemia, atypical granulopoiesis);
- enhanced destruction (splenomegaly, hemodialysis, autoimmune processes);
- gram-positive bacteria infections (typhoid), viruses (influenza, smallpox, hepatitis B, measles, mumps, AIDS), severe protozoal infections (malaria);
- protein starvation;
- side-effect of medical drugs abuse (semisynthetic penicillins, cephalosporins, sulfonamides in combination with trimethoprim, phenothiazines, antithyroid drugs).

### ***Eosinopenia***

Eosinopenia is a decrease in count of eosinophil less than  $0,02 \times 10^9/l$ . The complete absence of eosinophils called aneosinophilia. The causes are:

- stress;
- Itsenko-Cushing disease or injection of corticotropin and corticosteroids;
- athletic overexertion;
- burns, trauma;
- infectious disease (sepsis, dysentery, typhoid fever and acute appendicitis);
- agranulocytosis.

### ***Basopenia***

Basopenia is a reducing the number of basophils below  $0,01 \times 10^9/l$ . Reasons leading to basopenia:

- thyrotoxicosis;
- Cushing's syndrome;
- hemorrhagic syndrome;
- medicines (progesterone);
- agranulocytosis.

### ***Monocytopenia***

Monocytopenia is a rare condition. Monocytopenia is a decrease in count of monocyte less than  $0,09 \times 10^9/l$ . The causes are:

- radiation sickness;
- severe septic conditions;
- acute severe infectious disease.

### ***Lymphopenia***

There is a decrease in count of lymphocytes less than  $1,2 \times 10^9/l$ . The reasons are:

- protein deficiency (fasting);
- bone marrow failure (radiation damage, the use of immunosuppressive drugs);
- hereditary and acquired immunodeficiencies;
- lymphogranulomatosis;
- accelerated death of lymphocytes (in infections caused by lymphotropic viruses: measles, poliomyelitic, human immunodeficiency virus; under the action of cytotoxic drugs; the action of antilymphocytic antibodies (collagenoses);
- loss of lymphocytes (fistulas and drainage of thoracic duct);
- violation of lymphocyte migration (may occur under the stress and hypercortisolism, when there is a transition of their in tissues and enhanced apoptosis of lymphoid cells).

**The value of leukopenias:** in severe leukopenia there is a decrease the resistance of the organism (mainly anti-infection and anti-tumor). This is due to the leukocytes are involved in the implementation of humoral and cell immunity and phagocytic responses.

### **Agranulocytosis**

It is a clinical hematological syndrome characterized by the excessive decrease in granulocyte count in absolute numbers (neutrophils, eosinophils, basophils). Decreasing of granulocytes  $< 0,75 \times 10^9/l$  or/ and decreasing total amount of WBC  $< 1,0 \times 10^9/l$ .

#### **Classification of agranulocytosis**

- by clinical course: flash-like, acute, subacute, recurrent, cyclic;
- by origin: congenital, acquired;
- by mechanism: immune, myelotoxic.

#### **Pathogenesis:**

The basis of myelotoxic agranulocytosis is a depressing effect of drugs and other damaging factors on the proliferative activity of granulocyte elements of the bone marrow, resulting in develops hypoplasia of granulocytopoiesis. The possibility of severe granulocytopenia development is determined by the total dose of the received drug (arsenic, vincristin, myelosan). Myelotoxic granulocytosis is usually associated with anemia and thrombocytopenia.

The leading role in the pathogenesis of immune (haptens) agranulocytosis has the appearance of antibodies (agglutinins, lysine, etc.), the action of which is directed against one's own granulocytes in the peripheral blood or progenitor cells in the bone marrow. Medical drugs (amidopyrine, phenacetin, anti-tuberculosis drugs, and antiepileptic drugs) act as haptens, forming complexes with plasma proteins and membranes of leukocytes. Antibodies is produced on the resulting "alien" complex (antigen), is fixed on the surface of cells, causing their destruction. As a rule, at immune agranulocytosis there is a decreased contents only leukocyte.

**Clinical manifestations** of agranulocytosis: ulcerative necrotic angina (angina agranulocytotica), developing as a result of the suppression of defense reactions (loss of resistance to bacterial flora).

### **Panmyelophthisis**

It was described by P.Erlich in 1888. It is characterized suppression of bone marrow function: erythrocytes, thrombocytes and leukopoiesis. Thus there is a total devastation of the bone marrow: in it punctate can be founded only a few nuclear elements. In the blood are growing irreversible aplastic anemia (hypo-, normo- or hyperchromic character), leukopenia with agranulocytosis and thrombocytopenia.

## **LEUKEMOID REACTION**

**Leukemoid reaction** is a reactive functional state of the hematopoietic system, lymphatic and immune systems arising in the background of various diseases. Changes in blood look like leukemia. However leukemoid reaction is not transformed into the leukemia, which they resemble and they end after the completion of the basic pathological process.

There is no transformation of normal hemopoietic cell into tumor cell in bone marrow. There is an activation of normal cell proliferation.

**Etiology:** BAS, viruses, bacteria, helminth.

#### **Mechanism:**

- increase in the number and activity of leukopoietic stimulators
- increase in stimulators of WBC differentiation
- decrease in inhibiting factors of cell proliferation

Table 14. Differences leukemoid reactions from leukemia

	<b>Leukemoid reactions</b>	<b>Leukemia</b>
<b>Etiology</b>	Infectious agents; BAS, activate the output of blood cells from hematopoietic organs; state,	Carcinogens

	<b>Leukemoid reactions</b>	<b>Leukemia</b>
	leading to increased "consumption" of blood cells; various immunopathological condition.	
<b>Mechanisms of development</b>	Activation of normal hematopoiesis and entry of excess blood cells into the bloodstream. Suppression of normal hematopoiesis and braking output of blood cells into the bloodstream (cytopenia forms of leukemoid reactions).	Transformation of normal hematopoietic cells into the tumor.
<b>Bone marrow</b>	Focal hyperplasia of normal hematopoietic cells (in proliferative leukemoid reactions). Hypoplasia of the hematopoietic tissue (at cytopenia forms of leukemoid reactions).	Generalized hyperplasia of tumor hematopoietic cells. Usually many blasts and immature leukemic cells.
<b>Peripheral blood smear</b>	The presence of blasts and immature forms of WBC (in proliferative responses); leukopenia (cytopenia forms of leukemoid reactions); platelets are usually small with normal aggregation, no thrombocytopenia. Signs of degeneration of blood cells. No basophilia, no eosinophilia (observed in Marked eosinophilia)	Cytopenia combined with the presence in the blood of leukemic blast cells; hiatus leukemic in AML; signs of cell degeneration are usually absent (observed in B-lymphoid leukemia). Platelets frequently qualitatively abnormal, large, with abnormal aggregation, thrombocytopenia may occur; eosinophilia, basophilia (in CML)

Table 15. Types of leukemoid reactions and their characteristics

<b>Types of leukemoid reaction</b>	<b>Causes</b>	<b>Peripheral blood smear</b>
<b>1. Myeloid type</b>		
Neutrophilic:		
Pseudoblastic	Outcome of immune agranulocytosis; primary tuberculosis; severe toxic infections (diphtheria, tetanus etc.); sepsis	a lot of blast cells
Promyelocytic		a lot of typical promyelocytes
Like chronic myeloid leukemia	Infections (bacterial, viral, fungus); inflammation (chronic vasculitis, dermatitis, podagra, myositis etc.); intoxications (metabolism impairments, endocrine pathologies, uremia); malignant neoplasms (breast cancer, neoplasm in kidney, liver, lungs); lymphogranulomatosis	Neutrophilia with hyperregenerative nuclear shift to the left, normal number of eosinophils, basophils, degenerative changes in neutrophils (toxic granulation, karyopyknosis)
Marked eosinophilia	Parasitosis (filariasis, lambliasis, opisthorchiasis and others); allergic reactions (bronchial asthma, allergic reactions, drug-induced allergic reaction); collagenoses (rheumatoid arthritis, nodular periarteritis, scleroderma systematica); Löffler endocarditis; immune deficient state (Wiskott-Aldrich syndrome, IgA deficiency); malignant neoplasms (thyroid gland, stomach, renal cancer, lymphogranulomatosis, Hodgkin's disease, CML); idiopathic hereditary forms	Increased number of eosinophils (>15%) and changes in cell morphology (nucleus and cytoplasm vacuolization)
<b>2. Monocytic-lymphocytic type</b>		
Like acute	Infectious mononucleosis	Lymphocyte number – $20 \times 10^9/l$

Types of leukemoid reaction	Causes	Peripheral blood smear
lymphoblastic leukemia		and more, increased number of monocytes, «atypical mononuclears» (>10%), neutropenia
Acute infectious lymphocytosis	Enteroviral infection caused by Coxsackie virus; cat scratch disease; bacterial infections (whooping-cough, yersiniosis, tuberculosis and others); protozoal invasion (toxoplasmosis, malaria)	Lymphocyte number — 15–100×10 <sup>9</sup> /l and more, lymphocytosis (>60%) without changes in cell morphology, monocytosis
Stress-lymphocytosis	Cardiovascular pathology (cardiovascular collapse, acute heart failure, myocardial infarction, septic shock and others); immediate hypersensitivity reactions; surgical treatment; trauma; epilepsy	Short-lasting leukocytosis up to 5×10 <sup>9</sup> /l and more
Long-lasting lymphocytosis	Rheumatoid arthritis, malignant tumors (thymoma); chronic inflammatory diseases (sarcoidosis, Wegener's granulomatosis); delayed hypersensitivity reactions; hyposplenism, smoking	Long-lasting lymphocytosis 3,8×10 <sup>9</sup> /l and over
Reactive monocytosis	Infectious inflammatory disease (tuberculosis, chronic pyelonephritis, sarcoidosis, sprue); malignant neoplasms (breast and ovarian cancer, lymphogranulomatosis, multiple myeloma)	Increased monocyte number (>0,8×10 <sup>9</sup> /l)

Among leukemoid reactions monocyte-lymphocytic type most important in practical terms is leukemoid reaction with a picture of acute lymphoblastic leukemia in infectious mononucleosis.

### Infectious mononucleosis

**Etiology:** EBV, herpes virus simplex, CMV, rubella virus, hepatitis B, adenoviruses

**Pathogenesis:** is spread via saliva. Incubation period is 4-7 weeks. The virus replicates first within epithelial cells in the pharynx and later within B cells (by CD21). The host immune response involves cytotoxic (CD8-positive) T cells against infected B lymphocytes, resulting in enlarged, atypical lymphocytes (Downey cells). In case of T-lymphocyte reactions absence (T-lymphocyte reactions are cytotoxic to virus) uncontrolled B-lymphocyte proliferation takes place and B-cellular lymphoma may develop.

**Symptoms** usually persist 2-3 weeks. There are:

- fever;
- pharyngitis with edema and adenoidal hypertrophy, tonsillitis;
- lymphadenopathy – tender, bilateral and symmetrical;
- mild to moderate splenomegaly in 50-75 %;
- atypical features include skin rash, hepatitis and encephalitis.

**Hematological signs:**

- leucocytosis = 12-18 x10<sup>9</sup>/l
- atypical mononuclear cells
- EBV-specific antibodies (to viral capsid antigen and to nuclear antigen)
- high titers of heterophile antibodies

### Questions for self-control of knowledge:

1. What are pathological forms of white blood cells?
2. What is a biological significance of leukocytosis and leukopenia?
3. In what situations occurs a physiological leukocytosis?

4. Definition of leukemoid reactions. What are their etiology and mechanisms of development. Describe a peripheral blood smear and manifestation in leucopoiesis organs.
5. What is a difference leukemoid reaction from leukemia?
6. Which leukemoid reaction is manifested infectious mononucleosis?
7. What are hematologic criteria for agranulocytosis.
8. What is panmyelophthisis?
9. What are pathological form of white blood cells and when they occur?
10. What is leukocytosis? Specify the types, etiology, pathogenesis, importance of leukocytosis.
11. What is leukopenia? What are types, causes, mechanisms of development and manifestation of leukopenia? What is value of leukopenia for body?

**Tasks for self-managed student work:**

1. Infectious mononucleosis.
2. Agranulocytosis.
3. Role of neutrophils in inflammation.

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