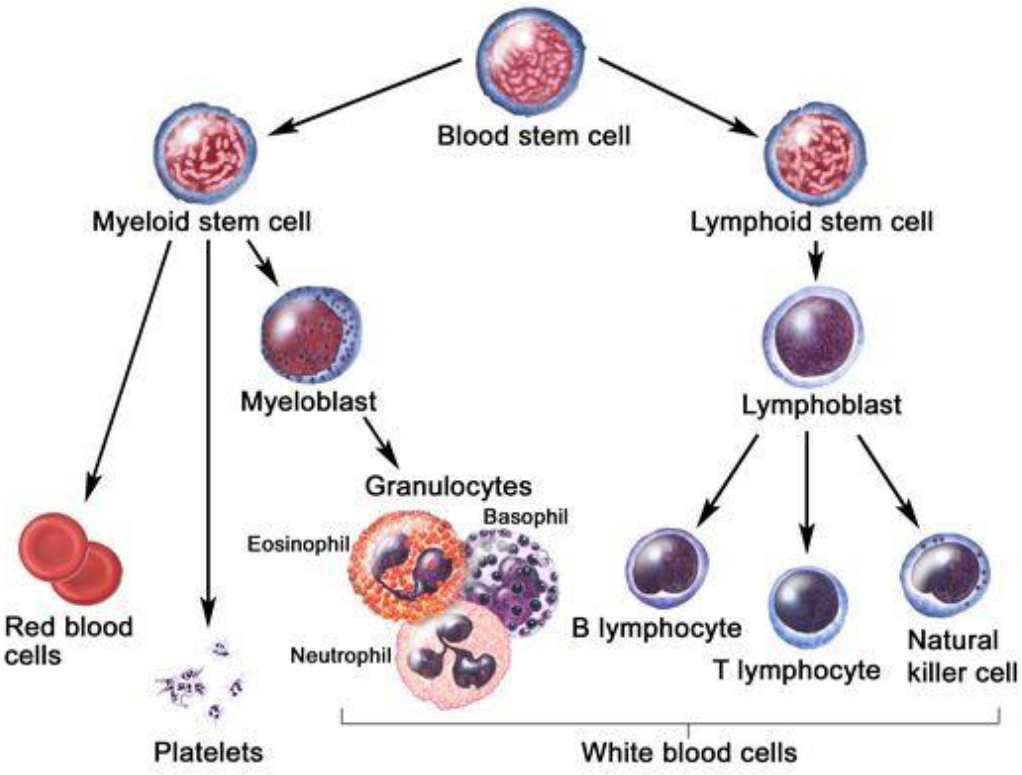
STATE UNIVERSITY
«UZHHOROD NATIONAL UNIVERSITY»
MEDICAL FACULTY N 2
Department of the Physiology and Pathophysiology

Sheiko N.I., Slyvka Y.I.

PATHOPHYSIOLOGY OF BLOOD

METHODICAL INSTRUCTIONS

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



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

Editors:
Sheiko N.I. - assistant of the Department of Physiology and Pathophysiology, medical faculty №2 of “UzhNU”

Slyvka Y.I. – associate professor of the Department of Physiology and Pathophysiology, medical faculty № 2 of “UzhNU”

Reviewers:
prof. Horlenko O.M.
PhD Palamarchuk O.S.

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Methodological instruction to practical lesson № 16
Module 2. Pathophysiology of organs and systems

Theme: PATHOPHYSIOLOGY OF THE BLOOD SYSTEM. ERYTHROCYTOSES. ANEMIAS, CAUSED BY HEMORRAGE

Student should know:

- Typical disorders in the blood system, changes of general volume of blood, anemia, erythrocytosis
- Classification of typical disorders in the system of blood

Student should be able to:

- Analyze causative-consequence relationships, to be able to explain pathological and adaptative-compensatory changes in pathogenesis of typical disorders in the system of blood.
- Apply knowledge of principles and classifications of anemias for the analysis of their signs.
- Apply knowledge of reasons and pathogenesis of anemias for their prophylaxis and treatment.

LIST OF CONTROL QUESTIONS

1. Changes of general volume of blood. Characteristic of hypo- and hypervolemias, reasons and mechanisms of development.
2. Hemorrhage: etiology, pathogenesis. Pathological and adaptative-compensatory changes in pathogenesis of hemorrhage. Signs and consequences of hemorrhage (hypovolemia, anemia, insufficiency of blood circulation/shock). Principles of therapy of hemorrhage. A concept about posthemotransfusion reactions and complications, mechanisms of their development and means of prophylaxis.
3. Erythrocytoses: determination of concept, types (absolute, relative; primary, second), etiology, pathogenesis.
4. Anemias: determination of concept, clinical and haematological signs, principles of classification (according to etiology, pathogenesis, character of course, type of erythropoesis, regeneratory ability of bone marrow, color index, changes of sizes of red blood cells). Etiology, pathogenesis, haematological characteristic of posthemorrhagic anemia (acute and chronic).

The ***circulating blood volume*** (CBV) in adults is about 5 liters (about 7% of the body weight). Centrifugation of the blood shows that about 45% consists of cells and 55% of plasma. The index that shows the contents of the cell elements, erythrocytes mainly, in the CBV is named ***packed cell volume*** (PCV) or hematocrit. In norm it is 42-47%. An increase in the PCV results from a rise in the red cell mass (erythrocytosis) or a fall in plasma volume (hemoconcetration). Conversely, a decrease in the PCV follows reduction in red cell mass (anemia) or a rise in plasma volume (hemodilution). Plasma contains 65-80 grams protein per liter. They include: albumin - 54%, globulin- 38%, fibrinogen - 8%.

The blood performs various **functions**. They are:

1) *Transport* — transfer of substrates, hormones, electrolytes, cells, fluids, enzymes, BAS, etc.
2) *Respiratory* — transportation of oxygen and CO_2 .
3) *Trophic* — transfer of nutrients to tissues and removal of metabolic products.
4) *Protective* — phagocytosis, bactericidal properties, immune reactions, transportation of antibodies and immune lymphocytes.
5) *Hemostatic* — maintenance of the liquid state of the blood in norm and its coagulation in response to hemorrhage.

Blood volume disorders manifest themselves as ***hypovolemia*** and ***hypervolemia***, that is blood volume decrease or increase in comparison with the norm (***normovolemia***). In their turn, in accordance with hematocrit index, ***normo-, hypo- and hypervolemia*** are subdivided into ***simple (normocythemic), polycythemic and oligocythemic*** ones.

Simple hypovolemia (blood volume reduction without hematocrit index changes) arises immediately after acute blood loss and persists until the fluid does not come from tissues into the blood.

Oligocythemic hypovolemia (blood volume decrease with plasma prevalence) is observed after acute blood loss till normal blood volume is completely restored by tissue fluid.

Polycythemic hypovolemia (blood volume reduction due to plasma volume decrease with relative prevalence of erythrocytes) develops in dehydration of the organism (diarrhea, vomiting, increased perspiration and hyperventilation). Simple hypervolemia (blood volume increase in case of normal blood cell-plasma correlation) occurs right after transfusion of a large amount of blood (under experimental conditions).

Oligocythemic hypervolemia (blood volume increase at the expense of plasma) develops in water retention in the organism due to renal disorders or if blood substitutes are injected.

Polycythemic hypervolemia is blood volume increase at the expense of an increased amount of blood cells. It is observed in hypobaria (atmospheric pressure reduction) as well as in different diseases connected with oxygen deficiency (heart failure or emphysema) with compensatory activation of erythropoiesis.

Polycythemic hypervolemia appears in tumorous hyperplasia of the bone marrow and has no defense significance (polycythemia rubra and vera, erythremia, leukemia).

Oligocythemic normovolemia occurs in anemia of different types.

Polycythemic normovolemia is observed in transfusion of any amount of red cells.

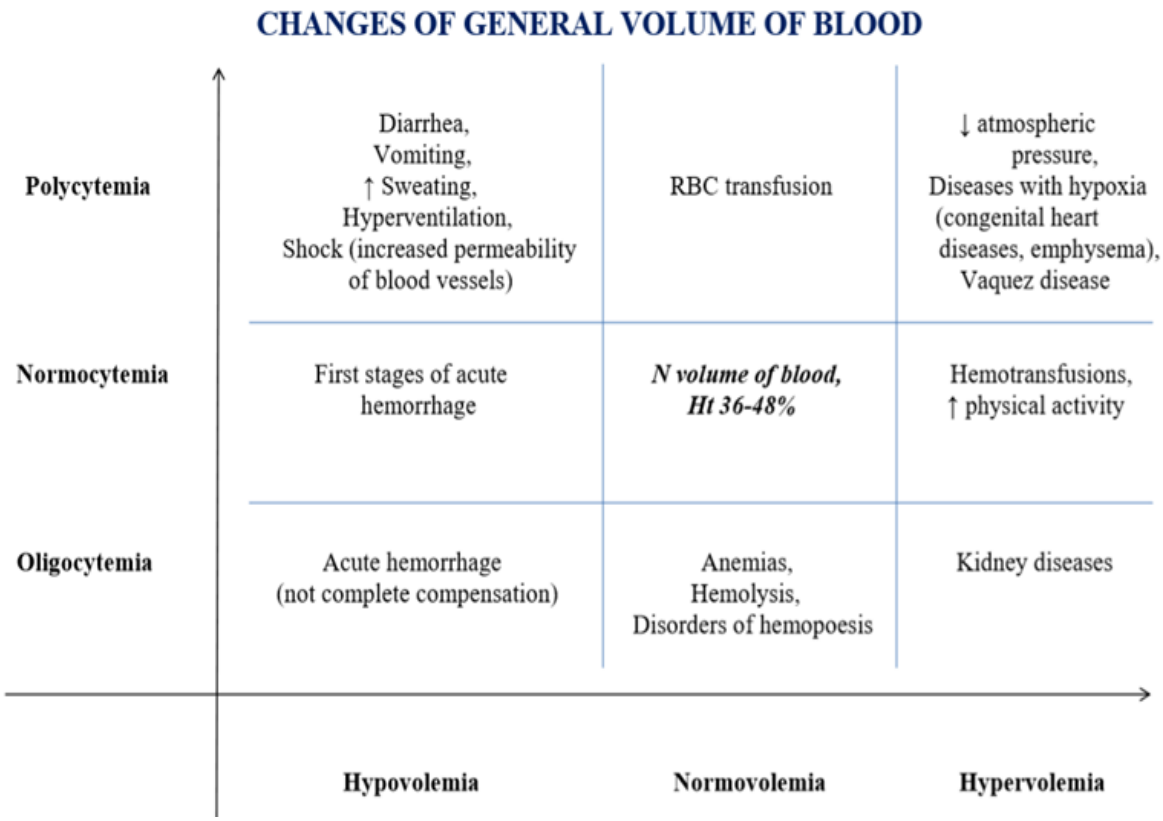

Fig. 1 Changes in general blood volume

Hemorrhage is a pathological process, which is characterized by a complex of pathologic disorders and compensatory reactions as a result of bleeding from vessels.

Etiological factors are those, which impair vessel integrity. The causes of hemorrhage are numerous. They may be exogenous and endogenous. More often it is vessel rupture due to a mechanical trauma. Endogenous causes include traumas caused by diseases that attack the vessel
wall (e.g. inflammation, atherosclerosis, necrosis, tumor, ulcer, erosive cancer, fallopian tube rupture in extrauterine pregnancy, etc.). Platelet deficiency and a lack of any clotting factor may cause hemorrhage. Endocrine disturbance may cause hemorrhage as it is in metrorrhagia (uterine bleeding).

Blood loss pathogenesis consists of two groups of events — ***pathological changes*** and ***compensatory reactions***.

Pathological Changes

Pathological changes in bleeding concern not only the blood system but the whole organism — the cardiovascular and respiratory systems, metabolism, pigment balance, etc. *Pathological changes are:*

• decrease of the circulating blood volume (hypovolemia);
• decrease of erythrocyte and hemoglobin content;
• disorder of hemodynamics — decrease of arterial blood pressure, decrease of the venous blood entering the heart, decrease of systolic output;

• disorder of microcirculation in tissues;
• deficiency of tissue oxidation and respiratory function of the blood due to the development of circulatory, hemic and tissue hypoxia;
• disorders of the functions of the vitally important organs (the nervous system and heart as a result of hypoxia);
• disorders of tissue metabolism;
• acid-base imbalance (non-respiratory metabolic acidosis).

Secondarily blood loss may cause or aggravate arrhythmia, insufficiency of coronary blood supply and external respiration, as well as disorders of hemostasis and renal filtration.

Compensatory Reactions

Compensatory reactions are divided into *urgent (immediate)* and *nonurgent (delayed)*.

Immediate Compensatory Reactions are directed at the renovation of blood volume and arterial blood pressure restoring blood supply of the vitally important organs. They are:
• spasm of the peripheral blood vessels;
• blood coagulation (thrombosis), which stops hemorrhage;
• reflex acceleration and intensification of cardiac contractions;
• restoration.of the circulating blood volume at the expense of blood reserves;
• redistribution of the blood towards increased blood supply of the most important organs (lungs, heart, brain, kidneys) at the expense of decreased blood circulation in the skin, spleen, muscles and intestines;
• reflex ventilation increase due to acceleration and deepening of respiration contributing to compensation of oxygen deficiency in the organism;
• erythrocyte quantity restoration at the expense of reserves (in the liver, spleen and bone marrow);
• increase of hemoglobin capacity to return oxygen to tissues (activation of oxyhemoglobin dissociation);
• decrease of diuresis;
• thirst;
• redistribution of the interstitial fluid in the vessels.

Delayed Compensatory Reactions develop later as:
• increased hemopoiesis;
• restoration of the protein content of the blood (normalized in 8—10 days after blood loss due to an increase of protein synthesis in the liver).

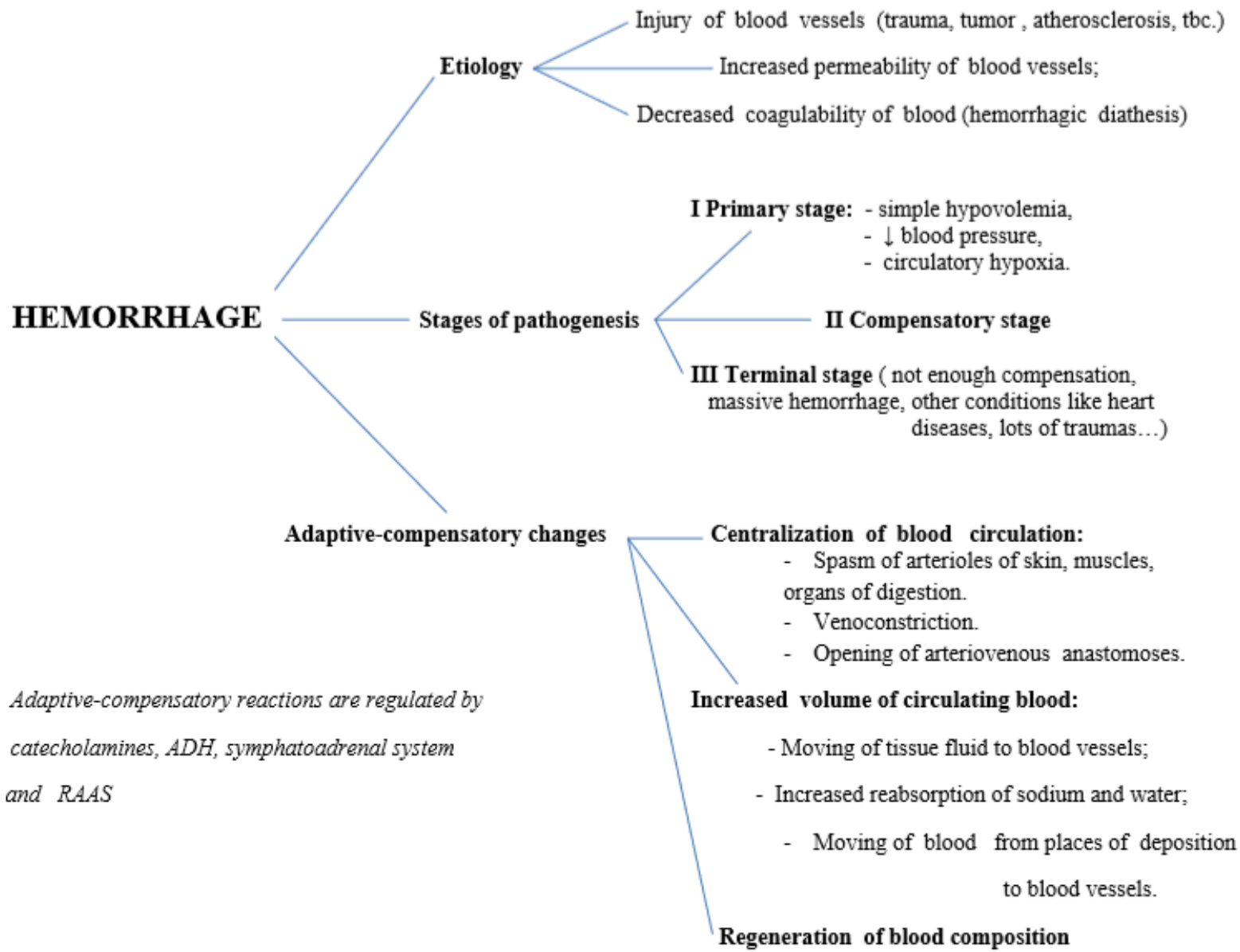

Fig 2. Hemorrhage

Erythrocytosis is an increase of erythrocyte content in the blood to more than 6 T/l, of hemoglobin content — to 10.55 mmol/1 (170 g/1) and of packed cell volume — to more than 0.52.

Classification

According to etiology, erythrocytosis is divided into *acquired and hereditary*. In accordance with pathogenesis it is divided into *true* (absolute, which is caused by erythropoiesis activation in the bone marrow and an increase of circulating erythrocyte mass) and *false* — relative and hemoconcentration (results from plasma volume decrease and thus is not accompanied by an increase of circulating erythrocytes mass). Absolute erythrocytosis in its turn is subdivided into *primary* (as an independent disease) and *secondary* (symptomatic), the latter — into *physiological* ('compensatory) and *pathological.*

Etiology

Primary absolute erythrocytosis is caused by tumorous transformation of erythrocytic stem cells with intensification of their proliferation independently from erythropoietin. It is true polycythemia (erythremia, or Vaquez disease), which is a variety of chronic leukemia.

Secondary absolute erythrocytosis (acquired) is caused by an increased production of hemopoietic factors. Here are some examples.

• Hypoxic, respiratory, circulatory hypoxia (mountain disease, chronic diseases of the organs of respiration and blood circulation).

• Local (ischemic) hypoxia of the kidneys (hydronephrosis, stenosis of the renal arteries) resulting in erythropoietin hyperproduction.

• Overproduction of erythropoietin by some tumors (hypernephroma, liver cancer).

• Neurohumoral regulation disorder with excitation of the sympathetic part of the vegetative nervous system.

• Hyperfunction of some endocrine glands, when catecholamines, corticotropin, thyroid hormones, glucocorticoids, androgens increase the need for oxygen and thus contribute to hypoxia development and erythropoietin formation in the kidneys.

Hereditary absolute erythrocytosis may result from a genetically determined deficit of 2,3-diphosphoglycerate (regulator of hemoglobin oxygenation and deoxygenation) in erythrocytes. The affinity of hemoglobin to oxygen increases and its return to tissues decreases. Tissue hypoxia develops, erythropoietin production increases, erythropoiesis activates.

Relative erythrocytosis results from the effect of such factors, which cause:

• organism dehydration and hemoconcentration (increased perspiration, prolonged vomiting, diarrhea, polycytemic hypovolemia);

• blood redistribution with polycythemic hypovolemia (shock, burn).

Anemia is an independent disease or a hematological syndrome, which is characterized by an absolute decrease of the content of hemoglobin and erythrocytes with morphological changes of erythrocytes.

Classification of anemia

The following types of anemia are distinguished:

***I. According to etiology*:**

-hereditary anemia

-acquired anemia

II. According to pathogenesis:

- posthemorrhagic anemia, i.e. due to blood loss
- hemolytic anemia, i.e. due to excessive blood destruction
- dyserythropoietic anemia, i.e. due to failure of red cell production

III. According to a type of erythropoiesis:

-with erythroblastic type

-with megaloblastic type

IV. According to an ability of the bone marrow for red cell regeneration:

o -regenerative (RC=0.2-2%)

o -hyporegenerative (RC<0.2%)

o -aregenerative (RC=0%)

o -hyperregenerative (RC>2%)

V. According to the CI (or MCHC):

o -normochromic (CI=0.85-1.05)

o -hypochromic (CI<0.85)

o -hyperchromic (CI>1.05)

VI. According to the size of red cells (or MCV):

 -normocytic (80-100 fl)

 -microcytic (<80 fl)

 -macrocytic (>100 fl)

Posthemorrhagic anemia is a type of anemia that develops as a result of blood loss (acquired anemia). The etiological factors (exogenous and endogenous) of posthemorrhagic anemia are those, which cause vessel injury and lead to bleeding. Endogenous reasons include tumor and other necrotic processes (atherosclerotic changes, inflammation, etc.) that destroy vessels

Pathogenesis, clinical picture and hematological indices are different depending on the type of blood loss — acute or chronic.

Acute posthemorrhagic anemia occurs after acute blood loss in case of traumas of large blood vessels or inability of the organism to stop bleeding because of hemostasis disorder. Immediately after blood loss and during the first hours the quantitative indices of the peripheral blood are delusively normal because erythrocytes, hemoglobin and plasma are equally reduced (simple hypovolemia).

Immediate compensatory reactions directed at the restoration of the total blood volume and arterial blood pressure develop (peripheral blood vessel spasms, restoration of the circulating blood volume due to the reserved blood, decrease of diuresis, etc.). Then, erythrocyte release from the depots (the liver and spleen) partly restores the cellular blood composition. After restoration of the total blood volume (in some hours) a reduction of erythrocyte and hemoglobin concentration is recorded. Delayed mechanisms of compensation are observed later as increased hemopoiesis. On the 4th—5th day after acute blood loss, proliferation of the erythrocytic stem cells of the bone marrow may be observed (it is provided by erythropoietin).

Chronic posthemorrhagic anemia develops due to repeated blood loss caused by a damage of the small blood vessels in some diseases (stomach ulcer, uterine problems, hemorrhoids, etc.) as well as in hemostasis disorders (hemorrhage syndrome).

KROK 1 mcqs _ A is correct answer:

1. A 32-year-old patient was admitted to the hospital with gross blood loss due to auto accident trauma. Ps - 110Bpm, RR- 22 pm, BP- 100/60mm Hg. What changes in the blood will occur in an hour after the blood loss?

A Hypovolemia
B Erythropenia
C Hypochromia of erythrocytes
D Leukopenia
E Hypoproteinemia

2. A patient's blood was analyzed and the decreased erythrocyte's sedimentation rate (ESR) was discovered. What disease from the listed below is accompanied with decreased ESR?

A Polycytemia
B Hepatitis
C Splenomegaly
D Vitamin B deficiency
E Myocardial infarction

3. Blood sampling for bulk analysis is recommended to be performed on an empty stomach and in the morning. What changes in blood composition can occur if to perform blood sampling after food intake?

A Increased contents of leukocytes
B Increased contents of erythrocytes
C Increased plasma proteins
D Reduce contents of thrombocytes
E Reduced contents of erythrocytes

4. A patient underwent a surgery for excision of a cyst on pancreas. After this he developed hemorrhagic syndrome with apparent disorder of blood coagulation. Development of this complication can be explained by:

A Activation of fibrinolytic system
B Activation of Christmas factor
C Activation of anticoagulation system
D Insufficient fibrin production
E Reduced number of thrombocytes

5. On the fifth day after the acute blood loss a patient has been diagnosed with hypochromic anemia. What is the main

mechanism of hypochromia development?

A Release of immature red blood cells from the bone marrow

B Impaired iron absorption in the intestines

C Increased destruction of red blood cells in the spleen

D Impaired globin synthesis

E Increased excretion of body iron

6. In a car accident a man got injured and lost a lot of blood. What changes in peripheral blood are most likely to occur on the 2nd day after the injury?

A Erythropenia

B Hypochromia

C Anisocytosis

D Microplania

E Significant reticulocytosis

7. After the prolonged vomiting a pregnant 26-year-old woman was found to have the reduced volume of circulating blood. What change in the total blood volume can be the case?

A Polycythemic hypovolemia

B Simple hypovolemia

C Oligocythemic hypovolemia

D Polycythemic hypervolemia

E Oligocythemic hypervolemia

8. A patient has severe blood loss caused by an injury. What kind of dehydration will be observed in this particular case?

A Iso-osmolar

B Hyposmolar

C Hyperosmolar

D Normosmolar

E ---

9. In a dysentery patient undergoing treatment in the contagious isolation ward, a significant increase in packed cell volume has been observed (60%). What other value will be affected by this change?

A Increasing blood viscosity

B Increasing volume of blood circulation

C Leukopenia

D Thrombocytopenia

E Increasing erythrocyte sedimentation rate (ESR)

10. A mother consulted a doctor about her 5-year-old child who develops erythemas, vesicular rash and skin itch under the influence of sun. Laboratory studies revealed decreased iron concentration in the blood serum, increased uroporphyrinogen I excretion with the urine. What is the most likely inherited pathology in this child?

A Erythropoietic porphyria

B Methemoglobinemia

C Coproporphyria

D Intermittent porphyria

E Hepatic porphyria

11. 38-year-old patient with an uterine hemorrhage lasting for 2 days was delivered to the admission ward. Which of the following will be revealed in the patient’s blood?

A Decrease in the hematocrit index

B Increase in the colour index

C Leukocytosis

D Deceleration in ESR

E Eosinophilia

12. A 27-year-old patient with injury to the neck has lost approximately 30% of the blood volume. The patient’s condition is severe: blood pressure is 60/40 mmHg, heart rate is 140/min., respiratory rate is 30/min., conscious. Characterize the condition of the patient’s circulatory system:

A. Hypovolemic shock

B. Cardiogenic shock

C. Collapse

D. Coma

E. Arterial hypertension

13. A 42-year-old patient complains of pain in the epigastral area, vomiting; vomit masses have the color of coffee-grounds; the patient suffers from melena. Anamnesis records gastric ulcer disease. Blood formula: erythrocytes- 2, 8 · 10^{12}/l, leukocytes- 8 · 10^{9}/l, Hb-90g/l. What complication is it?
A. Hemorrhage
B. Penetration
C. Perforation
D. Canceration
E. Pyloricstenosis
14. 10 minutes after the beginning of heavy physical work a person demonstrates increase of erythrocyte number in blood from 4, 0 · 10^{12}/l to 4, 5 · 10^{12}/l. What is the cause of this phenomenon?
A. Erythrocytes exit from depot
B. Suppression of erythrocyte destruction
C. Erythropoiesis activation
D. Increase of cardiac output
E. Water loss
15. Blood test of an athlete shows thefollowing: erythrocytes - 5, 5 · 1012/l, hemoglobin - 180 g/l, leukocytes - 7 · 109/l, neutrophils - 64%, basophils - 0,5%, eosinophils - 0,5%, monocytes - 8%, lymphocytes - 27%. These values primarily indicate the stimulation of:
A. Erythropoiesis
B. Leukopoiesis
C. Lymphopoiesis
D. Granulocytopoiesis
E. Immunogenesis
16. A 30-year-old patient's blood test revealed the following: erythrocyte count is 6 · 1012/l, hemoglobin is 10,55 mmol/l. Vaquez's disease was diagnosed. Name the leading part of pathogenesis in this case:
A. Neoplastic erythroid hyperplasia
B. Iron-deficiency
C. B12-deficiency
D. Hypoxia
E. Acidosis
17. A patient suffers from posttraumatic hemorrhage that resulted in development of hemorrhagic shock. What volume of circulating blood was lost by the patient?
A. 25-40%
B. 40-50%
C. 12-25%
D. 50-75%
E. 3-20%

Tests for Self-Control (give correct answers)

1. A healthy driver had acute massive bleeding as a result of a car crash. In half an hour he was hospitalized in the state of posthemorrhagic shock. What is the state of his blood volume?

A. Oligocythemic normovolemia.
B. Oligocythemic hypovolemia.
C. Simple hypovolemia.
D. Polycythemic hypovolemia.
E. Oligocythemic hypervolemia

2. A healthy driver had acute massive bleeding as a result of a car crash but was hospitalized only in a day. What is the state of his blood volume?

A. Oligocythemic normovolemia.
B. Oligocythemic hypovolemia.
C. Simple hypovolemia.
D. Polycythemic hypovolemia.
E. Oligocythemic hypervolemia.

Recommended literature:

Basic

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Methodological instruction to practical lesson № 17
Module 2. Pathophysiology of organs and systems

Theme: HEMOLYTIC ANEMIAS AND ANEMIAS, CAUSED BY DISORDERS OF ERYTHROGENESIS

Student should know:

- Typical disorders in the blood system, changes of general volume of blood, anemia, erythrocytosis
- Classification of typical disorders in the system of blood

Student should be able to:

- Analyze causative-consequence relationships, to be able to explain pathological and adaptative-compensatory changes in pathogenesis of typical disorders in the system of blood.
- Apply knowledge of principles and classifications of anemias for the analysis of their signs.
- Apply knowledge of reasons and pathogenesis of anemias for their prophylaxis and treatment.

LIST OF CONTROL QUESTIONS

1. Etiologic classification (inherited, acquired) of hemolytic anaemias. Characteristic of causal factors of the acquired hemolytic anaemias. Ways of realization of genetic defects in pathogenesis of the inherited hemolytic anaemias (membrano-, enzymo-, hemoglobinopathias).
2. Hemolysis of red blood cells, intra- and extravascular as mechanisms of development of hemolytic anaemias. Characteristic clinical signs of hemolysis of red blood cells (icterus, hemoglobinuria, disseminating coagulation of blood, dyscholia, cholelythiasis, splenomegaly), their possible association with the type of hemolisis. Pathological forms of red blood cells, specific for the inherited hemolytic anaemias.
3. Classification of anaemias, related to disorders of erythrogenesis (defficite, dysregulatory, hypo-, aplastic etc), general characteristic of reasons and mechanisms of development.
4. Etiology, pathogenesis, typical changes of peripheral blood, at iron deficient anaemias. A concept about iron refractory anaemias.
5. Anaemias, caused by insufficiency of vitamin B12 and/or pholic acid. Reasons of origin and mechanisms of development of absolute and relative deficit of vitamin of B12 and pholic acid. Malignant anaemia of Addison-Birmer. Characteristic of general disorders in organism at the deficit of vitamin B12 and/or pholic acid. Haematological picture of a vitamin B12-, pholic acid defficient anaemias.

The hemolytic disorders are characterized by an *increased destruction of red cells* and shortening of their lifetime. There is a compensatory *increase in*

erythropoiesis, but anemia develops when the rate of destruction exceeds that of production. Hemolysis can be caused by either

-an intrinsic erythrocyte defect or

-an abnormal marrow or systemic environment.

The intrinsic erythrocyte defects are hereditary. These disorders can result from a defect in:

- red cell membrane-membranopathias
- red cell enzyme-enzymopathias
- hemoglobin structure-hemoglobinopathias.

An abnormal marrow or systemic environment is an acquired abnormality (the red cell itself is normal) In most hemolytic disorders red cells are destroyed by macrophages in the spleen, liver and bone marrow i.e., by *extravascular hemolysis*. *Intravascular hemolysis* with escape of hemoglobin into the circulation is due to severe red cell membrane damage by antibody and complement, toxic chemicals or mechanical trauma. Two most common causes of extravascular hemolytic anemia are *hereditary spherocytosis and glucose-6-phosphate dehydrogenase deficiency*.

Hereditary spherocytosis or Minkowski-Chauffard syndrome is a classic example of a red cell membrane defect. The disease is inherited as autosomal dominant trait. In hereditary spherocytosis, a genetically determined abnormality occurs in a membrane polypeptide spectrin, a component of the membrane skeleton. The red cell membrane defect results in membrane instability. Red cells become spherocytic as surface-to-volume ratios decline and this can occur because of loss of membrane surface (microspherocytes). The surface-tovolume ratio of red cells influences the deformability of a red cell membrane, and being altered in disease it causes a shortening of red cell survival. The cells become less deformable as they become more spheroidal. The microspherocytes are sequestered selective by the reticuloendothelial cells of the spleen and then become destroyed. The diagnosis is suggested when hemolysis is associated with microspherocytes in the peripherial blood and is confirmed by an increased osmotic fragility of the red blood cells. The osmotic fragility test is a useful measurement of the surface-to-volume ratio. When red cells are placed in hypotonic salt solution they swell, rupture and hemoglobin escapes. With normal red cells, the first trace of lysis is usually seen in 0,44-0,46% saline, so-called minimal osmotic resistance; and all red cells are hemolyzed in 0,28-0,32% saline, so-called maximal osmotic resistance. Initial lysis occurring above minimal osmotic résistance is abnormal indicating increased fragility. The spleen occupies a central role in this disorder. This can be confirmed by the following fact: following splenectomy, survival of red cells returns to normal.

Glucose-6-phosphate dehydrogenase deficiency is a hereditary disease characterized by abnormally low levels of glucose-6-phosphate dehydrogenase (G6PD) resulting in hemolytic anemia. G6PD deficiency is among the commonest inherited diseases in the world, affecting up to 40% of persons of Mediterranean, South East Asian and Negro ancestry. The deficiency is most common in areas where malaria is endemic, reflecting the protection against falciparum malaria. The defect is an X-linked recessive disorder hence it is expressed only in males and homozygous

females. Enzyme G6PD is responsible for maintaining the level of nicotinamide adenine dinucleotide phosphate (NADPH). The NADPH in turn maintains the supply of reduced glutathione in the cells. Glutathion is used to inactivate free radicals which cause oxidative damage to cells. The principal effect of G6PD deficiency is a fall in NADPH production with a decrease in reduced glutathione. Red cells as oxygen carriers are at substantial risk of damage from oxidizing free radicals except for the protective effect of G6PD/NADPH/glutathione. People with G6PD deficiency are therefore at risk of hemolytic anemia in states of oxidative stress. Oxidative stress can result from infection and from chemical exposure to medication and certain foods. For instance, broad beans contain high levels of vicine, divicine, convicine and isouramil, all of which are oxidants. The drugs which can act as oxidants include antimalarias, sulphonamides, nitrofuranton, aspirin and vitamin K.

Hemoglobinopathias result from abnormalities in synthesis of the globin chains, the haem groups being normal. Two main varieties occur:
1) production of abnormal globin chains- sickle cell anemia
2) lack of synthesis of globin chains-thalasseemias

a) Sickle cell anemia results from a point mutation in the β chain of the hemoglobin molecule, with an abnormal substitution of a single amino acid, valine for glutamic acid. Sickle hemoglobin (HbS) is formed. The biochemical anomaly in the β chain alters the solubility of hemoglobin. When the HbS becomes deoxygenated (at low pH and with decreased oxygen tension) it precipitates out of solution in the red cells that results in change their shape and deformability. Such red cells become sickle-shaped and get stuck in the small blood vessels with consequent vascular obstruction, occlusion, and then hemolysis of red cells. The factors associated with sickling and consequent blood vessel occlusion in persons with sickle cell disease include: cold, stress, physical exertion, infection, hypoxia, acidosis, dehydration and even such trivial incidents as reduced oxygen tension induced by sleep.

b) Thalassemias In contrast to sickle cell anemia, thalassemias result from absent or defective synthesis of α (α-thalassemias) or β (β-thalassemias) chains of hemoglobin. The β-thalassemias sometimes are called. Cooley‘s anemia or Mediterranean anemia (they are most common in the Mediterranean region). In α- and β-thalassemia, defective globin chain production leads to deficient hemoglobin production and the development of a hypochromic anemia. In imbalance in globin chain production results in abnormal hemoglobins that are functionally inadequate. The red cells are deformed (became microcytic) that contributes to their destruction and anemia.

Acquired hemolytic anemias Several factors exogenous to red blood cells produce hemolysis by direct membrane destruction or by antibody mediated lysis. They include: drugs, chemicals, toxins, venoms, infections, such as malaria, and mechanical factors, such as prosthetic heart valves, arterio-venous shunts. Most

hemolytic anemias are immune mediated, i,e., caused by antibodies that damage the red cell membrane. Autoantibodies may be produced by a person in response to drugs and disease (lymphoma, carcinoma, sarcoidosis or one of the collagen disorders) – autoimmune destruction of red cells. Antibodies may come from an exogenous source, for example, in transfusion reactions and hemolytic disease of the newborn – blood group incompatibilities.

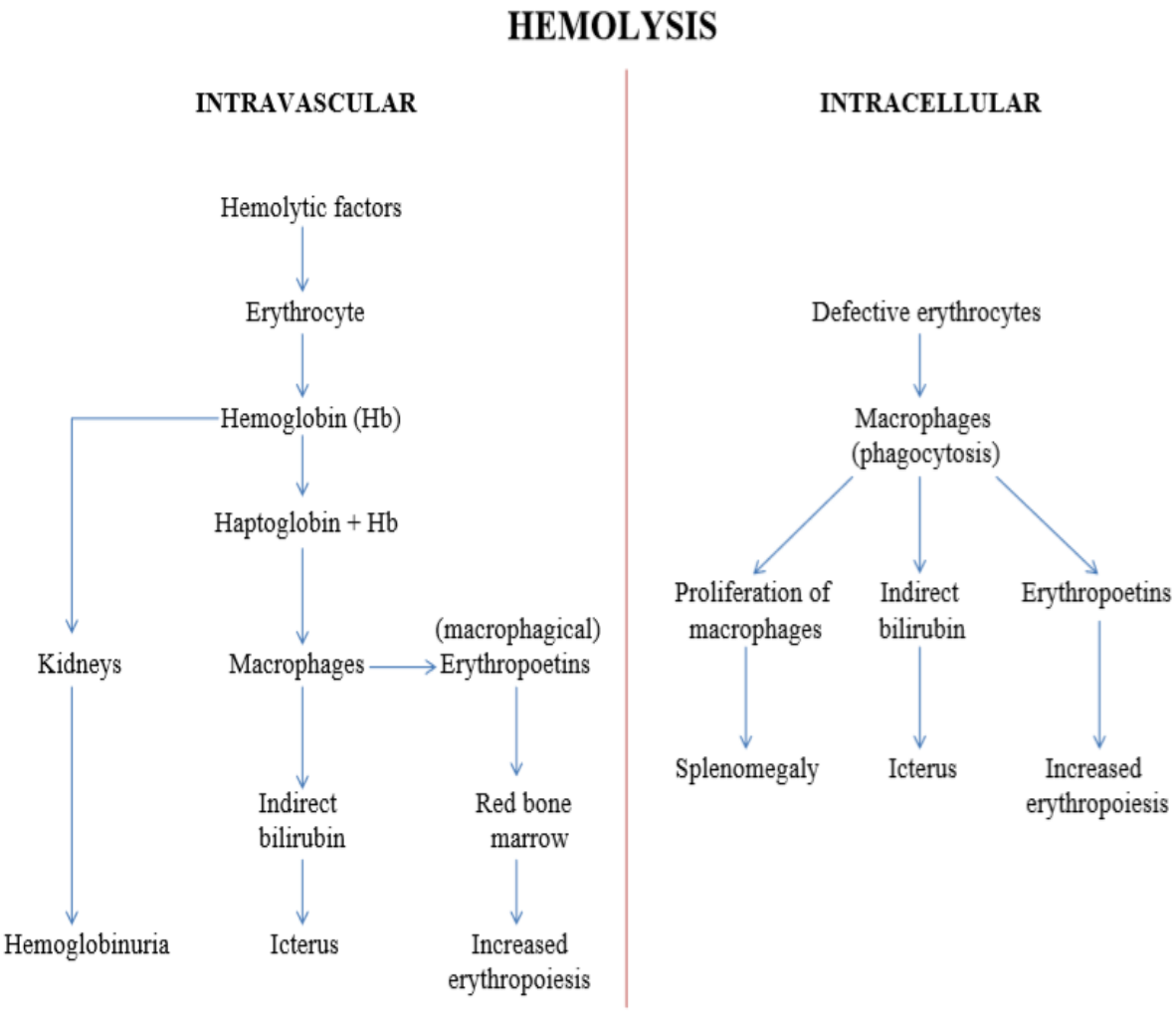

Fig.3 Hemolysis

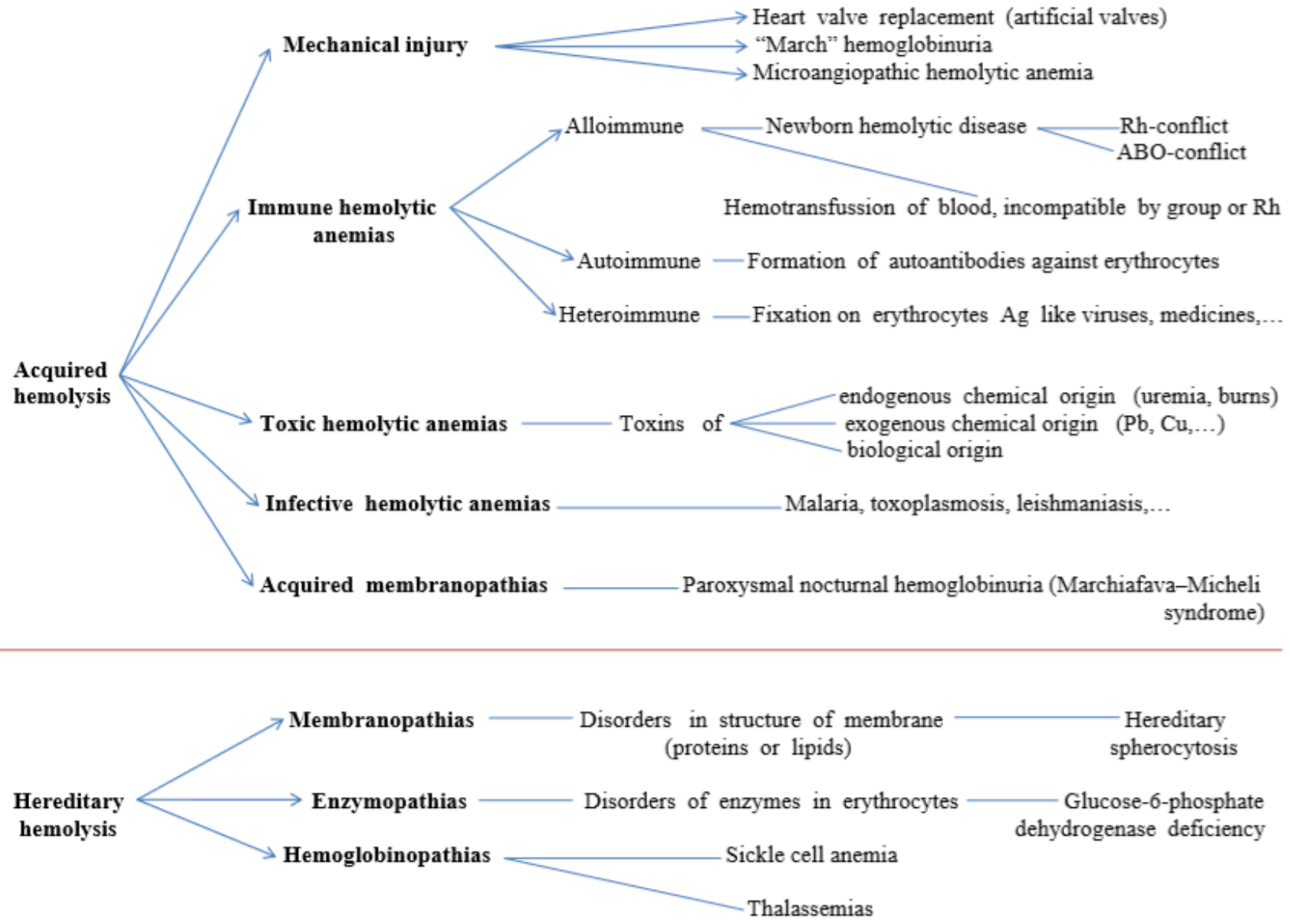

Fig.4 Types of Hemolysis

Dyserythropoetic anemias may result from:
-deficiency of nutrients for hemoglobin synthesis (iron, proteins)
-deficiency of nutrients for DNA synthesis (cobalamin or folic acid)
-hypoplasia of bone marrow, causing depression of erythropoiesis -metaplasia, when marrow is replaced by non-functional tissue

Iron-deficiency anemia It is the most common anemia affecting persons of all ages. 80% of all anemias are iron-deficiency ones. Iron-deficiency anemia may be caused by:
-chronic low-grade blood loss, such as heavy menstrual bleeding or bleeding from the gastrointestinal tract;
-low dietary intake that is important in infants before weaning, especially in developing countries;
-disturbances in iron absorption (hypoacidic gastritis, gastrectomy)

Because iron is a component of heme, a deficiency leads to decreased hemoglobin synthesis and consequent impairment of oxygen delivery. Impaired oxygen transport mediates such manifestation of iron-deficiency anemia as fatigability, palpitations, dyspnea, angina and tachycardia. Changes in the blood and bone marrow: red cells become hypochromic and microcytic, poikilocytosis is present. Characteristic of the blood in this anemia is not so much the decrease in the number of erythrocytes as the diminished hemoglobin. Hence the CI drops very much below unity to 0.60.5. Changes in other tissues occur because of depletion of iron-containing enzymes in the tissues. The nails become striated and brittle and may eventually become spoon-shaped (koilonychias). Atrophic glossitis, fissuring of the angles of the mouth and dysphagia due to folding of lax mucosa in the upper esophagus may occur.

B12-- deficiency anemia (megaloblastic anemia) This anemia is characterized by an abnormality of hemopoiesis known as megaloblastic type which affects production of granulocytes and platelets as well as red cells. The effect on erythropoiesis is most conspicuous. The commonest cause of megaloblastic anemia is deficiency of either vitamin B12 or folic acid. These substances, which act as coenzymes, are important for normal cell division.

Causes of vitamin B12-deficiency include:

-malabsorption of B12 due to deficiency of the intrinsic factor (Castle factor)-pernicious anemia;

-lack of vitamin B12 or folic acid in the food;

- increased requirements in of vitamin B12 or folic acid (pregnancy)

-disturbance of absorption of vitamin B12 in the intestine (ilea resection, infestation with tape warms) In deficiency of vitamin B12 (cyanocobalamin), a conversion of folic acid into tetrahydrofolic one is disturbed. It leads to the disturbance of synthesis of timidinmonophosphate, one of the components of DNA. It results in enlarged red cells and deficient cell maturation. Megaloblastic type of erythropoiesis occurs.

In both vitaminB12 and folic acid deficiency red cells, granulocytes and platelets are reduced in number, i.e. pancytopenia occurs. The red cells show an

increased MCV (macrocytosis) and in MCHC (hyperchromia). They may be abnormal in shape (poikilocytosis). The number of erythrocytes are sharply decreased and the color index is more than unity (sometimes as high as 1.7) since the erythrocytes contain more hemoglobin than normal. The reticulocyte count is reduced. The presence megaloblasts, megalocytes, erythrocytes with Jolly bodies and Cabot's ring bodies are observed. Anemia is also characterized by a diminished red blood osmotic fragility and their increased destruction.

Hypoplastic (aplastic) anemias These anemias develop as a result of bone marrow depression. Inciting or causative agents may be radiation, drugs (especially chemotherapy), viruses (especially AIDS, hepatitis C virus), toxins (especially benzene derivates) or unknown agents. Aplastic anemia describes a primacy condition of bone marrow stem cell that results in a reduction of all three hematopoietic cell lines – red blood cells, white blood cells and platelets – with fatty replacement of bone marrow. *Metaplastic (myelophthisic) anemias* In these conditions, the marrow is replaced by foreign invaders', e.g. carcinomas, leukemias, granulomas.

ANEMIAS

According to:	Posthemorrhagic anemias		Hereditary hemolytic anemias				Dyserythropoetic anemias		
			Membrano-pathias	Enzymo-pathias	Hemoglobinopathias				
	Acute	Chronic	Hereditary spherocytosis	Glucose-6-phosphate dehydrogenase deficiency	Sickle cell anemia	Thalassemias	Iron-deficiency anemia	B_{12} – deficiency anemia	Hypoplastic anemia
Etiology	Acquired	Acquired	Hereditary	Hereditary	Hereditary	Hereditary	Acquired	Acquired	Acquired
Pathogenesis	Post-hemorrhagic	Post-hemorrhagic	Hemolytic	Hemolytic	Hemolytic	Hemolytic	Dys-erythropoetic	Dys-erythropoetic	Dys-erythropoetic
Type of erythropoiesis	Erythro-blastic type	Erythro-blastic type	Erythro-blastic type	Erythroblastic type	Erythro-blastic type	Erythro-blastic type	Erythro-blastic type	Megalo-blastic type	Erythro-blastic type
Ability for red cell regeneration	Regenerative	Hypo-regenerative	Hyper-regenerative	Hyper-regenerative	Hyper-regenerative	Hyper-regenerative	Hypo-regenerative	Hypo-regenerative	Hypo- or aregenerative
The CI	Normo-chromic at the beginning, then hypochromic	Hypo-chromic	Hypochromic	Hypochromic	Hypo-chromic	Hypo-chromic	Hypo-chromic	Hyper-chromic	Normo-chromic
The size of red cells	Normocytic	Microcytic	Microcytic	Normocytic	Normocytic	Microcytic	Microcytic	Macrocytic	Normocytic

Fig. 5 Classification and general characteristics of anemias

KROK 1 mcqs_A is correct answer

1. A 37-year-old woman complains of headache, vertigo, troubled sleep, numbness of limbs. For the last 6 years she has been working at a gas-discharge lamp-producing factory in a lead-processing shop. Blood test findings: low hemoglobin and RBC level, serum iron concentration exceeds the norm by several times. Specify the type of anemia:
A. Iron refractory anemia
B. Iron-deficiency anemia
C. Minkowsky-Shauffard disease
D. Hypoplastic anemia
E. Metaplastic anemia

2. A patient is diagnosed with chronic atrophic gastritis attended by deficiency of Castle's intrinsic factor. What type of anemia does the patient have?
A. *B*12-deficiency anemia
B. Iron refractory anemia
C. Hemolytic anemia
D. Iron-deficiency anemia
E. Protein-deficiency anemia

3. Biochemical analysis of an infant's erythrocytes revealed evident glutathione peroxidase deficiency and low concentration of reduced glutathione. What pathological condition can develop in this infant?
A. Hemolytic anemia
B. Pernicious anemia
C. Megaloblastic anemia
D. Sicklemia
E. Iron-deficiency anemia

4. Patient with hypochromic anemia has splitting hair and loss of hair, increased nail brittling and taste alteration. What is the mechanism of the development of these symptoms?
A Deficiency of iron-containing enzymes
B Deficiency of vitamin B12
C Decreased production of parathyrin
D Deficiency of vitamin A
E Decreased production of thyroid hormones

5. Substitution of the glutamic acid on valine was revealed while examining initial molecular structure. For what inherited pathology is this typical?
A Sickle-cell anemia
B Thalassemia
C Minkowsky-Shauffard disease
D Favism
E Hemoglobinosis

6. A 34 year old woman was diagnosed with hereditary microspherocytic hemolytic anemia (Minkowsky-Shauffard disease). What mechanism caused haemolysis of erythrocytes?
A Membranopathy
B Enzymopathy
C Hemoglobinopathy
D Autoimmune disorder
E Bone marrow hypoploasia

7. From the group of children who were eating sweet sappy watermelon two kids developed the signs of poisoning: rapid weakness, dizziness, headache, vomiting, edema, tachycardia, cyanosis of mouth, ears, tips of the fingers cyanosis. High concentration of nitrates was detected. What is the leading mechanism of the pathogenesis of the poisoning in the two children?
A Insufficiency of met-Hb-reductase

B Insufficiency of superoxiddismutase
C Block cytochrome oxidase
D Insufficiency glutathione pyroxidase
E Insufficiency of catalase

8. A patient was diagnosed with autoimmune hemolytic cytotoxic anemia. What substances are antigens in II type allergic reactions?
A Modified receptors of cell membranes
B Antibiotics
C Hormones
D Serum proteins
E Inflammation modulators
9. A patient with hypochromic anemia has splitting and loss of hair, increased nail brittling and taste alteration. What is the mechanism of the symptoms development?
A Deficiency of iron-containing enzymes
B Deficiency of vitamin B_12
C Decreased production of parathyrin
D Deficiency of vitamin A
E Decreased production of thyroidhormones
10. A patient, who suffers from congenital erythropoietic porphyria, has skin photosensitivity. The accumulation of what compound in the skin can cause it?
A Uroporphyrinogen 1
B Protoporphyrin
C Uroporphyrinogen 2
D Coproporphyrinogen 3
E Heme
11. Substitution of the glutamic acid on valine was revealed while examining initial molecular structure. For what inherited pathology is this symptom typical?
A Sickle-cell anemia
B Thalassemia
C Minkowsky-Shauffard disease
D Favism
E Hemoglobinosis
12. A 38-year-old woman was admitted to the admission-diagnostic department with uterine bleeding. What are the most likely changes of blood?
A Reduction of haematocrite rate
B Increase of haematocrite rate
C Leukopenia
D Leucocytosis
E Polycythemia
13. Examination of a 43 y.o. anephric patient revealed anemia symptoms. What is the cause of these symptoms?
A Reduced synthesis of erythropoietins
B Enhanced destruction of erythrocytes
C Iron deficit
D Vitamin B12 deficit
E Folic acid deficit
14. A 3 year old child with fever was given aspirin. It resulted in intensified erythrocyte haemolysis. Hemolytic anemia might have been caused by congenital insufficiency of the following enzyme:
A Glucose 6-phosphate dehydrogenase
B Glucose 6-phosphatase
C Glycogen phosphorylase
D Glycerol phosphate dehydrogenase
E γ-glutamiltransferase
15. Surgical removal of a part of stomach resulted in disturbed absorption of vitaminB12, it is excreted with feces. The patient was diagnosed with anemia. What factor

is necessary for absorption of this vitamin?
A Gastromucoprotein
B Gastrin
C Hydrochloriacid
D Pepsin
E Folic acid

16. Hemoglobin catabolism results in release of iron which is transported to the bone marrow by a certain transfer protein and used again for the synthesis of hemoglobin. Specify this transfer protein:
A Transferrin (siderophilin)
B Transcobalamin
C Haptoglobin
D Ceruloplasmin
E Albumin

17. A pregnant woman underwent AB0 blood typing. Red blood cells were agglutinated with standard sera of the I and II blood groups, and were not agglutinated with the III group serum. What is the patient's blood group?
A B(III)
B 0(I)
C A(II)
D AB(IV)
E –

18. Human red blood cells do not contain mitochondria. What is the main pathway for ATP production in these cells?
A Anaerobic glycolysis
B Aerobic glycolysis
C Oxidative phosphorylation
D Creatine kinase reaction
E Cyclase reaction

19. When defining blood group according to the AB0 system, using salt solutions of monoclonal antibodies, agglutination didn't occur with any of the solutions. What blood group is it?
A 0 (I)
B A (II)
C B (III)
D AB (IV)
E –

20. A patient suffering from chronic myeloleukemia has got the following symptoms of anemia: decreased number of erythrocytes and low haemoglobin concentration, oxyphilic and polychromatophilic normocytes, microcytes. What is the leading pathogenetic mechanism of anemia development?
A Substitution of haemoblast
B Intravascular hemolysis of erythrocytes
C Deficiency of vitamin B12
D Reducesynthesis of erythropoietin
E Chronic haemorrhage

21. A patient is diagnosed with irondeficiency sideroachrestic anemia, (Identify pathogenesis of this type of anemia)
A Failure to assimilate iron leading to iron accumulation in tissues
B Excessive iron intake with food
C Disorder of iron absorption in bowels
D Increaseiron assimilation by body
E –

22. In the blood of a 26-year-old man18%of erythrocytes of the spherical, ball shaped, flat and thorn-like shape have been revealed. Other erythrocytes were in the form of the concavoconcave disks. How is this phenomenon called?
A Physiological poikilocytosis
B Pathological poikilocytosis
C Physiological anisocytosis
D Pathological anisocytosis
E Erytrocytosis

23. As a result of increased permeability of the erythrocyte

membrane in a patient with microspherocytic anaemia (Minkowsky-Shauffard disease) cells receive sodium ions and water. Erythrocytes take form of spherocytes and can be easily broken down. What is the leading mechanism of erythrocyte damage in this case?

A Electrolytic osmotic
B Protein
C Nucleic
D Calcium
E Acidotic

24. A 34 year old woman was diagnosed with hereditary microspherocytic hemolytic anemia (Minkowsky-Shauffard disease). What mechanism caused haemolysis of erythrocytes?

A Membranopathy
B Enzymopathy
C Hemoglobinopathy
D Autoimmune disorder
E Bone marrow hypoploasia

25. From the group of children who were eating sweet sappy watermelon two kids developed the signs of poisoning: rapid weakness, dizziness, headache, vomiting, edema, tachycardia, cyanosis of mouth, ears, tips of the fingers cyanosis. High concentration of nitrates was detected. What is the leading mechanism of the pathogenesis of the poisoning in the two children?

A Insufficiency of met-Hb-reductase
B Insufficiency of superoxiddismutase
C Block cytochrome oxidase
D Insufficiency glutathione pyroxidase
E Insufficiency of catalase

26. A patient with hypochromic anemia has hair with split ends and suffers from hair loss. The nails are brittle. Gustatory sensations are affected. What is the mechanism of development of these symptoms?

A. Iron enzymes deficiency
B. Vitamin B12 deficiency
C. Low production of parathyroid hormone
D. Vitamin A deficiency
E. Low production of thyroid hormones

Tests for Self-Control (give correct answers)

1. The scleras and skin of a 20-year-old patient periodically become yellow; the patient feels sick. Diagnosis: Minkowski—Chauffard disease. What is typical of blood investigation in this case?

A. Agranulocytosis.
B. Anulocytosis.
C. Microspherocytosis.
D. Macrocytosis.
E. Thrombocytosis.

2. A 1.5-year-old child was hospitalized with symptoms of nitrate poisoning: cyanosis, dyspnea, convulsions. What form of hemoglobin caused the pathology?

A. Carbohemoglobin.
B. Methemoglobin.
C. Carboxyhemoglobin.
D. Sulfhemoglobin.
E. Oxyhemoglobin.

3. A 3-year-old child was hospitalized with hemoglobinopathy (sickle-cell anemia). What acid

replaced glutaminic acid in the p-chain of HbS?
A. Arginine.
B. Serine.
C. Tyrosine.
D. Phenylalanine.
E. Valine.

4. A patient who has arrived from Tunis has oc-thalassemia with erythrocyte hemolysis and jaundice. Presence of what cells in the blood is typical of this illness?
A. Target cells.
B. Spheroidal erythrocytes.
C. Polychromatophilic erythrocytes.
D. Normocytes.
E. Reticulocytes.

5. A patient is ill with iron deficiency anemia. As a consequence there may develop atrophic and dystrophic processes in the digestive tube (glossitis, gingivitis, caries, esophagitis). What is the cause of such changes associated with this type of anemia?
A. Decreased activity of glycolysis.
B. Increasing activity of transaminase.
C. Increasing activity of proteases.
D. Decreased activity of iron-containing enzymes.
E. Increasing activity of catalase.

Recommended literature:

Basic

1. Simeonova N.K. Pathophysiology/ N.Simeonova.// Kyiv, Ukraine. – 2010. – 280-290 pp.
2. Victor N. Jelski, Svetlana V. Kolesnikova. Handbook Of Pathophysiology Part 2: Pathophysiology of organs and systems. - Donetsk, Ukraine. – 2011. – 3-20 pp.
3. Krishtal N.V. Pathophysiology: textbook/ N.Krishtal et al.// Kyiv: AUS Medicine Publishing, 2017. - 337-346 pp.

Additional

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

Methodological instruction to practical lesson № 18
Module 2. Pathophysiology of organs and systems

Theme: MORPHOLOGICAL PICTURE OF BLOOD AT DIFFERENT TYPES OF ANEMIA

Student should know:

- Typical disorders in the blood system, changes of general volume of blood, anemia, erythrocytosis
- Classification of typical disorders in the system of blood

Student should be able to:

- Analyze causative-consequence relationships, to be able to explain pathological and adaptative-compensatory changes in pathogenesis of typical disorders in the system of blood.
- Apply knowledge of principles and classifications of anemias for the analysis of their signs.
- Apply knowledge of reasons and pathogenesis of anemias for their prophylaxis and treatment.

LIST OF CONTROL QUESTIONS

1. Pathological, degenerative and regenerative forms of red erythrocytes.
2. Pathological forms of erythrocytes specific to hereditary hemolytic anemias. Typical changes of peripheral blood at iron-deficient anemias.
3. Hematological characteristic of B_{12}-deficiency anemias and/or pholic acid deficit.
4. Peculiarities of diagnosis of different types of anemias according to ability of regeneration of red bone marrow, color index.

Regenerative Forms of Erythrocytes

If a patient has a normal type of hemopoiesis *(normoblastic, erythroblastic*), the following forms of erythrocytes relate to the regenerative ones — ***reticulocyte (polychromatophil), normoblast and erythroblast.*** All of them are normal predecessors of mature erythrocytes (normocytes) and are normally located in the bone marrow. It is these forms of erythrocytes that get into the peripheral blood in pathology (reticulocytes are normally present in the peripheral blood in the content of 0.2—2 %).

If a patient has a pathological *(megaloblastic)* type of hemopoiesis with ***megalocytes*** as final products, ***megaloblasts*** (cells of pathologic regeneration) are mature cell predecessors. Reticulocytes are absent in this type of hemopoiesis.

Degenerative Forms of Erythrocytes

In pathological conditions, erythrocytes change their size, form and coloration. They may also contain pathological inclusions. All these cells are degenerative forms of erythrocytes.

A change in size is termed ***anisocytosis***. A normal erythrocyte is called ***normocyte*** and is 7—8 p in diameter, a ***microcyte*** is less than 6.5 p, a ***macrocyte*** is more than 8 p., ***megalocyte*** is a giant erythrocyte sized 10—15 p and more (the final product of megaloblastic hemopoiesis).

A change in form is termed ***poikilocytosis.*** Pathological erythrocytes are diverse — *ovalocyte, spherocyte, sickle-shaped, target cell,* etc. Some anemias manifest themselves through appearance of specific pathologic forms of erythrocytes, which serve as a diagnostic sign.

A change in coloration concerns its intensity and hues. A normal erythrocyte ***(,normochromic***) has a zone of central enlightenment (pallor). It is connected with the normal form of a biconcave disc. The color index equals 1. If an erythrocyte contains a decreased amount of hemoglobin (***hypochromic*** erythrocytes, the color index is less than 1), the zone of central pallor is larger, sometimes only the erythrocyte membrane is visible (***anulocyte)***. If an erythrocyte is enlarged (megalocyte) and its form is changed from a biconcave disc to spherical, the color index exceeds 1 and erythrocyte looks ***hyperchromic.***

The pathological inclusions in erythrocytes are nucleus remainders because blast cells free themselves from the nuclei not by expulsion but by intracellular destruction (karyorrhexis and karyolysis). Jolly's bodies, Cabot's rings and granulosity refer to pathological inclusions.

Blood picture at different types of anemia

Chronic posthemorrhagic anemia:

The quantity of erythrocytes and hemoglobin is decreased as well as the color index (hypochromic anemia). Investigation of the blood smear shows the following changes:

• Appearance of regenerative forms of erythrocytes (reticulocytes), which is a defense reaction, but regenerative forms are not as numerous as in case of acute posthemorrhagic anemia. Single normoblasts may appear.

• Appearance of degenerative forms of erythrocytes — hypochromic erythrocytes, microcytes with anisocytosis and poikilocytosis.

• The ratio of regenerative and degenerative cells content moves in favor of degenerative ones. The reason lies in the fact that the bone marrow is also affected by chronic hypoxia.

Acquired hemolytic anemia:

Acquired hemolytic anemia is erythroblastic according to the type of hemopoiesis, regenerative according to erythropoiesis activation, normo- or hypochromic according to the color index (or pseudohyperchromic due to absorption of hemoglobin on the surface of erythrocytes). Blood smear analysis can show cells of physiologic regeneration (reticulocytes, some normoblasts), degeneratively changed erythrocytes (poikilocytosis, anisocytosis, and fragmented erythrocytes). A great amount of normoblasts and even erythroblasts are observed in newborns with

hemolytic disease. If hemolytic crises are repeated, anemia obtains hyporegenerative or aplastic character.

Hereditary hemolytic anemia:

As in other anemias, the content of erythrocytes and hemoglobin is decreased. Proliferation of the erythrocytic stem cells of the bone marrow is activated but often erythropoiesis is not effective because the nuclear forms of erythrocytes are destroyed in the bone marrow. Nevertheless, reticulocytosis, polychromatophilia and normoblasts may be observed in the peripheral blood. Specific degenerative forms of erythrocytes are detected — microspherocytes in Minkowski—Chauffard disease, sickle-like erythrocytes in corresponding anemia, target cells and erythrocytes with basophilic granules in thalassemia. These cells are the most important in diagnostics.

Iron-deficiency anemia:

The quantity of hemoglobin is always reduced. The quantity of erythrocytes can be lowered or normal, but erythrocytes are always small in size (microcytes) — 5 n instead of 7—8 |i (microcytic anemia). The color index is low — 0.6 and less (up to 0.4). Erythrocytes are hypochromic. The reason lies in a) Hb synthesis decrease, b) Hb content decrease exceeding erythrocyte amount, c) small size of erythrocytes. Hypochromic blood shadows are observed in the blood smear. Anisocytosis and poikilocytosis are also observed. The amount of the regenerative forms of erythrocytes (reticulocytes) depends on the regenerative ability of the erythrocytic stem cells of the bone marrow. Their quantity may be sufficient or decreased. So, iron deficiency anemia is erythroblastic, hypochromic, regenerative or more often hypogenerative anemia.

B_{12}-deficiency anemia:

Blood picture is characterize by the following quantitative signs:

• a significant decrease of the amount of erythrocytes (2—3 ТД and less);
• a decrease of hemoglobin content (70—80 g/1 and less);
• an increase of the color index to exceed 1 (1.2—1.4 and more);
• leukopenia (decreased amount of leukocytes);
• thrombocytopenia (decreased amount of thrombocytes).

The following morphological disorders of the blood cells (signs of degeneration) are detected in a blood smear:

• Erythrocytes are significantly enlarged (megalocytes with the diameter 10— 12 i and more, 20 i has been recorded in some patients).
• Erythrocytes (megalocytes) are hyperchromic, without a zone of central pallor due to their large volume and changed form.
• Poikilocytosis, anisocytosis.
• Pathologic inclusions (nucleus remainders) in megalocytes — Jolly's bodies.
• Cabot's rings and basophilic granules.
• A large quantity of nuclear forms of erythrocytes (megaloblasts).
• Physiologic regeneration cells (reticulocytes) are absent.

• Leukocytes have a large size and a hypersegmented nucleus (right-side nuclear shift in leukoformula).

So, vitamin B_{12} and folate deficiency anemia is megaloblastic and hyperchromic.

Clinical tasks

1). The patient is 49 years old. After injuries related to traffic accidents he is treated in the trauma department for 5 days.

A blood test is the following:

RBC - 2,1x10^12/liter
Hb – 60 g/liter
CI – ?
Rt – 13%
MCV – 83 fl
Serum iron - 15 mkmol/l
Anisocytosis +
Poikilocytosis +
Megalocytes –
Megaloblasts -

Determine the type of anemia according to:

1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes
5. Pathogenesis.

Describe the main causes of this anemia.

2). The patient is 46 years old. He complains of general weakness, dizziness, shortness of breath. Patient suffers from gastritis for last seven years.

A blood test is the following:

RBC - 3,7x10^12/liter
Hb – 72 g/liter
CI – ?
Rt – 1,5%
MCV – 75 fl
Serum iron - 7 mkmol/l
Anisocytosis +++
Poikilocytosis +++
Megalocytes –
Megaloblasts -

Determine the type of anemia according to:

1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes
5. Pathogenesis.

Describe the main causes of this anemia.

3). The patient is 40 years old. He complains of general weakness, shortness of breath, disorders of the gastrointestinal tract (sore mouth, epigastric pain, diarrhea). Tongue is red and cracked.
A blood test is the following:
RBC - 1,7x10^12/liter
Hb – 74 g/liter
CI – ?
Rt – 1%
MCV – 139 fl
Serum iron - 14 mkmol/l
Anisocytosis +++
Poikilocytosis +
Jolly's bodies+
Cabot's rings+
Megalocytes ++
Megaloblasts +++
Determine the type of anemia according to:
1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes
5. Pathogenesis.

Describe the main causes of this anemia.

4). The patient is 37 years old. Has undergone ionizing radiation at a nuclear station. He complains of general weakness, dizziness, shortness of breath.
A blood test is the following:
RBC - 1,04x10^12/liter
Hb – 36 g/liter
CI – ?
Rt – 0,1%
MCV – 92 fl
Serum iron - 15 mkmol/l
Anisocytosis -
Poikilocytosis -
Megalocytes - Megaloblasts –
WBC – 2,3 x10^9/liter 4-9
Platelets - 100 x10^9/liter 180-360
Determine the type of anemia according to:
1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes

5. Pathogenesis.

Describe the main causes of this anemia.

5). The girl is 4 years old. Her skin is pale and yellow. Splenomegaly is present. A blood test is the following:

RBC - 0,9x10^12/liter
Hb – 70 g/liter
CI – ?
Rt – 160%
MCV – 133 fl
Serum iron - 18 mkmol/l
Indirect bilirubin 85 mkmol/l
Anisocytosis +++
Poikilocytosis - spherocytes
Megalocytes - Megaloblasts –

Determine the type of anemia according to:

1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes
5. Pathogenesis.

Describe the main causes of this anemia.

6). The patient is 62 years old. He complains of shortness of breath at rest, cough. He is sick for over 15 years. Lips and nails cyanosis is present. There is no swelling in the legs. Month ago he was treated from the heart failure.

A blood test is the following:

RBC - 6,6x10^12/liter
Hb – 168 g/liter
CI – ?
Rt – 12%
MCV – 94 fl
Serum iron - 23 mkmol/l
Anisocytosis +
Poikilocytosis +
Megalocytes -
Megaloblasts –

Determine the type of anemia according to:

1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes
5. Pathogenesis.

Describe the main causes of this anemia.

7). A blood test is the following:
RBC - 2,9x10^12/liter
Hb – 50 g/liter
CI – ?
Rt – 1,8%
MCV – 64 fl
Serum iron - 40 mkmol/l
Anisocytosis ++
Poikilocytosis +
Megalocytes -
Megaloblasts –
Siderocytes in bone nerrow +++
Determine the type of anemia according to:
1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes
5. Pathogenesis.

Describe the main causes of this anemia.

8). A blood test is the following:
RBC - 2,8x10^12/liter
Hb – 85 g/liter
CI – ?
Rt – 34%
MCV – 74 fl
Serum iron - 35 mkmol/l
Anisocytosis ++
Poikilocytosis ++ microspherocytes
Megalocytes -
Megaloblasts –
Splenomegaly
Indirect bilirubin – 30 mkmol/l
Osmotic resistance of RBC - min. 0,6%, max. 0,2% NaCl
Deficiency of glucose-6-phosphatdehydrogenase in RBC
Determine the type of anemia according to:
1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes
5. Pathogenesis.

Describe the main causes of this anemia.

9). Patient, 19 years old, a student, complains of general weakness, dizziness. About a month took chloramphenicol.
A blood test is the following:
RBC - 1,8x10^12/liter
Hb – 54 g/liter
CI – ?
Rt – 0,1%
MCV – 84 fl
Serum iron - 35 mkmol/l
Anisocytosis -
Poikilocytosis -
Megalocytes -
Megaloblasts –
WBC - 2,2 x 109 / l
Platelets- 94 x 109/ l
Determine the type of anemia according to:
1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes
5. Pathogenesis.

Describe the main causes of this anemia.

10). A blood test is the following:
RBC - 3,3x10^12/liter
Hb – 81 g/liter
CI – ?
Rt – 1,5%
MCV – 68 fl
Serum iron - 8 mkmol/l
Anisocytosis ++
Poikilocytosis ++
Megalocytes -
Megaloblasts –
Osmotic resistance of RBC - min. 0,48, max. 0,32% NaCl
Determine the type of anemia according to:
1. Color index
2. An ability of the bone marrow for red cell regeneration.
3. Type of hemopoiesis
4. Size of erythrocytes
5. Pathogenesis.

Describe the main causes of this anemia.

KROK 1 mcqs_A is correct answer

1. 2 years ago a patient underwent resection of pyloric part of stomach. He complains of weakness, periodical dark shadows beneath his eyes, dyspnea. In blood: Hb - 70 g/l, erythrocytes - 3,0*1012/l, colour index - 0,7. What changes of erythrocytes in blood smears are the most typical for this condition?
   A Microcytes
   B Megalocytes
   C Schizocytes
   D Ovalocytes
   E Macrocytes
2. A 55 y.o. woman consulted a doctor about having continuous cyclic uterine hemorrhages for a year, weakness, dizziness. Examination revealed skin pallor. Hemogram: Hb- 70 g/l, erythrocytes - 3,2*1012/l, color index - 0,6, leukocytes - 6,0*109/l, reticulocytes - 1%; erythrocyte hypochromia. What anemia is it?
   A Chronic posthemorrhagic anemia
   B Hemolytic anemia
   C Aplastic anemia
   D B12-folate-deficiency anemia
   E Iron-deficiency anemia
3. A 56 year old patient came to a hospital with complaints about general weakness, tongue pain and burning, sensation of limb numbness. In the past he underwent resection of stomach. In blood: Hb- 80 g/l; erythrocytes - 2,0*1012/l; colour index - 1,2, leukocytes - 3,5*109/l. What anemia type is it?
   A B12-folate deficient
   B Hemolytic
   C Posthemorrhagi
   D Aplastic
   E Iron-deficient
4. A 25 year old Palestinian woman complains of weakness, dizziness, dyspnea. In anamnesis: periodically exacerbating anemia. In blood: Hb - 60 g/l, erythrocytes - 2,5*1012/l, reticulocytes - 35o/oo, anisocytosis and poikilocytosis of erythrocytes, a lot of target cells and polychromatophils. What type of anemia is it?
   A Thalassemia
   B Sickle-cell anemia
   C Minkowsky-Shauffard disease
   D Addison-Biermer disease
   E Glucose 6-phosphate dehydrogenase-deficient anemia
5. A 15 year old girl has pale skin, glossitis, gingivitis. Blood count: erythrocytes - 3,3*1012/l, hemoglobin - 70 g/l, colour index - 0,5. Examination of blood smear revealed hypochromia, microcytosis, poikilocytosis. What type of anemia is it?
   A Iron-deficient
   B B12-folic acid-deficient
   C Sickle-cell
   D Hemolytic
   E Thalassemia
6. Examination of a 52-year-old female patient has revealed a decrease in the amount of red blood cells and an increase in free hemoglobin in the blood plasma (hemoglobinemia). Color index is 0,85. What type of anemia is being observed in the patient?
   A Acquired hemolytic
   B Hereditary hemolytic
   C Acute hemorrhagic
   D Chronic hemorrhagic

E Anemia due to diminished erythropoiesis

7. A 37-year-old female patient complains of headache, vertigo, troubled sleep, numbness of limbs. For the last 6 years she has been working at the gas-discharge lamp-producing factory in the lead-processing shop. Blood test findings: low hemoglobin and RBC level, serum iron concentration exceeds the norm by several times. Specify the type of anemia:
   A Iron refractory anemia
   B Iron-deficiency anemia
   C Minkowsky-Shauffard disease
   D Hypoplastic anemia
   E Metaplastic anemia
8. Patient 54 year-old, 5th day after surgical operation. Blood count: Erythrocytes 3, 6∗ 1012/l, Hemoglobin95 g/l, Erythrocyte's hemoglobin content(color index) 0,78; Leukocytes 16 ∗ 109/l, Platelets 450 ∗ 109/l Blood picture: anizocytosis, poikilocytosis, reticulocytes-3,8%. What anemia does this patient have?
   A Acute posthemorragic anemia
   B Acquired hemolytic anemia
   C Anemia from iron deficiency
   D Hypoplastic anemia
   E Chronic posthemorragic anemia
9. A 55 y.o. woman consulted a doctor about having continuous cyclic uterine hemorrhages for a year, weakness, dizziness. Examination revealed skin pallor. Hemogram: Hb- 70 g/l, erythrocytes -3, 2 · 1012/l, color index - 0,6, leukocytes- 6, 0·109/l, reticulocytes - 1%; erythrocyte hypochromia. What anemia is it?
   A Chronic posthemorrhagic anemia
   B Hemolytic anemia
   C Aplastianemia
   D B12-folate-deficiency anemia
   E Iron-deficiency anemia
10. A 20 year old patient complains of general weakness, dizziness, quick fatigability. Blood analysis results: Hb- 80g/l. Microscopical examination results: erythrocytes are of modified form. This condition might be caused by:
   A Sickle-cell anemia
   B Hepatocellular jaundice
   C Acute intermittent porphyria
   D Obturative jaundice
   E Addison's disease
11. 2 years ago a patient underwent resection of pyloric part of stomach. He complains of weakness, periodical dark shadows beneath his eyes, dyspnea. In blood: Hb - 70 g/l, erythrocytes - 3, 0 ·1012/l, colour index - 0,7. What changes of erythrocytes in blood smears are the most typical for this condition?
   A Microcytes
   B Megalocytes
   C Schizocytes
   D Ovalocytes
   E Macrocytes
12. A 56 year old patient came to a hospital with complaints about general weakness, tongue pain and burning, sensation of limb numbness. In the past he underwent resection of forestomach. In blood: Hb- 80 g/l; erythrocytes - 2, 0·1012/l; colour index - 1,2, leukocytes - 3, 5 · 109/l. What anemia type is it?
   A B12-folate deficient
   B Hemolytic
   C Posthemorrhagic
   D Aplastic
   E Iron-deficient

13. A 15 year old girl has pale skin, glossitis, gingivitis. Blood count: erythrocytes - 3, 3 cot 1012/l, hemoglobin - 70 g/l, colour index - 0,5. Examination of blood smear revealed hypochromia, microcytosis, poikilocytosis. What type of anemia is it?
A Iron-deficient
B B12-folic acid-deficient
C Sickle-cell
D Hemolytic
E Thalassemia

14. A 25 year old Palestinian woman complains of weakness, dizziness, dyspnea. In anamnesis: periodically exacerbating anemia. In blood: Hb – 60 g/l, erythrocytes - 2, 5 · 1012/l, reticulocytes - 35o/oo, anisocytosis and poikilocytosis of erythrocytes, a lot of target cells and polychromatophils. What type of anemia is it?
A Thalassemia
B Sickle-cell anemia
C Minkowsky-Shauffard disease
D Addison-Biermer disease
E Glucose 6-phosphate dehydrogenase deficient anemia

15. A woman has come to the hospital with complaints of general weakness, dizziness, and dyspnea. Resently she has been taking levomycetin (chloramphenicol) for prevention of enteric infection. Blood test: erythrocytes - 1.9 · 1012/L, hemoglobin - 58 g/L, color index - 0.9, leukocytes - 2.2 G/L, reticulocytes - 0.3%. What type of anemia is it indicative of?
A. Hypoplastic
B. Metaplastic
C. Aplastic
D. Hemolytic
E. Iron-deficiency

Tests for Self-Control (give correct answers)

1. A 36-year-old patient is ill with a respiratory viral infection. He was treated with sulphanilamide drugs. Later hyporegenerative normochromic anemia, leukopenia, thrombocytopenia were found. In the bone marrow the amount of megakaryocytes is decreased. What anemia is it?
A. Posthemorrhagic.
B. Hemolytic.
C. Hypoplastic.
D. Vitamin B12 and folate deficiency.
E. Iron deficiency.

2. Microcythemia and poikilocytosis were found in the patient's blood smear. Of what anemia are these changes characteristic?
A. Microspherocytic.
B. Vitamin B12 and folate deficiency.
C. Hypoplastic.
D. Sickle-cell anemia.
E. Iron deficiency.

3. A patient had stomach resection performed. Later vitamin B12 deficiency anemia developed. What color index is characteristic of this anemia?
A. 0.4.
B. 0.5.
C. 0.8.
D. 1.0.
E. 1.4.

4. A woman complains of headache, giddiness, and dyspnea caused by physical load. During the last 3 years extensive menstrual bleedings were marked. Visual inspection findings: the patient has a normal body type, the skin is pale and dry. Analysis of the blood: hemoglobin — 90 g/1, erythrocytes — 3.7 • 10l2/l, the color index — 0.7, SSE — 20 mm/h, hypochromia of erythrocytes, anisocytosis, poikilocytosis. What type of anemia is it?

A. Megaloblastic.
B. Hemolytic.
C. Acute posthemorrhagic.
D. Vitamin B12 and folate deficiency.
E. Chronic posthemorrhagic.

5. A woman is 6 months pregnant. The amount of erythrocytes and hemoglobin is reduced, the color index is 1.4, there are megalocytes, megaloblasts. What type of anemia is it?

A. Iron deficiency.
B. Vitamin B12 and folate deficiency.
C. Myelotoxic.
D. Aplastic.
E. Metaplastic.

Recommended literature:

Basic

1. Simeonova N.K. Pathophysiology/ N.Simeonova.// Kyiv, Ukraine. – 2010. – 276-290 pp.
2. Victor N. Jelski, Svetlana V. Kolesnikova. Handbook Of Pathophysiology Part 2: Pathophysiology of organs and systems. - Donetsk, Ukraine. – 2011. – 3-20 pp.
3. Krishtal N.V. Pathophysiology: textbook/ N.Krishtal et al.// Kyiv: AUS Medicine Publishing, 2017. - 335-346 pp.

Additional

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

Methodological instruction to practical lesson № 19-20
Module 2. Pathophysiology of organs and systems

Theme: LEUKOCYTOSES, LEUKOPENIAS. LEUKOSES

Student should know:

- Mechanisms of development and reasons of origin of disorders of cellular composition of "white" blood, be able to estimate their clinical consequences;
- Features of tumor transformation of stem cells of bone marrow at acute and chronic leukosis.
- General laws of development of disorders of cellular composition of peripheral blood at acute and chronic leukoses.

Student should be able:

- To estimate the role of genetic anomalies and anomalies of constitution in leukogenesis.
- To characterize the periods of risk in origin of leukoses ("peaks of leukoses") in children; to explain principles of diagnostics of leukoses.
- To analyze the features of etiology, pathogenesis and results of therapy of leukoses in children and adults.
- To estimate advantages of transplantation of bone marrow as the most effective method of treatment of leukoses.

LIST OF CONTROL QUESTIONS

1. Leukocytosis, principles of classification. Reasons and mechanisms of development of reactive leukocytosis. Neutrophilic, eosinophilic, basophilic, lympho- and monocytic leukocytosis. A concept of the nuclear shift of neutrophils, its varieties.
2. Leucopenia, principles of classification. Reasons, mechanisms of development of leukopenias, agranulocytosis (neutropenia). Pathogenesis of basic clinical signs.
3. Acquired and inherited disorders of structure and function of leucocytes. Leukemoid reactions.
4. Hemoblastoses, general characteristic of their basic groups. Leukoses as tumors. Principles of classification of leukoses (acute, chronic; myelo-, lympho-; primary, secondary).
5. Etiology of leukoses: characteristic of leukosogenic factors of physical, chemical, biological nature. Mechanisms of their transforming action on the stem cells of bone marrow. Anomalies of genotype and constitution as factors of risk of origin and development of leukoses. Children "peaks" of leukoses.
6. Typical laws and features of pathogenesis of acute and chronic leukoses: disorder of cellular composition of marrow and peripheral blood; morphological, cytogenetic, cytochemical, immunophenotypic characteristics; systemic disorders in the organism. Progression of leukoses, concept of "blastic crisis". Metastases of leukoses.
7. Principles of diagnostics and treatment of leukoses.

There are five forms of leukocytes — granulocytes (neutrophils, eosinophils, basophiles) and agranulocytes (lymphocytes and monocytes). Formation of leukocytes

Class of leukocytes	Increased	Decreased

(leukopoiesis) is accomplished in the bone marrow and lymph nodes.

All immature granulocytes (myeloblasts, promyelocytes, myelocytes, metamyelocytes, band cells) are located in the bone marrow. All mature leukocytes are divided into three pools. The majority of mature leukocytes are located in tissues. This amount cannot be calculated. They perform their functions in tissues. A small quantity of leukocytes is located in the blood. In their turn, these leukocytes are redistributed into two pools. Half of them are located near the vascular wall (marginal pool). They get into the circulating pool after food intake, muscle or physical overload and nervous excitement (under catecholamine influence) and also under pathological conditions.

Mature leukocytes are partially located in the peripheral blood, and partially in the bone marrow as a reserve.

Leukocytosis is an increase in the total amount of leukocytes in the peripheral blood to more than 9 G/l. Morphological (degenerative) changes of leukocytes may accompany the quantitative ones.

Types

There are several classifications of leukocytosis. *Physiological* (after food intake, physical and emotional load, in pregnancy) and *pathological* (in diseases) — according to its value. *Reactive, redistributive and tumorous* in accordance with pathogenesis. *Neutrophilic, eosinophilic, basophilic, lymphocytosis, monocytosis* are distinguished depending on the type of leukocytes being increased. *Absolute and relative* (it refers to each form of leukocytosis).

Etiology

Etiological factors are exogenous and endogenous as well as *physical, chemical and biological.* Ionizing radiation causes redistributive leukocytosis during the first day of radiation disease. Toxic chemicals (of exogenous and more often endogenous origin from a ruined tissue) cause absolute reactive leukocytosis. Infection is the most potent activator of leukopoiesis and phagocytosis, which has a protective value.

Neutrophils	Acute inflammation (abscess, sepsis,…); Acute hemolysis; Miocardial infaction; Endogenous intoxication,…	Viral infections; Toxic damage by some drugs; Aplastic conditions; Ketoacidosis; Starvation,…
Eosinophils	Allergic reactions type I; Helminths; Chronic myeloleucosis; Some infectious diseases,…	Pancytopenia; Increased production of corticosteroids (stress, Cushing's syndrome); Acute leukemias;
Basophils	Allergic reactions type I; Autoimmune diseases; Hemolytic anemias; Chronic leukemias; Primary policytemia,…	–
Lymphocytes	Acute infective diseases (viral); Some chronic diseases (tuberculosis); Chronic lympholeucosis,…	Immune deficiency; Viral infections (AIDS, Herpes); Cytostatic drugs; Rheumatic diseases; Stress,…
Monocytes	Acute infective diseases (infective mononucleosis, rubella, …); Some rheumatic diseases; Malaria,…	Rare condition – some types of leucosis.

Fig. 6 Changes in amount of WBC

Pathogenesis

There are the following principal mechanisms of leukocytosis pathogenesis.

• Reactive activation of leukopoiesis, which is more often partial, resulting in hyperproduction of a certain type of leukocytes. Leukocytosis is absolute. It is caused by an increased production of humoral activators (colony-stimulating factor, etc.). Leukocytosis may be accompanied by suppression of leukocyte maturation in the bone marrow and, sometimes, by production of pathologic forms.

• Tumorous hyperplasia (neoplasia) of the leukopoietic tissue results in production of pathologic leukocytes (leukemia).
• Acceleration of leukocyte release from the bone marrow into the blood may result from an increased permeability of the bone marrow barrier.
• Redistribution of leukocytes from the marginal pool into the circulating one causes relative leukocytosis.

Different types of leukocytosis have peculiarities in their etiology, pathogenesis and significance.

Blood Picture

Blood picture in leukocytosis is estimated by the total number of leukocytes and leukoformula. It shows whether the quantitative changes of different forms of leukocytes are absolute or relative. Young forms of neutrophilic leukocytes appear in the peripheral blood — the nuclear shift to the left. Degenerative changes in leukocytes are registered in the course of blood smear investigation.

Ultimately, in most cases leukocytosis has a positive value. It is a sign of activated reactivity. Reactive hyperplasia of the leukocytic tissue leads to organism resistance increase. The most evident protective role of leukocytosis is seen in inflammation and immune response. Neutrophilic leukocytosis and monocytosis have parallel participation in phagocytosis. As it has been said, eosinophils play a compensatory role in allergic reactions. Lymphocytes play a decisive role in immune response.

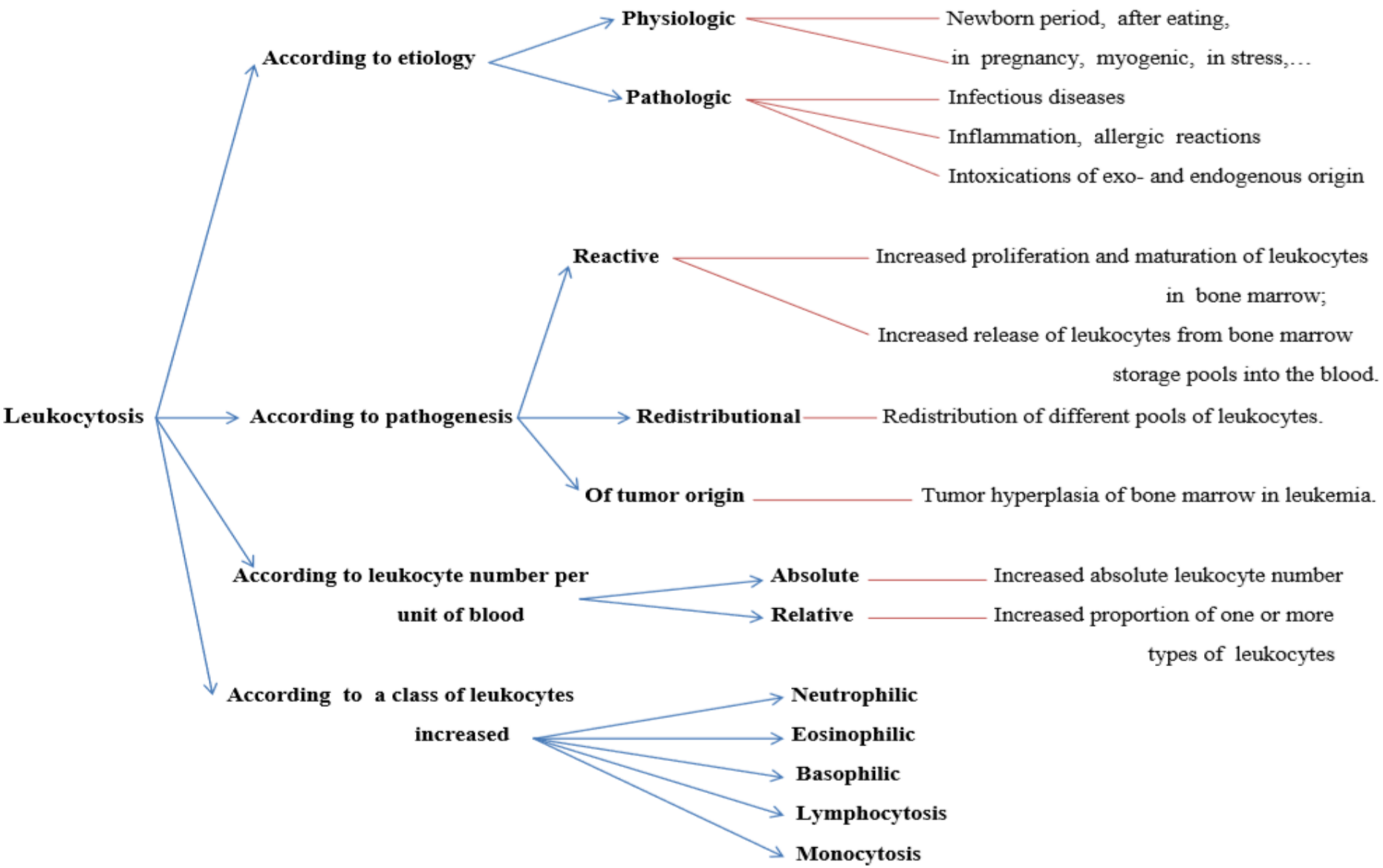

Fig 7. Leukocytosis

Leukopenia is a decrease of the total quantity of leukocytes in the peripheral blood below 4 G/l.

Types

There are several classifications of leukopenia. Acquired and genetically determined (hereditary) leukopenia is distinguished depending on the participation of genetic mechanisms. Neutropenia, eosinopenia, lymphopenia and monocytopenia are distinguished depending on the type of leukocytes being decreased. Besides, leukopenia may be absolute and relative.

Etiology

Etiological factors of leukopenia are those of external and internal media, which lead to a decreased formation of leukocytes in the bone marrow and lymph nodes, their increased destruction or redistribution.

Etiological factors are divided into:

• physical (ionizing radiation);

• chemical:

•• poisons, which have a leukodepressive quality;

•• medicines (aspirin, amidopyrine, sulfanilamides, barbiturates, cytostatics and glucocorticoid hormonal preparations);

•• vitamin B12 and folic acid deficiency;

• biological:

•• infectious (severe infections, for example, typhus, viruses of influenza, measles, rickettsia toxin, miliary tuberculosis agent);

•• immune (the effect of antileukocyte antibodies);

•• hormonal (stress, redistributive leukopenia);

•• genetic (mutations).

Pathogenesis

There are some pathogenetic varieties of leukopenia. They are:

1. Decreased leukocyte production in the hemopoietic tissue.
2. Increased leukocyte destruction in the blood and hemopoietic tissue.
3. Excessive loss of leukocytes.
4. Redistribution of leukocytes in the vessels.
5. Decelerated leukocyte release from the bone marrow.

The hematologic manifestations of leukopenia consist in a decrease of the total quantity of leukocytes or only of one form of them. The main consequence of leukopenia at the level of the whole organism is organism resistance decrease caused by reduction of phagocytic activity and anti body formation. Immunological and

inflammatory defense reactions get reduced. Immunodeficiency is an example of genetically determined reduction of leukocyte quantity and functional ability. Such patients suffer from infectious and oncological diseases, especially in hereditary neutropenia and T- and B-lymphocyte deficiency. An example of severe areactivity is AIDS. Leukopenia always has a negative value.

Clinical tasks

№	leukocytes	Basophils 0-1	Eosinophils 1-5	neutrophil			Lymphocytes 20-40	Monocytes 2-8
				J 0-1	B 1-5	S 45-65		
1.	**15***10^9/л	**3**	**2**	**4**	**10**	**69**	**10**	**2**
2	**18***10^9/л	**2**	**2**	**5**	**8**	**69**	**12**	**2**
3	**14***10^9/л	**0**	**1**	**0**	**1**	**42**	**35**	**21**
4	**16***10^9/л	**0**	**32**	**0**	**1**	**50**	**14**	**3**
5	**4***10^9/л	**0**	**3**	**0**	**2**	**79**	**12**	**4**
6	**2,1***10^9/л	**0**	**0**	**0**	**0**	**39**	**55**	**6**
7	**0,3***10^9/л	**0**	**0**	**0**	**0**	**5**	**85**	**10**
8	**12***10^9/л	**1**	**0**	**3**	**12**	**65**	**16**	**3**
9	**10***10^9/л	**1**	**9**	**0**	**4**	**56**	**26**	**4**
10	**15***10^9/л	**0**	**0**	**4**	**10**	**68**	**15**	**3**
11	**21***10^9/л	**2**	**0**	**2**	**12**	**75**	**8**	**1**
12	**25***10^9/л	**3**	**0**	**6**	**17**	**67**	**5**	**2**
13	**1***10^9/л	**0**	**0**	**0**	**1**	**49**	**45**	**5**
14	**9***10^9/л	**1**	**0**	**0**	**1**	**79**	**17**	**2**
15	**14***10^9/л	**0**	**0**	**0**	**2**	**41**	**45**	**12**

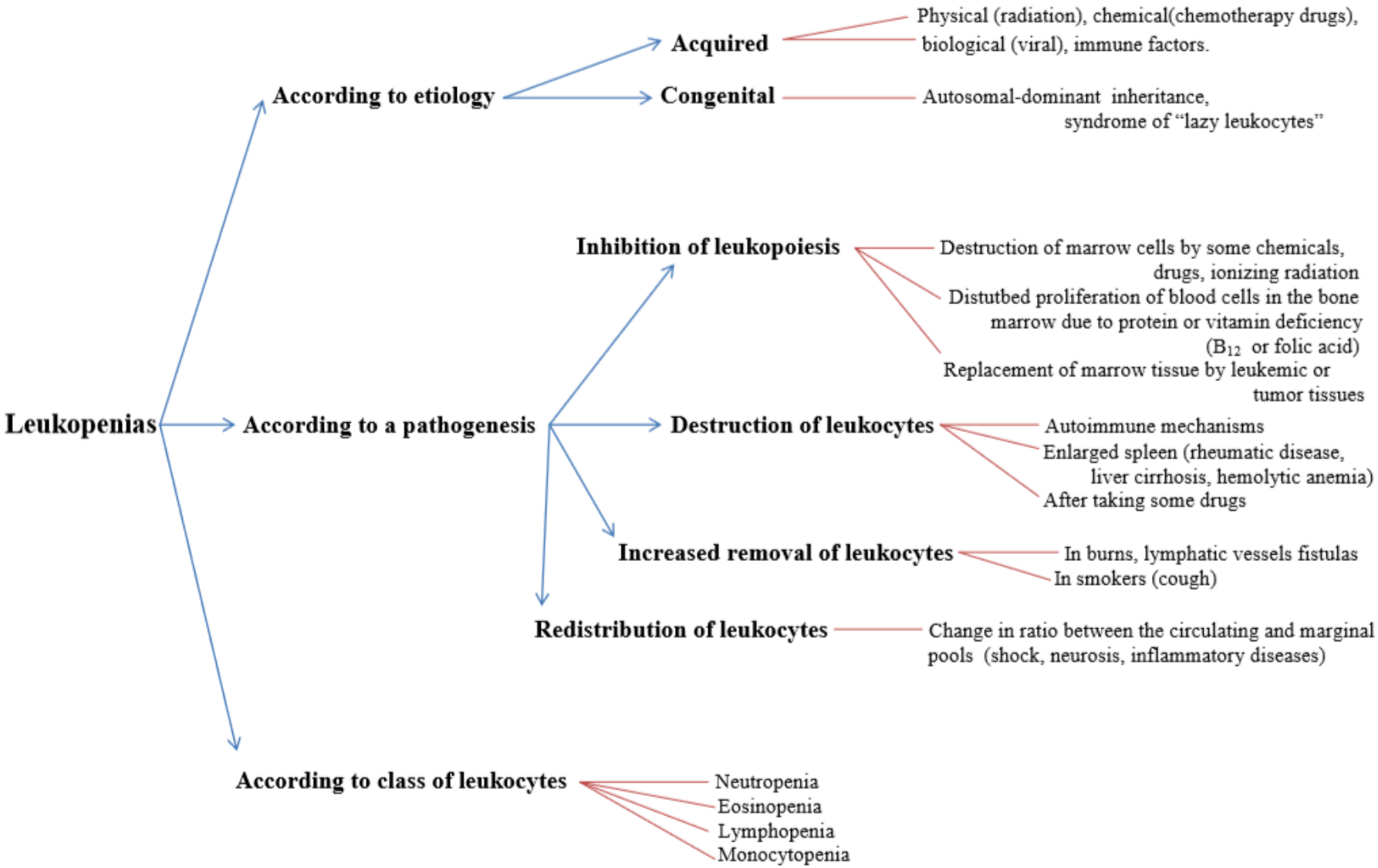

Fig. 8 Leukopenias

Leukemoid Reaction

Leukemoid reaction is an acute increase of immature forms of leukocytes in the peripheral blood. It is observed in patients with instable hemopoiesis in response to acute infections (sepsis) and acute erythrocyte hemolysis. The blood picture resembles leukemia but differs from it by etiology, pathogenesis and significance. The cause is often known (it is always infection) contrary to leukemia. The pathogenesis is different as well — it is hyperreactive but not neoplastic hyperplasia of the leukopoietic tissue. Leukemoid reaction is temporary, reversible and does not turn into leukemia.
There are two types of leukemoid reaction — myeloid and lymphoid depending on the type of cells, which underwent proliferation.

Leukemia is a pathology of the hemopoietic tissue of neoplastic nature.

Classification of leukemia is based on such morphological aspects.

• Predominance of specific forms of leukocytes in the leukoformula. Neoplastic transformation and growth of a single lineage of the bone marrow or lymphoid tissue (erythroid, myeloid, lymphoid, monocytic, megakaryocyte) underlies the classification.

• The point of the complete stop of hemopoietic cell differentiation at a certain intermediate stage, i.e. the level of differentiation.

Leukemia is divided into acute and chronic.

Acute leukemia is subdivided into myeloblastic, lymphoblastic, monoblastic, megakaryoblastic, nondifferentiated forms and acute erythromyelosis. The substrate of tumor growth is the bone marrow blast cells of the I—IV classes (or precursors of lymphocytes) that proliferate and lose their ability to differentiate. The nondifferentiated form originates from cells of the II and III classes, which are not identified morphologically.

Chronic leukemia is divided into myelocytic, lymphocytic, monocytic, megakaryocyte and chronic erythromyelosis. Neoplastic transformation occurs in hemopoietic cells of the II—IV classes but they mature up to cells of the V and VI classes, which are determined in the peripheral blood. Chronic lympholeukemia is a lymphoproliferative process.

Etiology

Etiological factors, which cause leukemia, are the same as those of neoplasia. All of them are mutagens (cancerogens). They are divided into physical (ionizing radiation), chemical (cancerogens), biological (DNA- and RNA-containing viruses and genetic anomalies).

Pathogenesis

In leukemia, the neoplastic process develops in the hemopoietic tissue. As in any other type of neoplasia, leukemia pathogenesis proceeds in three stages — neoplastic (leukemic) transformation, promotion, and progression. The first two are preclinical, the third is a terminal stage with clinical manifestations.

Peculiarity of a neoplasm in the hemopoietic tissue lies in the fact that solid tumors are not formed in the bone marrow. Malignant cells (leukocyte predecessors) are mobile, leave the bone marrow and appear in the peripheral blood immediately after the process starts. They are found and can be calculated in the patient's blood smear at the beginning of the disease. According to peripheral blood investigation, two stages of leukemic pathogenesis are distinguished - monoclonal and polyclonal.

Clinical manifestations are identical in all types of leukemia. They are fatigue, weakness, fever, night sweats, decrease in weight, exhaustion of the organism. Several pathophysiological syndromes determine the manifestations. They are *anemic, hemorrhage and DIC syndromes, immunological insufficiency, some extramedullary syndromes* together with hematological syndrome, which is different in various types of leukemia. Acute leukemia leads to death of the patient in several weeks. Cancerous cachexia and secondary infection are the reasons for death.

Clinical tasks

1.The following laboratory data of blood had been obtained in the patient:
WBC – 11 . 109/л Eosinophils – 0 %
Basophils – 0% Neutrophils: juvenile – 0%
Banded – 0% Segmented – 29%
Lymphocytes – 9% Monocytes – 1%
Neutrophils with toxic punctuate inclusions –
absent
Blasts undifferentiated forms –
absent
Erythroblasts – absent
Lymphoblasts – absent
Botkin-Gumprecht shadows – absent
Myeloblasts – 60
Promyelocytes – 1
Diagnosis:

2. The following laboratory data of blood had been obtained in the patient:
WBC – 75 . 109/л Eosinophils – 5%
Basophils – 7% Neutrophils: juvenile – – 20%
Banded– 22% Segmented – 18%
Lymphocytes – 2% Monocytes – 1%
Myelocytes – 10%
Neutrophils with toxic punctuate inclusions –
absent
Blasts undifferentiated forms –
absent
Erythroblasts – absent
Lymphoblasts – absent

Botkin-Gumprecht shadows – absent
Myeloblasts – 5
Promyelocytes– 10
Diagnosis:

3. The following laboratory data of blood had been obtained in the patient:
WBC – 12 . 109/л Eosinophils – 0 %
Basophils– 0% Neutrophils: juvenile – 0%
Banded– 1% Segmented – 20%
Lymphocytes – 40% Monocytes– 1%
Neutrophils with toxic punctuate inclusions –
absent
Blasts undifferentiated forms –
absent
Erythroblasts – absent
Lymphoblasts – 38%
Botkin-Gumprecht shadows – absent
Myeloblasts – absent
Promyelocytes – absent
Diagnosis:

4. The following laboratory data of blood had been obtained in the patient:
WBC – 320 . 109/л Eosinophils – 0 %
Basophils – 0% Neutrophils: juvenile – 0%
Banded – 3% Segmented – 10%
Lymphocytes – 65% Monocytes – 2%
Neutrophils with toxic punctuate inclusions –
absent
Blasts undifferentiated forms –
absent
Erythroblasts – absent
Lymphoblasts – 20%
Botkin-Gumprecht shadows +
Myeloblasts – absent
Promyelocytes – absent
Diagnosis:

5. The following laboratory data of blood had been obtained in the patient:
WBC – 9,4 . 109/л Eosinophils – 0 %
Basophils – 0% Neutrophils: juvenile – 0%
Banded – 0% Segmented – 5%
Lymphocytes – 8% Monocytes – 2%
Neutrophils with toxic punctuate inclusions +
Blasts undifferentiated forms – 85%
Erythroblasts – absent

Lymphoblasts – absent
Botkin-Gumprecht shadows – absent
Myeloblasts– absent
Promyelocytes– absent
Diagnosis:

6. The following laboratory data of blood had been obtained in the patient:
WBC – 7. 1012/л
Haemoglobin – 189 г/л Leukocytes – 15 . 109/л
Eosinophils – 5% Basophils– 5%
Neutrophils: juvenile – 6% Banded – 14%
Segmented – 48 % Lymphocytes – 16%
Monocytes – 2% Myelocytes – 2%
Neutrophils with toxic punctuate inclusions –
absent
Blasts undifferentiated forms – absent
Erythroblasts – 2%
Lymphoblasts – absent
Botkin-Gumprecht shadows – absent
Myeloblasts– absent
Promyelocytes – 2%
Diagnosis:

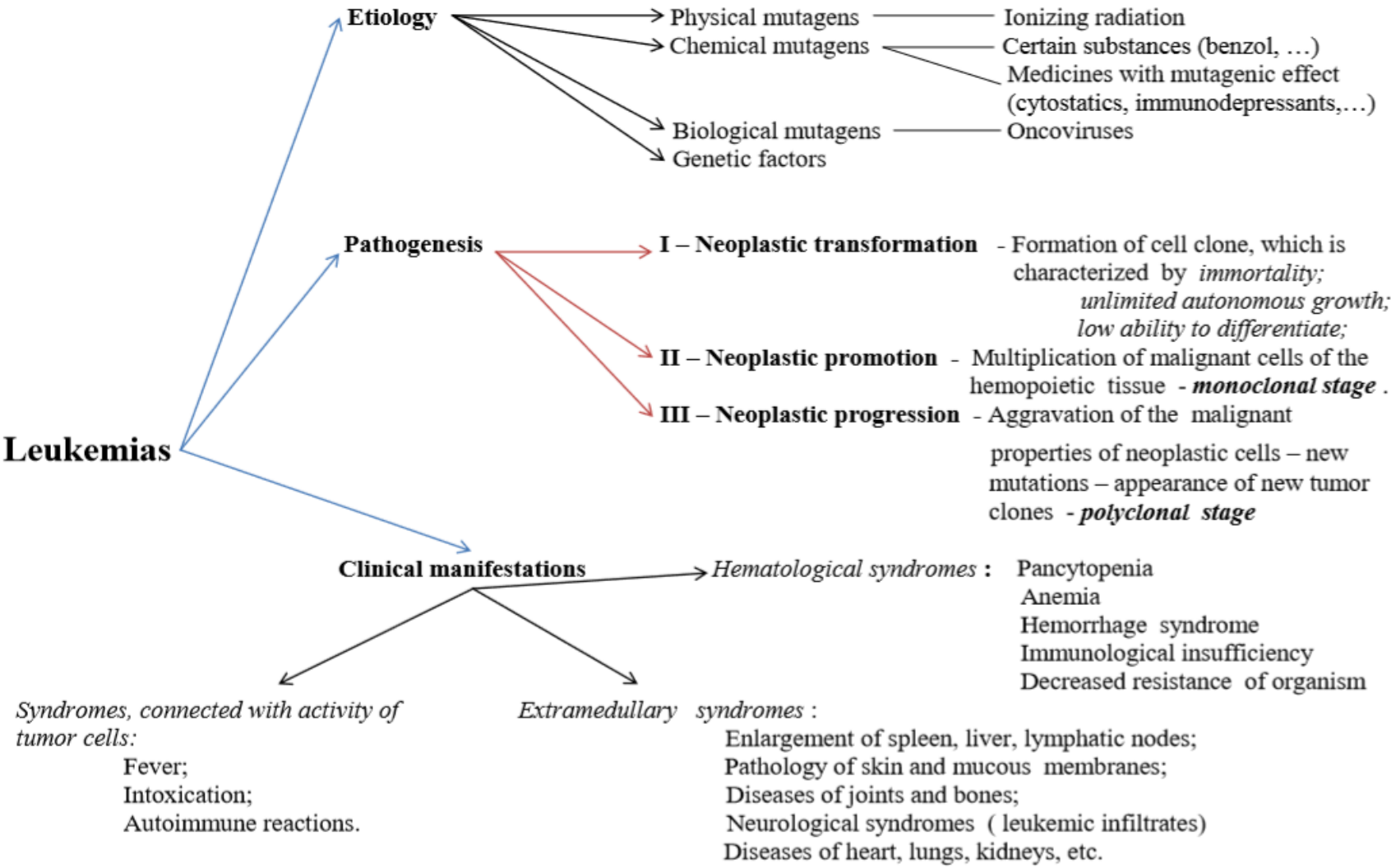

Fig. 9. Leukemias

KROK 1_mcqs_ A is correct answer:

1. In result of the damage of one of the Atomic Power Plant reacttor the run-out of radioelements happened. People in the increased radiation zone were radiated with approximately 250-300 r. They were immediately hospitalized. What changes in the blood count would be typical?
A Lymphopenia
B Leukopenia
C Anemia
D Thrombopenia
E Neutropenia
2. Having helped to eliminate consequences of a failure at a nuclear power plant, a worker got an irradiation doze of 500 roentgen. He complains of headache, nausea, dizziness. What changes in leukocytes quantity can be expected 10 hours after irradiation?
A Neutrophilic leukocytosis
B Lymphocytosis
C Leukopenia
D Agranulocytosis
E Leukemia
3. 24 hours after appendectomy blood of a patient presents neutrophilic leukocytosis with regenerative shift. What is the most probable mechanism of leukocytosis development?
A Amplification of leukopoiesis
B Redistribution of leukocytes in the organism
C Decelerated leukocyte destruction
D Deceleratieemigration of leukocytes to the tissues
E Amplification of leukopoiesis and decelerated emigration of leukocytes to the tissues
4. Two hours after an exam a student had a blood count done and it was revealed that he had leukocytosis without significant leukogram modifications. What is the most probable mechanism of leukocytosis development?
A Redistribution of leukocytes in the organism
B Leukopoiesis intensification
C Deceleration of leukocyte lysis
D Deceleration of leukocyte migration to the tissues
E Leukopoiesis intensification and deceleration of leukocyte lysis
5. Examination of a patient admitted to the surgical department with symptoms of acute appendicitis revealed the following changes in the white blood cells: the total count of leukocytes is 16*109/l. Leukocyte formula: basophils - 0, eosinophils - 2%, juvenile forms - 2%, stabnuclear - 8%, segmentonuclear - 59%, lymphocytes - 25%, monocytes- 4%. The described changes can be classified as:
A Neutrophiliwith regenerative left shift
B Neutrophilia with right shift
C Neutrophilia with degenerative left shift
D Neutrophilic leukemoireaction
E Neutrophilia with hyperregenerative left shift
6. A 47 year old man with myocardium infarction was admitted to the cardiological department. What changes of cellular composition of peripheral blood are induced by necrotic changes in the myocardium?
A Neutrophilic leukocytosis B Monocytosis C Eosinophilileukocytosis D Thrombocytopenia E Lymphopenia
A 5 year old child is ill with measles. Blood analysis revealed increase of total number of leukocytes up to

13*109/l. Leukogram: basophils - 0, eosinophils - 1, myelocytes - 0, juvenile neutrophils - 0, band neutrophils - 2, segmented neutrophils - 41, lymphocytes - 28, monocytes - 28. Name this phenomenon:
A Monocytosis
B Agranulocytosis
C Lymphocytosis
D Eosinopenia
E Neutropenia
7. Two hours after an exam a student had a blood count done and it was revealed that he had leukocytosis without significant leukogram modifications. What is the most probable mechanism of leukocytosis development?
A Redistribution of leukocytes in theorganism
B Leukopoiesis intensification
C Deceleration of leukocyte lysis
D Deceleration of leukocyte migration to the tissues
E Leukopoiesis intensification and deceleration of leukocyte lysis
8. Parents of a 3 year old child have been giving him antibiotics with purpose of preventing enteric infections for a longtime. A month later the child's condition changed for the worse. Blood examination revealed apparent leukopenia and granulocytopenia. What is the most probable mechanism of blood changes?
A Myelotoxic
B Autoimmune
C Redistributive
D Age-specific
E Hemolytic
9 A 26 year old man is in the torpid shock phase as a result of a car accident. In blood: 3, 2 · 109/l. What is the leading mechanism of leukopenia development?
A Redistribution of leukocytes in bloodstream
B Leikopoiesis inhibition
C Disturbed going out of mature leukocytes from the marrow into the blood
D Lysis of leukocytes in the blood-forming organs
E Intensified elimination of leukocytes from the organism
10. In allergic diseases, a dramaic increase in basophilic leukocyte number in patients' blood is observed. This phenomenon is due to the following basophil function:
A Participation of heparin and histamine in metabolism
B Phagocytosis of microorganisms and small particles
C Immunoglobulin synthesis
D Phagocytosis of immune complexes
E Participation in blood clotting
11. Examination of a patient 24 hours after appendectomy revealed neutrophilic leukocytosis with a regenerative shift. What is the most likely mechanism of leukocytosis development?
A Intensification of leukopoiesis
B Intensification of leukopoiesis and deceleration of leukocyte migration to the tissues
C Deceleration of leukocyte breakdown
D Redistribution of the leukocytes in the organism
E Deceleration of leukocyte migration to the tissues
12. Two hours after an exam a student had a blood count done and it was revealed that he had leukocytosis without significant leukogram modifications. What is the most

probable mechanism of leukocytosis development?
A Redistribution of leukocytes in the organism
B Leukopoiesis intensification
C Deceleration of leukocyte lysis
D Deceleration of leukocyte migration to the tissues
E Leukopoiesis intensification and deceleration of leukocyte lysis
13. A child is pale, pastose, muscular tissue is bad developed, lymph nodes are enlarged. He often suffers from angina and pharyngitis, blood has signs of lymphocytosis. The child is also predisposed to autoallergic diseases. What type of diathesis can be presumed in this case?
A Lymphohypoplastic
B Exudative
C Gouty
D Asthenic
E Hemorrhagic
14. As a result of a road accident a 26-year-old man is in the torpid phase of shock. Blood count: leukocytes - 3, 2 · 109/l. What is the leading mechanism of leukopenia development?
A Leukocyte redistribution in the bloodstream
B Leukopoiesis inhibition
C Faulty release of mature leukocytes from the bone marrow into the blood
D Leukocyte destruction in the hematopietic organs
E Increased excretion of the leukocytes from the organism
15. A 23 y.o. patient complains of weakness, temperature rise up to 38-40oC. Objectively: liver and spleen are enlarged. Hemogram: Hb- 100 g/l, erythrocytes - 2,9*1012/l, leukocytes - 4,4*109/l, thrombocytes – 48*109/l, segmentonuclear neutrophils - 17%, lymphocytes - 15%, blast cells - 68%. All cytochemical reactions are negative. Make a hematological conclusion:
A Undifferentiated leukosis
B Chronic myeloleukosis
C Acute myeloblastileukosis
D Acute lymphoblastic leukosis
E Acute erythromyelosis
16. Parents of a 3 year old child have been giving him antibiotics with purpose of preventing enteric infections for a long time. A month later the child's condition changed for the worse. Blood examination revealed apparent leukopenia and granulocytopenia. What is the most probable mechanism of blood changes?
A Myelotoxic
B Autoimmune
C Redistributive
D Age-specific
E Hemolytic
17. A 23 y.o. patient complains of weakness, temperature rise up to 38 −400C. Objectively: liver and spleenare enlarged. Hemogram: Hb-100 g/l,erythrocytes - 2, 9 · 1012/l, leukocytes -4, 4 · 109/l, thrombocytes - 48 · 109/l, segmentonuclear neutrophils - 17%,lymphocytes - 15%, blast cells - 68%.All cytochemical reactions are negative. Make a hematological conclusion:
A Undifferentiated leukosis
B Chronic myeloleukosis
C Acute myeloblastileukosis
D Acute lymphoblastic leukosis
E Acute erythromyelosis
18. Autopsy of the patient revealed bone marrow hyperplasia of tubular and flat bones (pyoid marrow), splenomegaly (6 kg) and hepatomegaly (5 kg),
A Hodgkin’s disease

B Chronic lymphocytic leukemia
C Multiple myeloma
D Polycythemia vera
E Chronic myelogenous leukemia

19. Autopsy of a dead patient revealed bone marrow hyperplasia of tubular and flat bones (pyoid marrow), splenomegaly (6 kg) and hepatomegaly (5 kg), enlargement of all lymph node groups. What disease are the identified changes typical for?
A Chronic myelogenous leukemia
B Chronic lymphocytic leukemia
C Multiple myeloma
D Polycythemia vera
E Hodgkin's disease

20. A 59-year-old woman has been hospitalized in a surgical ward due to exacerbation of chronic osteomyelitis of the left shin. Blood test: leukocytes- 15, 0 · 10^9/l. Leukogram: myelocytes- 0%,metamyelocytes- 8%,stabneutrophils-28%,segmented neutrophils-32%,lymphocytes-29%, monocytes-3%.Such blood count would be called:
A. Regenerative left shift
B. Right shift
C. Hyperregenerative left shift
D. Degenerative left shift
E. Regenerative-degenerative left shift

21. Cellular composition of exudate largely depends on the etiological factor of inflammation. What leukocytes are the first to be involved in the focus of inflammation caused by pyogenic bacteria?
A. Neutrophil granulocytes
B. Monocytes
C. Myelocytes
D. Eosinophilic granulocytes
E. Basophils

22. A patient is 20years old, an athlete. He addressed a doctor with complaints of fatigue, fever up to38oC - 40oC. Objectively: the liver and spleen are enlarged, lymph nodes on palpation are slightly enlarged, dense, painless .Blood test:Hb-100g/l; erythrocytes- 2, 9 · 10^{12}/l; leukocytes- 4, 4 · 10^9/l. Leukogram:68% of blast cells. Cytochemical investigation of blast cells revealed negative reactions to glycogen, peroxidase, non-specific esterase, lipids. Name this disease:
A. Acute undifferentiated leukemia
B. Acute myeloid leukemia
C. Acute monoblastic leukemia
D. Acute lymphoblastic leukemia
E. Acute megakaryoblastic leukemia

23. A 7-year-old boy died of acute posthemorrhagic anemia caused by profuse hemorrhage in the gastrointestinal tract. Postmortem study revealed the following: macroscopically there were acutely enlarged various groups of the lymph nodes, thymomegaly, hepatosplenomegaly, and bright red bone marrow; microscopically there was hypercellular bone marrow with monomorphic infiltrations composed of blasts and diffuse-focal tumor infiltrations in the liver, spleen, lymph nodes, brain substance and tunics. Make the diagnosis:
A. Acute lymphoblastic leukemia
B. Acute myeloblastic leukemia
C. Acute undifferentiated leukemia
D. Acute monoblastic leukemia
E. Acute plasmablastic leukemia

24. A 54-year-old man complains of general weakness, frequent colds, and bruises constantly appearing on his body. Blood test: erythrocytes - 2.5 · 1012/L; Hb- 80 g/L; color index - 0.9; reticulocytes - absent; platelets - 50 · 109/L; leukocytes - 58 · 109/L;

leukogram: basocytes - 5%, eosinophils - 15%, myeloblasts - 6%, myelocytes - 10%, juvenile - 18%, stab neutrophils - 26%, segmented neutrophils - 10%, lymphocytes - 8%, monocytes - 2%, ESR - 40 mm/hour. What hematologic conclusion can be made?

A. Chronic myelogenous leukemia
B. Leukemoid response
C. Myeloblastic leukemia
D. Chronic lymphocytic leukemia
E. Basophilic eosinophilic leukocytosis

25. 24 hours after an appendectomy the patient's blood test shows neutrophilic leukocytosis with a regenerative shift. What is the most likely mechanism of absolute leukocytosis development in the patient's peripheral blood?

A. Intensification of leukopoiesis
B. Leukocyte redistribution
C. Decreased leukocyte disintegration
D. Deceleration of leukocyte migration to the tissues
E. Immunity activation

26. A patient presents with enlarged cervical lymph nodes. Other lymph nodes and internal organs are without changes. Peripheral blood test results are normal. Histological examination of biopsy material taken from the cervical lymph node shows smoothed-out pattern, absent follicles, homogeneous cell composition represented by lymphoblasts. The cells penetrate into the lymph node capsule. What diagnosis can be made?

A. Lymphoblastic leukemia
B. Myeloblastic leukemia
C. Erythroblastic leukemia
D. Sezary disease
E. Burkitt lymphoma

27. Hematologic study shows the following pattern: erythrocytes - 2, 8 · 1012/L, Hb - 80 g/L, color index - 0.85, reticulocytes - 0,1%, platelets - 160 thousand per microliter, leukocytes - 60 · 109/L. Basocytes - 2%, eosinophils - 8%, promyelocytes - 5%, myelocytes - 5%, juvenile - 16%, stab neutrophils - 20%, segmented neutrophils - 34%, lymphocytes - 5%, monocytes - 5%. This clinical presentation indicates the following blood pathology:

A. Chronic myeloleukemia
B. Acute myeloleukemia
C. Hypoplastic anemia
D. Undifferentiated leukemia
E. Hemolytic anemia

28. A patient operated on complicated appendicitis has the following changes of lood count: erythrocytes - 4, 0 · 1012*/l*,Hb - 120 g/l, color index - 0,9, leukocytes- 18 · 109*/l*, basophils - 0, eosinophils- 0, myelocytes - 0, juvenile - 0,stab neutrophils - 20, segmentonuclea neutrophils - 53, lymphocytes - 21,monocytes - 5. How is such nuclear shift of leukocytic formula called?

A. Degenerative left shift
B. Right shift
C. Regenerative left shift
D. Hyperregenerative
E. Regeneratively-degenerative

Tests for Self-Control (give correct answer)

1. Testing of the peripheral blood of a 42-year-old patient showed such results: hemoglobin — 80 g/1, erythrocytes — 3.2 T/l, leukocytes —

25 G/l; the leukocytic formula: basophiles — 5 %, eosinophils — 9 %, myeloblasts — 3 %, promyelocytes — 8 %; neutrophils: myelocytes -11%, metamyelocytes — 22 %, band — 17 %, segmented — 19 %, lymphocytes — 3 %, monocytes — 3 %. What kind of blood pathology is this?
A. Leukocytosis.
B. Acute myeloblasts leukemia.
C. Chronic myeloleukemia.
D. Lymphoid leukemia.
E. Erythromyeloleukemia.

2. Blood examination showed leukocytosis (50 G/l), lymphocytosis (80 %), smudge cells, anemia. What disease can it be?
A. Inflammation.
B. Chronic lympholeukemia.
C. Chronic myeloleukemia.
D. Acute myeloleukemia.
E. Tuberculosis.

Recommended literature:

Basic

1. Simeonova N.K. Pathophysiology/ N.Simeonova.// Kyiv, Ukraine. – 2010. – 297-320pp.
2. Victor N. Jelski, Svetlana V. Kolesnikova. Handbook Of Pathophysiology Part 2: Pathophysiology of organs and systems. - Donetsk, Ukraine. – 2011. – 23-35 pp.
3. Krishtal N.V. Pathophysiology: textbook/ N.Krishtal et al.// Kyiv: AUS Medicine Publishing, 2017. - 347-357 pp.

Additional

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

Methodological instruction to practical lesson № 21
Module 2. Pathophysiology of organs and systems

Theme 21: DISORDERS OF HEMOSTATIC SYSTEM

Student should know:

- Typical disorders in the system of hemostasis.
- Reasons of origin and mechanisms of development of disorders of vessel-platelet chain of hemostasis.

Student should be able to:

- To analyze general laws of origin, development and completion of the states of hypo- and hypercoagulation.
- To explain the role disseminated blood coagulation, analyze reasons of origin and mechanisms of its development, characterize typical clinical signs depending on clinical course.

LIST OF CONTROL QUESTIONS

1. General characteristic of typical disorders in the hemostatic system.
2. Hemorragic disorders in the hemostatic system. Insufficiency of vasculat-thrombocytic hemostasis. Angiopathies: types, reasons, mechanisms of development, pathogenesis of basic clinical signs. Thrombocytopenias: etiology, pathogenesis, mechanisms of disorders hemostasis. Trombocytopathias. Mechanisms of disorder of adhesion, aggregation of thrombocytes, elaborating of thrombocytic granules.
3. Disorder of coagulative hemostasis. Reasons of decline of activity of the system of blood coagulation and increase of activity of the anticoagulative and fibrinolytic systems. Basic signs of disorders of the separate stages of blood coagulation, their etiology and pathogenesis.
4. Trombophylic states: thrombosis, disseminated blood coagulation, localized intravessel blood coagulation. Principles of classification of disseminated blood coagulation (according to the course – acute, subacute, chronic; according to the starting mechanism of coagulation), etiology,pathogenesis. A role in pathology.

Hemostasis pathology is a disorder of the maintenance of the liquid state of the blood and its coagulation in response to vessel injury.

The hemostasis system has many components. These are platelets and other blood cells, vessel walls, extravascular tissue, BAS, vascular and tissue factors (extrinsic pathway), plasma factors of blood clotting (intrinsic pathway), which are closely associated with the kallikrein-kinin system.

There are two mechanisms of hemostasis:

• coagulative hemostasis;

• thrombocytovascular hemostasis.

Coagulative Hemostasis

The coagulative hemostatic system consists of blood proteins and is subdivided into three groups of mechanisms.

1. System of blood coagulation consists of blood proteins - procoagulants. Blood

coagulation proceeds in three stages (formation of the prothrombinase complex, thrombin and fibrin). Fibrin is the final product of coagulation. Then fibrin fiber retraction takes place (by platelet thrombasthenin). Vitamin K is part of the coagulative system (participates in the synthesis of the II, IX and X factors).

2. System of blood anticoagulation consists of anticoagulants. Heparin is an important substance. 3. System of fibrinolysis provides dissolution of fibrin fibers by plasmin, which is present in the blood in the inactive form (plasminogen, or profibrinolysin) and is activated by many factors (see below).

Thrombocytovascular Hemostasis

Plasma factors and their participation in hemostasis attracted attention of scientists at first. Later it became clear that an important role in maintaining the normal rheological state of the blood belongs to thrombocytes and the vascular walls (under physiological conditions platelets are situated near the endothelium and interact with it). It is they that initiate blood coagulation and thrombogenesis after vessel injury if there is a threat of blood loss. Thrombocytovascular hemostasis is subdivided into two groups of mechanisms :

Platelet Role

Platelets play a central role in hemostasis. Their role is the following.

• Angiotrophic function with respect to the endothelium of the vascular wall, which promotes maintenance of the liquid state of the blood.

• Blood coagulation after vessel injury (aggregation, adhesion to the endothelium and formation of thromboplastin, which starts blood coagulation).

• Production of prostaglandins (thromboxane) as initiators of platelet aggregation after vessel injury. • Formation of the primary (only by thrombocytes) thrombus after vessel injury.

• Production of vasoconstrictive substances (serotonin, adrenaline, noradrenaline), which promote arrest of bleeding.

Vessel Endothelium Role

The role of the vessel endothelium in hemostasis consists in two functions — antithrombotic (under physiological conditions) and prothrombotic (after vessel injury).

Antithrombotic function of the endothelium provides the so-called thromboresistance - prevention of platelet aggregation — and consists in maintaining the liquid state of the blood. This function is performed with the aid of several mechanisms:

• production of prostacyclin (PG), which prevents platelet aggregation;

• destruction of the agents, which stimulate thrombocyte aggregation (such as ADP);

• production of sulfated mucopolysaccharide, which resembles heparin (anticoagulant);

• plasminogen activation, which initiates fibrinolysis and prevents formation of intravascular clusters.

Prothrombotic function of the endothelium provides and initiates blood coagulation after vessel injury by starting thrombogenesis. This function is carried out with the aid of such mechanisms:

• Thromboplastin formation.

• Production of Willebrand factor, which initiates thrombogenesis (activating factor VIII).

It is produced in the endothelium but is accumulated in platelets and released during their degranulation. A thrombocyte clot can not be formed without it. This factor is necessary for thrombocyte aggregation, it stimulates adhesion of platelets to vessel wall collagen. Special receptors to this factor are found on the thrombocyte membrane. The rheological state of the blood depends on the balance of all the mentioned systems. Disorders of any of these components lead to hemostasis pathology.

HEMOSTASIS PATHOLOGY CLASSIFICATION

Some classifications of hemostasis disorders have been suggested.

1. Hypocoagulation and hypercoagulation are distinguished according to disorder direction.

2. *Local* (thrombosis, hemorrhage, hematoma) and *systemic* (blood loss, generalized DIC syndrome) disorders are distinguished according to localization.

3. *Acquired and hereditary* (coagulopathy, thrombocytopathy, angiopathy) disorders are distinguished according to the participation of genetic mechanisms.

Hemorrhage syndrome (corresponds to hypocoagulation), thrombophilic syndrome (corresponds to hypercoagulation) and DIC syndrome (disseminated intravascular coagulation syndrome) are the clinical terms, which determine hemostasis disorders.

In addition, disorders may be *acute and chronic*. Acute disorders refer to emergency medicine: acute hemorrhage, thromboembolism as well as DIC syndrome, which may lead to death in the absence of immediate medical care. Thrombophlebitis of the extremities is an example of a chronic disease.

Sometimes, as it is in anaphylactic shock, hypo- and hypercoagulation occur at the same time — hypocoagulation in the large vessels and hypercoagulation - in the microcirculatory bed.

ETIOLOGY AND PATHOGENESIS

Etiological factors of hemostasis pathology may be exogenous and endogenous as well as physical (mechanical injury of platelets, e.g. in the course of heart valve prosthetics, ionizing radiation), chemical (medicines, heparin overdose) and biological (microorganisms, viruses, immune and genetic factors). The etiology of various types of hemostasis pathology is different. The pathogenesis of numerous clinical and pathophysiological syndromes (hypo- and hypercoagulation, hemorrhage, excessive thrombogenesis, DIC syndrome) is different depending on what is the primary disorder (quantitative and qualitative platelet changes, vessel diseases, liver pathology, disorders of plasma proteins synthesis, etc.). Pathogenesis is absolutely opposite in two main syndromes — hypo- and hypercoagulation.

Hypocoagulation syndrome (hemorrhage syndrome) is a tendency to hemorrhage starting spontaneously or due to an insignificant injury.

Syndrome of hypercoagulation, or thrombophilic syndrome, is a tendency

toward thrombogenesis arising spontaneously or due to insignificant vessel injury.

DIC syndrome is a disorder of hemostasis, which manifests itself through massive formation of thrombi and microemboli in the vessels, mainly of the microcirculatory bed.

Etiology

DIC syndrome is never inherited but only acquired. The possible causes are the following:

- massive trauma of tissues, crush syndrome, operative trauma of the parenchymatous organs;
- massive burn;
- acute intravascular erythrocyte hemolysis;
- leukemia (destruction of a large amount of neoplastic cells);
- true erythrocytosis ;
- uremia (renal insufficiency);
- generalized infections, sepsis;
- all kinds of shock, terminal states;
- acute pancreanecrosis;
- peritonitis;
- side effects of the medicines, which influence hemostasis.

Pathogenesis DIC syndrome is the heaviest pathology of hemostasis. It is an imbalance of all hemostasis mechanisms. The main pathogenesis link is imbalance between the coagulation, anticoagulation and fibrinolytic systems and their simultaneous activation with further exhaustion of all of them. It occurs when a large quantity of procoagulants and blood clotting activators enters the blood in massive trauma, which leads to formation of numerous microclots in microcirculation vessels. Later hypocoagulation, thrombocytopenia and hemorrhage develop due to coagulation factor lack and increased functional activity of the anticoagulation system and fibrinolysis. The pathogenesis of DIC syndrome proceeds in two stages.

Stage of hypercoagulation is excessive procoagulant formation and activation of the blood coagulation system. A great amount of procoagulants enter the blood (tissue thromboplastin plays the main role). Intravascular formation of numerous microdots occurs. Blood circulation can stop, which is often incompatible with life. Microdots stop microcirculation and cause development of heavy dystrophic and functional disorders in organs (renal, cardiac and pulmonary insufficiency, brain damage). They are not compatible with life.

Stage of hypocoagulation starts as a reaction. The systems of anticoagulation and fibrinolysis get activated. The content of coagulation factors (thrombocytes, fibrinogen) significantly decreases as a result of their use in the previous phase. Fibrinolysis activates and this fact aggravates hemorrhage. Severe bleeding is difficult to stop. It is a terminal phase of syndrome. Complete exhaustion of all hemostasis systems underlies hemorrhage. Necrosis develops in the organs, where blood supply is impaired in the form of hemorrhage or thrombosis. In the kidneys, lungs, and heart it is incompatible with life.

HEMOSTASIS

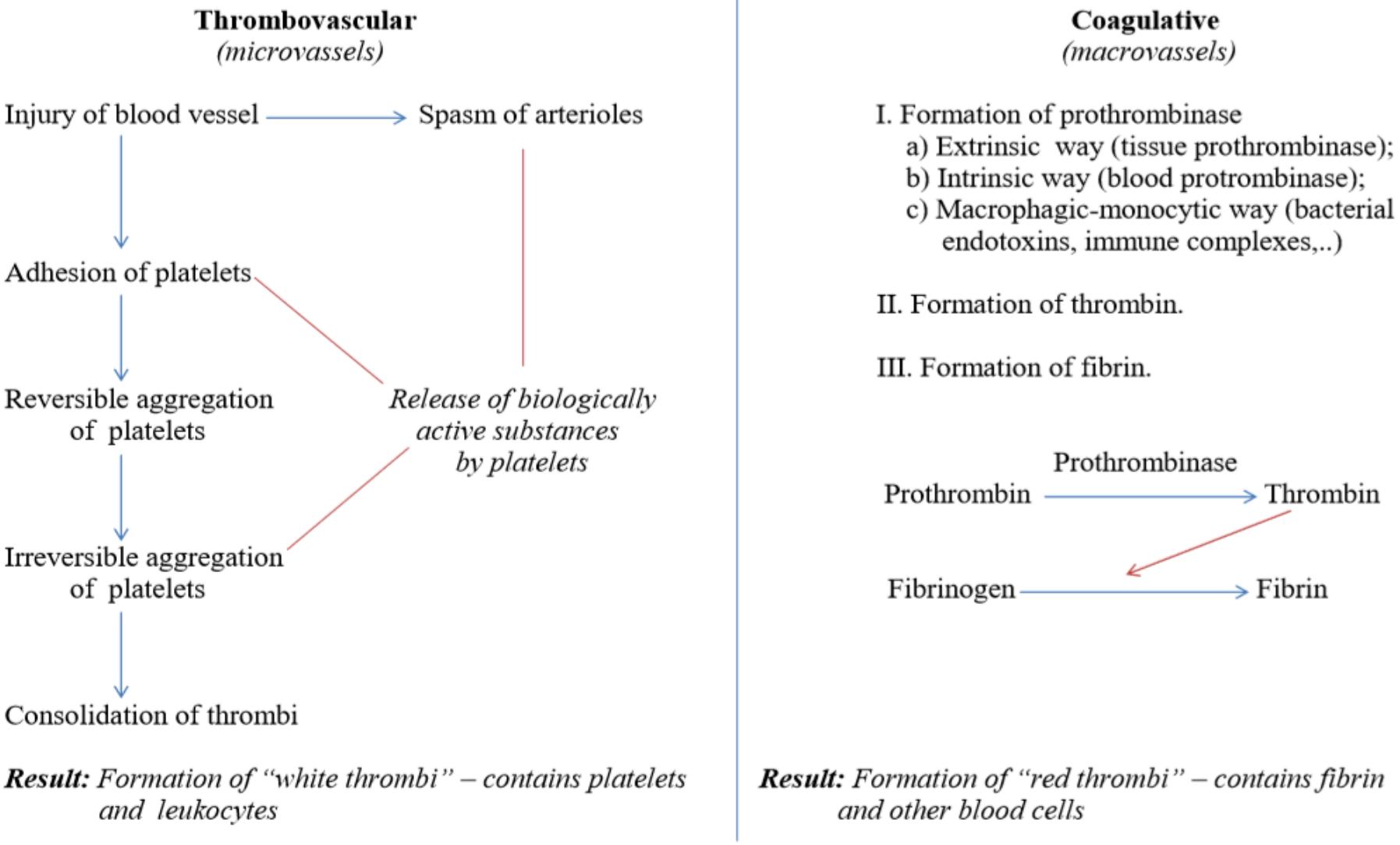

Fig.10 Hemostasis

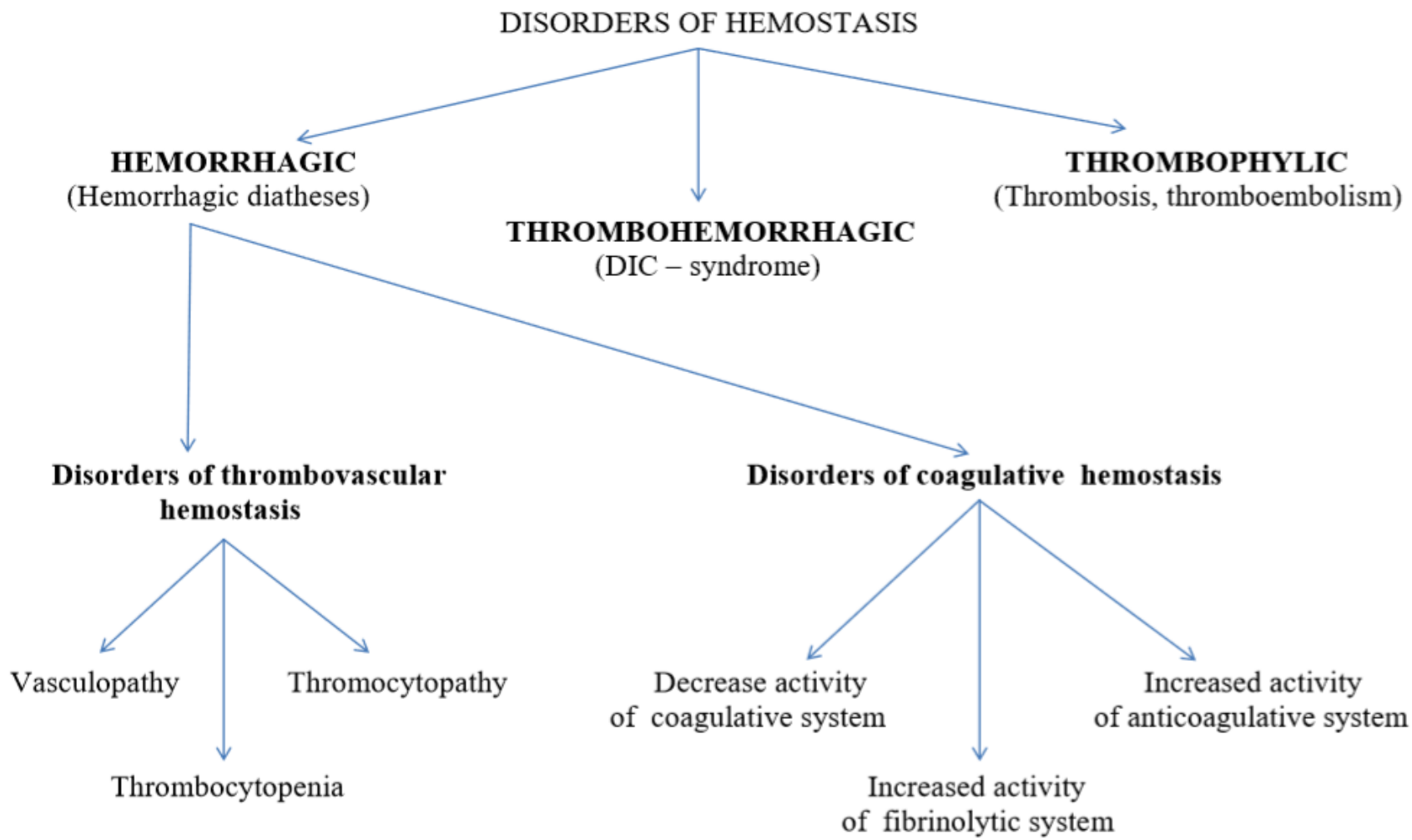

Fig.11 Disorders of hemostasis

KROK 1 mcqs_A is correct answer:

1. In patients with the biliary tract obstruction the blood coagulation is inhibited; the patients have frequent haemorrhages caused by the subnormal assimilation of the following vitamin:
A K
B E
C A
D D
E C

2. A patient underwent a surgery for excision of a cyst on pancreas. After this he developed haemorrhagic syndrome with apparent disorder of blood coagulation. Development of this complication can be explained by:
A Activation of fibrinolytic system
B Insufficient fibrin production
C Reduced number of thrombocytes
D Activation of anticoagulation system
E Activation of Christmas factor

3. A 43-year-old patient has thrombopenia, reduction of fibrinogen, products of degradation of fibrin presented in the blood, petechial haemorrhage along with septic shock. What is the most likely cause of the changes?
A DIC-syndrom
B Autoimmune thrombocytopenia
C Haemorrhagidiathesis
D Disorder of thrombocytes production
E Exogenous intoxication

4. A 70-year-old patient suffers from atherosclerosis complicated by the lower limb thrombosis that has caused gangrene on his left toes. What is the most likely cause of the thrombosis origin?
A Thrombocyte adhesion
B Prothrombinase activation
C Transformation of prothrombin into thrombin
D Transformation of fibrinogen into fibrin
E Impaired heparin synthesis

5. A patient with tissue trauma was taken a blood sample for the determination of blood clotting parameters. Specify the right sequence of extrinsic pathway activation.
A III – VII– X
B III – IV – Xa
C IV – VIII: TF – Xa
D IV – VIIa – Xa
E III – VIII: TF – Xa

6. A disaster fighter at a nuclear power plant developed hemorrhagic syndrome on the background of acute radiation disease. What is the most important factor of syndrome pathogenesis?
A Thrombocytopenia
B Vascular wall damage
C Increased activity of fibrinolysis factors
D Increase activity of anticoagulative system factors
E Decreased activity of coagulative factors

7. A patient was ill with burn disease that was complicated by DIC syndrome. What stage of DIC syndrome can be suspected if it is known that the patient's blood coagulates in less than 3 minutes?
A Hypercoagulation
B Transition phase
C Hypocoagulation
D Fibrinolysis
E Terminal

8. A patient suffers from the haemorrhagic syndrome that shows itself in frequent nasal bleedings, posttraumatic and spontaneous intracutaneous and intra-articular haemorrhages. After a laboratory study a patient was diagnosed with the type B haemophilia. This disease is provoked by the deficit of the following factor of blood coagulation:
A IX
B VIII
C XI
D V
E VII
9. There is an inhibited coagulation in the patients with bile ducts obstruction, bleeding due to the low level of absorbtion of a vitamin. What vitamin is in deficiency?
A K
B A
C D
D E
E Carotene
10. Punctata hemorrhage was found out in the patient after application of a tourniquet. With disfunction of what blood cells is it connected?
A Platelets
B Eosinophiles
C Monocytes
D Lymphocytes
E Neutrophiles
11. A 2-year-old child has got intestinal dysbacteriosis, which results in hemorrhagic syndrome. What is the most likely cause of hemorrhage of the child?
A Vitamin K insufficiency
B Activation of tissue thromboplastin
C PP hypovitaminosis
D Fibrinogen deficiency
E Hypocalcemia
12. Patients with bile ducts obstruction suffer from inhibition of blood coagulation, bleedings as a result of low level of vitamin assimilation. What vitamin is indeficiency?
A K
B A
C D
D E
E Carotene
13.To prevent postoperative bleeding 6 y.o. child was administered vicasol that is a synthetic analogue of vitamin K. Name post-translational changes of blood coagulation factors that will be activated by vicasol:
A Carboxylation of glutamin acid
B Phosphorylation of serine radicals
C Partial proteolysis
D Polymerization
E Glycosylation
14. A patient was ill with burn disease that was complicated by DIC syndrome. What stage of DIC syndrome can be suspected if it is known that the patient's blood coagulates in less than 3 minutes?
A Hypercoagulation
B Transition phase
C Hypocoagulation
D Fibrinolysis
E Terminal
15. As a result of posttranslative modifications some proteins taking part in blood coagulation, particularly prothrombin, become capable of calcium binding. The following vitamin takes part in this process:
A K
B C
C A

D B1
E B2

16. A 16 year old boy after an illness has diminished function of protein synthesis in liver as a result of vitamin K deficiency. It will cause disturbance of:
A Blood coagulation
B Erythrocyte sedimentation rate
C Anticoagulant generation
D Erythropoietin secretion
E Osmotic blood pressure

17. Plasmic factors of blood coagulationare exposed to post-translational modification with the participation of vitamin K. It is necessary as a cofactor in the enzyme system of γcarboxylation of protein factors of blood coagulation due to the increased affinity of their molecules with calcium ions. What amino acid is carboxylated in these proteins?
A Glutamic
B Valine
C Serine
D Phenylalanine
E Arginine

18.70-year-old patient suffers from atherosclerosis complicated by the lower limb thrombosis that has caused gangrene on his left toes. What is the most likely cause of the thrombosis origin
A Thrombocyte adhesion
B Transformation of fibrinogen into fibrin
C Impaired heparin synthesis
D Transformation of prothrombin into thrombin
E Prothrombinase activation

19. A 3-year-old boy with pronounced hemorrhagic syndrome doesn't have anti hemophilic globulin A (factor VIII) in the blood plasma. Hemostasis has been impaired at the following stage:
A Internal mechanism of prothrombinase activation
B External mechanism of prothrombinase activation
C Conversion of prothrombin to thrombin
D Conversion of fibrinogen to fibrin
E Blood clot retraction

20. A 12-year-old patient has been admitted to a hospital for hemarthrosis of the knee joint. From early childhood he suffers from frequent bleedings. Diagnose the boy's disease:
A Hemophilia
B Hemorrhagic vasculitis
C Hemolytic anemia
D B12 (folic acid)-deficiency anemia
E Thrombocytopenic purpura

21. A 46-year-old female is scheduled for a maxillofacial surgery. It is known that the patient is prone to high blood coagulation. What natural anticoagulant can be used to prevent blood clotting?
A Heparin
B Hirudin
C Sodium citrate
D Fibrinolysin
E None of the above-listed substances

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

E --

23. A 30-year-old patient with a past history of virus B hepatitis complains of prolonged nosebleeds. What drug will be most efficient in remedying this condition?

A Vicasolum
B Fraxiparine
C Foliacid
D Dipiridamol
E Asparcam

24. After a disease a 16-year-old boy is presenting with decreased function of protein synthesis in the liver as a result of vitamin K deficiency. This may cause disorder of:

A Blood coagulation
B Anticoagulant production
C Osmotic blood pressure
D Erythrocyte sedimentation rate
E Erythropoietin production

25. A clinic observes a 49 year old patient with significant prolongation of coagulation time, gastrointestinal haemorrhages, subcutaneous hematomas. These symptoms might be explained by the deficiency of the following vitamin:

A K
B B1
C B6
D H
E E

26. A disaster fighter at a nuclear power plant developed hemorrhagic syndrome on the background of acute radiation disease. What is the most important factor of syndrome pathogenesis?

A Thrombocytopenia
B Vascular wall damage
C Increased activity of fibrinolysis factors
D Increased activity of anticoagulative system factors
E Decreased activity of coagulative factors

27. A patient visited a dentist to extract a tooth. After the tooth had been extracted, bleeding from the tooth socket continued for 15 minutes. Anamnesis states that the patient suffers from active chronic hepatitis. What phenomenon can extend the time of hemorrhage?

A. Decrease of fibrinogen content in blood
B. Thrombocytopenia
C. Hypocalcemia
D. Increased activity of anticoagulation system
E. Decrease of albumine content in blood

28. A 3-year-old boy with pronounced hemorrhagic syndrome has no antihemophilic globulin A (factor VIII) in the blood plasma. Hemostasis has been impaired at the following stage:

A. Internal mechanism of prothrombinase activation
B. External mechanism of prothrombinase activation
C. Conversion of prothrombin to thrombin D. Conversion of fibrinogen to fibrin
E. Blood clot retraction

29. A patient visited a dentist to extract a tooth. After the tooth had been extracted, bleeding from the tooth socket continued for 15 minutes. Anamnesis states that the patient suffers from active chronic hepatitis. What phenomenon can extend the time of hemorrhage?

A. Decrease of fibrinogen content in blood B. Thrombocytopenia
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D. Increased activity of anticoagulation system
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Tests for Self-Control (give correct answer)

1. Heparin is a rapidly acting, potent anticoagulant that has many important clinical uses. Which of the following is an action of heparin?
A. activates prothrombin
B. acts with antithrombin to inhibit thrombin activity
C. decreases prothrombin time
D. inhibits calcium action
E. promotes vitamin K activity
2. A 61-year-old male presents to his family physician with the chief complaint of frequent diarrhea accompanied by weight loss. He reports a tendency to bruise easily and laboratory data reveal a prothrombin time of 19 seconds (normal = 11–14 seconds). The bruising and prolonged prothrombin time can be explained by a decrease in which of the following vitamins?
A. Vitamin A
B. Vitamin C
C. Vitamin D
D. Vitamin E
E. Vitamin K

Recommended literature:

Basic

1. Simeonova N.K. Pathophysiology/ N.Simeonova.// Kyiv, Ukraine. – 2010. – 322-337pp.
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Additional

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