The anatomo-physiologic peculiarities of hematopoietic system, the anemic and hemorrhagic syndromes

- Blood is a liquid tissue of the organism which surrounds all its cells. Blood consists of the formed elements (erythrocytes, leukocytes, thrombocytes) and the plasma. The latter contains of water, proteins, vitamins and a large number of active substances (hormones, enzymes, antibodies, etc.).
- The functions of blood are as follows: transport and protection. The transport function includes delivering of oxygen, nutrient substances, hormones, enzymes, other physiologically active substances to tissues and discharging of waste products of metabolism from tissues. The protection function is provided with leukocytes, which realize phagocytosis, and with immune agents, which resist microorganisms with their toxins and destroy foreign proteins. A quota of the formed elements of blood is 40-45 %, that of the plasma being 55-60 %.

Hemopoiesis is the process of origin and maturing of formed elements of blood in the hemopoietic organs. Formation of blood, or hemopoiesis, is parallel to cardiovascular development. The hemopoietic system originates in the mesoderm. There are 3 periods in the development of this system: out-of-embryo period, liver period and bone-marrow period. At about 13 to 15 days of gestation, angioblasts organize as “blood islands” in the mesoderm of the yolk sac. Spaces develop within these islands and become lined with angioblasts, forming the primitive blood vessels and endothelium. Cells of the endothelium give rise to primitive blood cells, megaloblasts. This all occurs outside the embryo, in the yolk sac. Blood is not formed within the embryo until the fifth week of gestation. This short period is called the out-of-embryo period, or megaloblastic haemopoiesis.

The primary site for hemopoiesis in the embryo is the liver, which grows larger as the process continues. The liver increases in size until, by the ninth week of gestation, it is responsible for about 10 % of the total fetal weight. This is the period of liver hemopoiesis. Later in gestation the reticuloendothelial system, comprised of the liver, spleen, bone marrow and lymph nodes, becomes the primary site of hemopoiesis as the yolk sac regresses. Megaloblasts are gradually replaced by erythroblasts. Erythro-, granulo-, and megakaryocytopoiesis take place in the spleen.

Active lymphopoiesis starts to appear in the spleen late, in the end of the 7th month of gestation. At 4-5 months of gestation, the bone marrow period of hemopoiesis starts. By term, the bone marrow is the main site for production of all red cells and most other cellular components of blood. However, the liver, spleen, and lymph nodes can be stimulated to produce blood cells during periods of extreme and continued demand.

The stem cell, the germinal cell for all blood cell production, is found within the reticuloendothelial system. The stem cell is a polypotent cell-precursor, it can keep up its population and can differentiate itself in more mature cells. In lymph nodes, reticulum cells will develop into lymphocytes and monocytes. Elsewhere in the reticuloendothelial system, reticulum cells will differentiate into either hemoblasts or myeloblasts. Haemoblasts undergo several other stages of transformation before emerging as erythrocytes, while myeloblasts may differentiate into granulocytic leukocytes or megakaryocytes (platelet precursors).

<table>
<tr><th colspan="5">The stem germinal cells</th></tr>
<tr><td colspan="4">Cells- precursors of myelopoiesis</td><td>Cells-precursors of lymphopoiesis</td></tr>
<tr><td rowspan="2">Erythro-blast</td><td rowspan="2">Megakaryo-blast</td><td colspan="2">Cells-precursors of granulocytes and macrophages</td><td rowspan="2">Lymphoblast</td></tr>
<tr><td>Myeloblast</td><td>Monoblast</td></tr>
<tr><td>Pronor-mocyte</td><td rowspan="4">Promegaka-riocyte</td><td>Promyelocytes</td><td rowspan="4">Promonocyte</td><td rowspan="4">Prolymphocyte</td></tr>
<tr><td>Normo-cyte</td><td>Myelocytes: baso-, eosino- and neutrophilic</td></tr>
<tr><td>Reticulo - cyte</td><td></td></tr>
<tr><td rowspan="2">Erythro-cyte</td><td rowspan="2">Thrombocyte</td><td>Metamyelocytes: baso-, eosino- and neutrophilic</td></tr>
<tr><td>Basophils Eosinocytes, Neutrophils</td><td>Monocyte</td><td>Lymphocyte</td></tr>
</table>

- During postnatal life the bone marrow produces erythrocytes, granulocytes, blood platelets and monocytes; lymphocytes are produced in the spleen, lymph nodes, intestinal follicles, Peyer's patches (aggregate nodules) and other lymphoid formations.
- Cells, circulating in the peripheral blood, continue to be functionally changed; the contents of enzymes and energy output in cells gradually decrease. Cells are aging and destroyed by phagocytes. The term of life of erythrocytes is 120 days, thrombocytes 9-11 days, leukocytes from 100 to 300 days, but some of them live only 3-4 days, while others more than 1.5 years. There is balance between formation and destruction of blood cells.
- The central nervous system, endocrine glands and kidney have influence on hemopoiesis, this influence is realized through erythro, leuko- and thrombopoietines.

• Blood must be liquid. This condition of blood is guaranteed by the hemocoagulation system, which supports blood in liquid condition, prevents thrombosis and hemorrhage and ensures stop of bleeding. Disorder of this system causes thrombosis and bleeding. The main components of this system are: vascular wall, blood cells and plasma factors.

The vascular chain of hemostasis consists of the intact vascular wall; the thrombocytic chain ensures adherence and aggregation of thrombocytes; besides, thrombocytes contain 9 factors, which take part in blood coagulation. The plasmatic chain contains 13 factors of blood coagulation. If a vascular wall is injured, local angiospasm begins, thrombocytes adhere to damaged endothelial cells and basal membrane, and thrombocytic aggregation takes place. All this process is realized for 2 minutes. During this period plasma factors, which were not in active condition, activate consecutively and are converted into active enzymes; a complex multiple cascade enzyme process takes place. The formation of thrombi and cessation of bleeding occur.

The process of coagulation may be represented by this scheme:

Stage I	Stage II	Stage III	Last stage
Thrombopla-stin formation	Prothrombin Thrombin	Fibrinogen Fibrin	Retraction of blood clot, fibrinolysis

- Retraction of blood clot occurs due to ability of thrombocytes to gather fibrin fibers in a clot. As result of this process, the volume of a clot decreases. Lysis of a clot, reconstruction of vascular permeability and blood flow occur under the influence of fibrinolysin.
- The ability of the fetus to synthesize clotting factors is genetically determined. In genetically normal fetuses and newborns, the production of adequate amounts of clotting factors depends on maturation of the liver and presence of vitamin K. The latter is produced in the gastrointestinal tract through the interaction of bacteria, food and time. Synthesis of prothrombin and factor VII cannot occur without it.

Blood type

This is determined at conception. The group indication appears in children quite early. Agglutinogens A and B can be discovered in 3-4-month-old fetuses. Erythrocytes contain agglutinogens α and β, serum agglutinins A and B. Blood of every person contains different agglutinogens and agglutinins. There are 4 groups of blood: I(0) – O; II(A) – A; III(B) – B; IV(AB). Rh factor is one of blood antigens; this can be positive (85 %) and negative (15 %). Blood of a newborn has an essential quality of Rh factor and it remains to be constant during the whole life.

Blood type

The HLA system (Human Leukocyte Antigen) is the system of human leukocyte antigens. It is a complex of genes situated on the 6^{th} chromosome; the complex has its genetic structures, i.e. locuses A, B, C and D. Every human being has a set of 4 paired antigens. A quantity of combinations of gene alleles only in A and B locuses exceeds 250 million, what confirms the individuality of every person and explains difficulties in selecting donors for organs transplantation. Mature erythrocytes do not have HLA on their cell membrane; this fact explains the possibility of blood transfusion without taking into consideration HLA phenotype.

Hemoglobin

- Fetal hemoglobin, or HbF, is a specialized form of hemoglobin, found only during gestation and in early infancy. HbF accounts from 70 % to 90 % of the total hemoglobin in the perinatal period.
- During the fetal life, oxygen supplement is lower than in the extrauterine life (pO_2 is 30 mm Hg in the umbilical venous blood, but 60 to 90 mm Hg in the arterial blood after birth). Fetus adaptation to hypoxia includes:

1) an increase in total hemoglobin concentration (150 to 200 g/l versus 110-130 g/l in the adult);

2) red cell mass is increased in the fetus to 5–6 million/ mm^3;

3) fetal hemoglobin has high hemoglobin-oxygen affinity.

Amount of blood

The total amount of blood of an adult is approximately 5-5.5 % of his body weight. The amount of blood in children is higher. In a newborn, the amount of blood makes 10.5-19.5 % of the body weight, in later infancy it is 9-12.5 %, in the school-age period it is approximately 7 % of the body weight.

There are many differences in morphofunctional characteristics of blood between children and adults.

Blood of the newborn infant

• Its red blood count is 5.0-7.0 · 10^{12}/l following birth, but by the 14th day, it usually drops down to 4.0 · 10^{12}/l. Hemoglobin level during the first two days may be as high as 170-220 g/l, falling to 165 g/l by the end of the 14th day. Anisocytosis (erythrocytes of unequal size) is typical for newborn infants. Anisocytosis is expressed by the presence of macrocytes (abnormally large erythrocytes with high hemoglobin content).

• The number of reticulocytes (immature or young erythrocytes) is from 50 to 100 per 1,000 mature erythrocytes during the first days; their number also drops rapidly down by 10-15 days of life and makes 5 to 10 per 1,000 mature erythrocytes.

• Osmotic fragility. Blood of the newborn contains erythrocytes with elevated and reduced osmotic fragility.

• Erythrocyte sedimentation rate (ESR) of the newborn is slower than in adult and is 2-3 mm/h; beginning with the age of 2 months ESR rises and reaches the level of 8-10 mm/h (the same as in adults).

• The number of thrombocytes varies during the first days of life within 100÷200·x 10^9/l.

- The picture of their white blood in newborns is quite specific.
- During the first 8-12 hours of life the number of leukocytes is as high as $25 \div 30 \times 10^9/l$; neutrophilic leukocytosis is marked, a regenerative deviation to the left is present; it means the presence of many immature neutrophils in peripheral blood.
- By the 10^{th}-15^{th} day white blood count gradually drops to an average of $10 \div 12 \times 10^9/l$; immature cells, as a rule, disappear from the peripheral blood almost completely; primary neutrophilosis is replaced by lymphocytosis.

- A gradual increase in the number of lymphocytes begins in the first days of life, attaining 50-60 % by the fifth day; this level is sustained throughout infancy; at the same time the number of neutrophils is gradually reduced to 30%.
- There are two intersections in numbers of neutrophils and lymphocytes: between the 4^{th} and 6^{th} days and between the 4^{th} and 5^{th} year.
- The coagulation (clotting) and bleeding times in the newborn are the same as normal for adults: coagulation time is 5-5.5 minutes; bleeding time is 1-3 minutes. Clot retraction is normal.

According to the opinion of some authors, high hemoglobin and red and white cell levels in the newborn are caused by the maternal hormones; the hormones circulating in the body of the pregnant woman and stimulating her hematopoietic system penetrate into the body of the fetus and thus stimulate its hematopoietic organs. The delivery of these hormones into the infant's blood ceases after birth, and therefore a rapid drop of hemoglobin, erythrocytes and leukocytes occurs.

- Blood in infancy has some characteristic features. Red blood count rates $4 \div 4.5 \times 10^{12}$/l, hemoglobin level is 95-140 g/l, and it easily drops to 70.0-80.0 g/l, so that the color index stays below norm. Anisocytosis is rather marked. Reticulocytes do not number more than 5-6 per 1,000 normal erythrocytes.
- The maximum and minimum osmotic fragility of erythrocytes is slightly elevated in comparison with the newborn period.
- Thrombocyte count varies between $200 \div 300 \times 10^{9}$/l.
- Coagulation, bleeding time, and clot retraction almost do not differ from what is normal in adults.

- White count is usually 10÷12 x 10^9/l in infants, lymphocytosis is marked (the level of lymphocytes is 50 %), neutrophil count during this period varies within the range of 35-40 %.
- It is possible to note the development of physiological anemia at the age of 3-4 months as a result of iron deficit, because breast and cow's milk is low in iron.

Blood of children from 2 to 6 years

- Between the ages of 2 and 6 years the level of hemoglobin is 105-140 g/l (averaging 120 g/l), red blood count is 4.5x10^{12}/l, with 2-3 % of reticulocytes, the color index is lower than norm and is 0.85-0.95. Anisocytosis is marked.
- White count gradually diminishes, becoming 8÷8.5x10^9/l by the age of 6 years.
- The number of lymphocytes gradually decreases, going down to 40-35 % by the age of 5-7 years. The number of neutrophils grows (the second intersection).

Blood of children between 6 and 14 years

- The composition of blood at this period is approximately the same as in the preceding period. Anisocytosis gradually disappears. Leukocyte count continues to fall, and by 14 years is $7 \div 7.5 \times 10^9$/l.
- Differential white count is characterized by a further rise in the number of neutrophils and a drop of lymphocytes. By 14 years the count indicates 60-65 % of neutrophils and 25-30 % of lymphocytes.

Blood of adolescents

- Red blood count is $4.5 \div 5 \times 10^{12}$/l. Hemoglobin is at a high level, averaging 140 g/l. White count is $6 \div 7.5 \times 10^9$/l.

Methods of the clinical and paraclinical investigation

- Clinical examination of the hematological system of children includes questioning, general examination, physical examination of the skin, lymph nodes, liver, spleen and bones.
- The most typical complaints are: bleeding, hemorrhage, enlargement of lymphatic nodes, paleness of the skin and mucous membranes, ossalgia.
- Complaints of the common character are: hyperthermia, headache, dizziness, weakness, exhaustion, memory disorders, poor appetite, exertional dyspnea.

Case history taking:

- – to establish the first day of appearance of symptoms, under which circumstances they appeared, especially bleeding and hemorrhage (spontaneously, under influence of some strong or superficial damaging);
- – to ask about the dynamics of symptoms (when fresh elements appeared, simultaneously or subsequently);
- – to ask about treatment, including the dose and duration of using the medicines, their effectiveness;
- - to get acquainted with results of laboratory and other methods of examination before the patient's admission to the hospital

• Life history is very important in cases of inheritable diseases (hemophilia) and possible tendency to pathology of the hematopoietic system and blood. The obstetric anamnesis is very important for infants.

The following signs must be assessed during examination:

– position of a patient (active, passive, forced);

– bleeding (its location, intensity, duration);

– color of the skin: a) pallor, b) jaundice;

– rash (macula, petechia, purpura, bruise), papule, exanthema, hemorrhage, hematoma, hemarthrosis;

– enlargement of lymph nodes;

– distended abdomen;

– edema;

– enlargement of the liver and spleen.

Paraclinical investigation includes:

blood count; coagulogram; puncture of the liver, spleen and bone marrow; study of myelogram; puncture of a lymph node; radiography, CT. The main methods of examination of the system of hemostasis are as follows: capillary resistance tests, thrombocyte count, tests of thrombocytic adhesion (aggregate functions), time of capillary bleeding according to Duke, retraction of blood clots.

- Myelogram gives information about the quality and quantity of bone marrow cells. In order to get some bone marrow, the breastbone is to be punctured. It is necessary to count not less than 500 cells and calculate percentage for every type of cells.
- The main peculiarity in the bone marrow of children of the first 3 years of life consists in a large quantity of lymphocytes: infancy – 10-18 %, at 3 years – 7-14 %, after 3 years – 2-8%.
- There are no significant differences in other parameters of the bone marrow of healthy children and adults.

- The main clinical symptoms of the blood system diseases are: pallor, jaundice, fatigue, irritability, seizures, enlargement of the liver, spleen, lymph nodes, petechia, ecchymosis, gastrointestinal hemorrhage, mucosal bleeding, bacteriemia, cellulitis, pharyngitis, oral ulceration.

- Combination of these symptoms may be various and depends on the nosological form of hemopathy.

Symptomatology of blood changes:

- I. Quantitative changes in red blood.

1. The increase in the number of erythrocytes (polyglobulia):

a) true polyglobulia is associated with intensification of bone marrow activity (in newborns, congenital heart disease, in polycythemia, etc.);

b) false transient polyglobulia results from condensation of blood due to fluid losses (acute dyspepsia, dysentery, excessive perspiration).

2. Reduced red blood counts and lower hemoglobin levels, i.e. conditions corresponding to the clinical concept of anemia:

- reduction of bone marrow function (starvation, infection, intoxication, tumors), congenital inferiority of the hematopoietic system (prematurity, tumors in the bone marrow);
- the number of erythrocytes may be reduced due to increased expenditure (chronic bleeding, erythrocytes disintegration during chronic infections, worms, malaria), hemolysis of erythrocytes (familial hemolytic jaundice).

II. Qualitative changes in red blood.

• Changes in the quality of blood elements are connected with changes in the process of blood formation. These are characterized by the appearance of embryonal precursors:

a) megaloblasts, megalocytes: these indicate return to the embryonal type of blood formation;

b) erythroblasts, normablasts: these demonstrate intensified bone marrow activity;

c) increased reticulocytes counts: these display intensified bone marrow function;

II. Qualitative changes in red blood.

d)the appearance of macrocytes: this is a sign of healthy blood regeneration;

e)hyperchromia indicates regeneration; this is a sign of functional deficiency of bone marrow;

f)anysocytosis is inequality in the size of erythrocytes; this is a sign of normal regeneration; poikilocytosis means different shape of erythrocytes and signals about degeneration of erythrocytes.

White blood:

I. Quantitative changes in white blood.

- Leukocytosis is an increase in the quantity of leukocytes more than 10 x 10^9/l (over 20 x 10^9/l is hyperleukocytosis). An increase in the number of white blood cells, leukocytosis, results from heightened activity of the bone marrow under the influence of some pathological and also physiological stimuli.

The following forms of leukocytosis are distinguished:

1. Physiological leukocytosis:

a) in the newborn (20,000-25,000),

b) in infancy (10,000-12,000).

2. Pathological leukocytosis, associated with local and generalized infection processes and intoxications:

a) pseudoleukocytosis results from condensation of blood, digestive leukocytosis is possible;

b) neutrophilic leukocytosis is associated with infections: sepsis diseases, pneumonia, scarlet fever, dysentery, rheumatic fever, meningitis.

• Leukemia is characterized by a particularly high leukocytosis (100,000 and higher) and the appearance of numerous immature forms. There are many different forms of leukemia, but myeloid (granulocytic) and lymphatic leukemia are more often.

• Besides determination of the total number of leukocytes, estimation of the nuclear shift of neutrophils is highly important. A deviation to the left (an increased number of young forms of leukocytes) is a sign of accelerated production of white blood cells. Presence of a deviation to the left and neutrophilosis is a favorable prognostic symptom. Prognosis is less favorable when a deviation to the left is not combined with an increase in the total white count.

- Lymphocytosis is an absolute and relative increase of the number of lymphocytes in peripheral blood. It is a stable physiological condition throughout infancy and early childhood.
- The number of lymphocytes increases in certain acute and chronic infections (pertussis, rubella, typhoid fever), during convalescence, certain forms of glandular fever, tonsillitis. Especially high lymphocyte counts are observed in lymphatic leukemia and in cases of so-called lymphatic reactions in children, more often in whooping cough.

- Monocytosis is a transient increase in the number of monocytes, it is typical for certain acute infections (malaria, measles, tuberculosis and infectious mononucleosis).
- Eosinophilia is observed in numerous pathological conditions. Normally blood contains 2-4 % of eosinophils, in some pathological conditions the amount goes up to 20-30 %, or even higher. Eosinophilia occurs in bronchial asthma, serum sickness, anaphylactic status, scarlet fever, leukemia, certain cases of lymphogranulomatosis, and in all types of worm diseases.
- Basophilia. Normally basophil count does not exceed 0.5-1 %. A rise is observed in association with acute and chronic leukemia, lymphogranulomatosis.

• Leukopenia is diminution in the number of leukocytes, it is a characteristic sign of certain infections (typhoid fever, measles, rubella). In sepsis, pneumonia leukopenia is an indication of depression of the hematopoietic organs and an unfavorable prognostic sign.

• Reduction of white blood count may result from the bone marrow hypofunction due to infections, chemical poisons (arsenic, benzene), ionizing radiation or lesion of the myeloid tissue (agranulocytosis).

• Neutropenia is a sign of a severe form of infection or sepsis. Absolute neutropenia is characteristic of agranulocytosis.

• Lymphopenia develops in certain infectious diseases in association with neutrophilic leukocytosis. Absolute lymphopenia is observed in lymphogranulomatosis, lymphosarcomatosis, and certain forms of myelosis.

• Monocytopenia is seen in severe septic and infectious processes.

• Eosinopenia is typical for typhoid fever, measles, pneumonia, septicemia, aggravation of tuberculosis and rheumatic fever.

II. Qualitative changes in white blood.

- High leukocytosis is rather often accompanied by a marked deviation to the left and appearance of primary and immature elements of white blood in the circulating flow such as myeloblasts (the youngest of the precursor cells of granulocytic series) or next intermediate forms of granulocytes (promyelocytes, myelocytes and juvenile neutrophils). It is typical for a number of infections.
- The deviation degree demonstrates activity with appearance of myelocytes; juvenile neutrophils are more typical for pyoseptic and infectious diseases, hemolysis, chronic leukemia, allergic reactions, bleeding.
- An increased quantity of juvenile and band forms is a sign, which demonstrates an increase in hematopoiesis.
- Hiatus leukemicus is such a type of content of all neutrophils when an increase in the quantity of immature forms (myelocytes, juvenile forms) and a small number of mature forms (segmental neutrophils) are present, but transitional forms (juvenile, band neutrophils) are absent. Hiatus leukemicus is a sign of acute leukemia.
- A deviation of the differential count to the right means an increased amount of mature leukocytes (segmental neutrophils), practically without any immature (band) neutrophils. It can be very rare and displays a disorder in the bone marrow hematopoiesis.

• Neutropenia is such a condition of the differential blood count when the quantity of neutrophils decreases more than by 1/3 versus the age norm. Pathogenesis of neutropenia (which may be leukopenia) can be caused by:

– disorder in the hematopoietic function of the bone marrow and incomplete going out of mature neutrophils into peripheral blood;

– acceleration of the destruction of formed elements;

– increase in the removal of neutrophils from hemocirculation.

• Neutropenia is a rather rare condition and appears in:

– some infectious diseases (malaria, measles, typhoid fever, influenza, severe forms of bacterial infections with an increased duration);

– tuberculosis;

– prolonged treatment by cytostatic medicines, sulfonamides, antibiotics;

– some type of anemia (B_{12}-folic-deficit, hypoplastic anemia);

– increased irradiation;

– aplasia of the bone marrow.

• Lymphocytosis is an increase in the quantity of lymphocytes which can cause leukocytosis. Its pathogenesis is based on an increased formation of a large number of lymphocytes from the lymphopoietic organs and their arrival in the circulating blood. The main causes are as follows:

– acute infectious diseases (whooping cough, viral hepatitis);

– chronic infectious diseases (tuberculosis, syphilis, brucellosis);

– chronic lympholeukosis.

• Lymphopenia is a decrease in the quantity of lymphocytes, caused by some hypofunction of the lymphopoietic organs; lymphopenia can produce leukopenia. Lymphopenia can occur in:

– congenital immunodeficiency;

– acquired immunodeficiency syndrome;

– lymphogranulomatosis.

True leukemia is differentiated from leukemoid reaction on the basis of bone marrow studies.

Thrombocytes

The number of blood platelets is normally 200,000-300,000.

• Thrombocytosis is typical for many infection diseases (pneumonia, rheumatic fever).

• Thrombopenia is found in severe forms of anemia, leukemia, idiopathic thrombocytopenic purpura.

Erythrocyte sedimentation rate (ESR).

The normal erythrocyte sedimentation rate is: in newborns – 0-2 mm/h, in infants – 2-4 mm/h, later – 4-10 mm/h.

• An increase of ESR is a sign of different pathology: an inflammatory process of any system (the higher ESR, the more acute pathological condition), infectious diseases, allergic reactions, malignant pathology.

• Decreased ESR is rare; it may be found out in dehydration, anaphylactic shock, dystrophy, peptic ulcer, heart failure, acute viral hepatitis.

The main pathological syndromes of hematological disease

1. Anemic syndrome.
2. Leukocytic and leukopenic syndromes.
3. Hemorrhagic syndrome:

a) hematomatic type;
b) petechial type;
c) vasculitic type;
d) angiomatotic type.

4. Syndrome of lymph node enlargement:
   - a) regional enlargement of lymph nodes;
   - b) generalized enlargement of lymph nodes.

There are 3 main group of etiological factors of anemia:

1. Anemia as a result of bleeding (posthemorrhagic). Decrease of quantity of erythrocytes and hemoglobin is marked in blood analysis, normochromia, reticulocytosis after some time.
2. Anemia as result of disorder of hematopoiesis.
3. Deficiency anemia (more often iron deficiency anemia), iron deficit due to disorder of its supply, absorption or intensive loses. Causes: exogenous insufficiency, if a child does not get necessary amount of iron with food (nutritional, or alimentary, anemia), exogenous insufficiency of iron in time of its intensive need (infectious diseases), endogenous insufficiency of iron due to disorders of its assimilation (diseases of the gastrointestinal system).

It is accepted, as a rule, to single out 3 degrees of anemia, depending upon the quantity of hemoglobin:

I	**Slight**	**110-90 g/l**
II	**Mild**	**90-70 g/l**
III	**Severe**	**Less than 70 g/l**

Laboratory criteria of anemia in the neonatal period:

0 – 14 days	**<145 g/l**
15 – 20 days	**<120 g/l**

- Iron deficiency anemia is the most often type of anemia in children of the first 3 years of life. Frequent anemia in children is caused by lability of their hematopoietic system. Many unfavorable factors (disorders of nutrition, hygienic regime, intercurrent diseases) can cause anemia in children. However after eradication of the cause the bone marrow function rapidly improves and blood count data become normal.
- In older children, posthemorrhagic anemia occurs as a result of gastrointestinal, renal or uterine bleeding.
- "True" anemia may be erroneously diagnosed in cases of hemodilution or hemocondensation caused by edema or dehydration of various origin.

Hemolytic syndrome

- Hemolysis is the process of destruction of erythrocytes, accompanied by hemoglobin going out from erythrocytes into plasma.
- Pathological hemolysis can be caused by exoerythrocytic and endoerythrocytic factors.

Exoerythrocytic factors:

– hemolytic poisons and toxins (snake, helminthes, bee, scorpions, arsenic, benzol, bacteria, chronic lead intoxication);

– transfusions of incompatible (by group and Rh factor) blood,

– doctors' mistakes in intravenous transfusions of hypotonic solutions;

– severe infections (malaria, sepsis);

– severe burns;

– presence of antibodies to erythrocytes.

Hemolytic disease of newborn due to Rh or group conflicts is an example of hemolysis.

• Endoerythrocytic hemolytic factors: congenital diseases (icterohemolytic anemia, acquired disorders).

Hemolytic syndrome is a sign of group of diseases, whose common sign is hemolysis of erythrocytes with development of anemia and an increased destruction of erythrocytes, and in the same time with some increase of erythropoiesis as compensation for anemia.

Hemolytic syndrome has such signs as:

- 1. Clinical:

  – severe general condition (fever, headache, pain in muscles, joints, consciousness disorders, such as collapse and coma);

  – pallor;

  – jaundice;

  – dyspnea;

  – enlargement of the liver and spleen;

Hemolytic syndrome has such signs as:

- 2. In laboratory analyses:

  – normochromic anemia;

  – degenerative changes of erythrocytes (poikilo-, anisocytosis);

  – hypergemoglobinemia;

  – neutrophilic leucocytosis with a deviation to the left;

  – hyperbilirubinaemia with indirect bilirubin;

  – large quantity of serum iron;

  – reticulocytosis;

  3. In urinalysis:

  – hemoglobinuria;

  – stercobilinogen, urobilinogen;

  4. in coprogram:

  – increase of stercobilinogen.

Disseminated intravascular coagulation (DIC) syndrome

• This, or thrombohemorrhagic, syndrome is a complex of nonspecific pathological symptoms, based on the arrival of exo- and endogenous factors to vessels; these factors activate the coagulative system of blood and aggregation of thrombocytes in the vital organs, causing their dysfunction. DICS is not an independent disease.

There are many causes of DICS development:

– generalized infections of bacterial and viral origins (sepsis by 50 %);

– embolism of amnionic fluid;

– shock;

– burns;

– dehydration (bleeding, dyspeptic disorder);

– injury;

- – dystrophic changes of organs;
- – acute intravascular hemolysis;
- – malignant diseases;
- – diseases of blood (hemorrhagic vasculitis, leukemia);
- – snake and insect bites;
- – massive bleeding;
- – allergic reactions to medicines and of other origins;
- – blood contact with a foreign surface (hemodyalysis and artificial hemocirculation apparatuses, etc.).

Pathogenesis and clinical signs

- The arrival of tissue thromboplastin is a start in the process of DICS (III factor), then through VII factor and other factors the external mechanism of coagulation is activated. Other factors, through activation of XII factor, cause activation of the internal mechanism of hemostasis. Sometimes the process can start from hemolysis. Vascular epithelium is affected by this whole process. Finally, a lot of microscopic clots of fibrin are organized, thereby thrombosing vessels.

There are 4 stages of the above syndrome

- I: the phase of hypercoagulation and aggregation of thrombocytes. The symptoms of this stage include hyperthermia, pallor and "marble" pattern of skin, convulsion syndrome and petechiae. Clotting time (Lee-White and Burker's tests) is accelerated (Lee-White test is less than 4 minutes).

- II: the transition phase with increased coagulopathy and thrombocytopenia, different directions of changes in coagulation tests:

a) clotting time and prothrombine index are typical for hypercoagulation;

b) thrombine time is prolonged due to deficit of fibrinogen.

- III: the phase of expressed hypocoagulation up to complete (absolute) absence of blood clotting.

Indices of clotting time will be increased or blood clotting cannot be realized.

- IV: the phase of restitution (in unfavorable cases – the phase of complication or lethal outcome occur).

Hemorrhagic diathesis

Hemorrhagic syndrome is a clinical manifestation of the organism's tendency to recurrent bleeding and hemorrhage spontaneously or under influence of a minor injury. Hemorrhagic syndrome is typical for a group of diseases which are called hemorrhagic diatheses.

Diatheses are divided into 3 groups according to the main pathological syndrome, which is based on 3 factors of hemostasis:

– coagulation system of blood;

– quality and quantity of thrombocytes;

– vascular wall (normally, formed elements of blood do not come through the vascular wall).

Hemorrhagic diatheses are classified as:

– coagulopathies (disorders of coagulation are the base of pathogenesis), hemophilia and others;

– thrombocytopathy (disorder of formation and quantity of thrombocytes) – Werlhof's disease and others;

– vasopathy (affection of the vascular wall) – Schönlein - Henoch's purpura and others.

- **Leukosis** is a malignat tumor originating in hemopoetic cells and accompanied by affection of the bone marrow with ousting of the normal hematopoetic sprout. The term "leukemia" is the synonym for the term "leukosis".
- The origin of leukosis is unknown. This disease is known to occur more often in cases of: X-ray radiation, ionizing irradiation, prolonged taking of cytostatic immunologic depressants, influence of radioactive and some chemical substances (benzol).
- Inherited predisposition to leukosis is noticed. All leukoses are divided into acute and chronic (not according to the duration of the disease, but by the character of disorder of hemopoiesis and blood cell composition).

- In compliance with the type of cell precursor of malignant hemopoietic cell (lymphoblast, erythroblast, megakaryoblast), it is possible to determine such types of acute leukosis as lymphoblastic, myeloblastic and megakaryoblastic. The form of leukosis, which originates in undifferentiated cells, is called undifferentiated leukosis.
- In children, acute leukosis is more common than chronic. The latter is characterized by increased proliferation of immature cells and their ability to differentiate to matured cells. Almost all malignant cells are represented by the morphologically matured cells (lymphocytes in case of lympholeukosis, monocytes in monocytic leukosis, erythrocytes in erythremia, and so on).

Malignant proliferation of blood cells from the bone marrow is the main pathogenic sign of acute leukosis. These changes are accompanied by haemorrhagic syndrome, necrotic-ulcerated and dysthrophic processes, infectious complications.

At the onset of the disease its symptoms have common features: general weakness, tiredness, dyspnea, tachycardia, dizziness.

The most typical symptoms appear in the acute stage of the disease:

– osteoalgia, arthralgia, pain in the sternum during a slight beating, then symptoms of leukosis rapidly develop;

– fever, hemorrhagic syndrome (petechiae, hemorrhages on the skin, in the subcutaneous tissue and brain). Hemorrhagic syndrome is caused by disorders of 3 haemostatic factors: thrombocytopenia, affection of the vascular wall (leukemic infiltration) and disorders of the coagulation system, ulcerous-necrotic process in the oral cavity and intestines, anemia.

It is possible to reveal during examination:

– enlargement of lymph nodes;

– Miculicz's syndrome, i.e. leukemic infiltration of the lacrimal gland tissue and saliva;

– myocardiodystrophy;

– tachycardia;

– low BP;

– pneumonia with leukemic meningoencephalitis.

Laboratory data

Bone marrow puncture:

– enlargement in the quantity of blast cells to 70-100 % of cells;

– decrease in the quantity of erythronormoblasts, cells of granulocytic type and megakaryoblasts.

Blood count:

– erythropenia (up to 1.0-1.5x10^9 /l);

– decrease of hemoglobin (down to 20-30 g/l);

– thrombocytopenia (below its critical level);

– leukocyte count can be different (from leukopenia to hyperleukocytosis);

– leukemic blast cells (the main count of leukograms), whose quantity can reach 100 %;

– hiatus leukemicus is an important sign;

– increase of ESR.

The anatomo-physiologic peculiarities of immune system in children

- The immune system defends the individual from infections such as bacteria, viruses, fungi, protozoa and their virulence factors. The immune system also impedes the development of malignant diseases. The cost of this protection is allergy, autoimmune diseases and rejection of organ transplantations.
- All organs of the immune system may be divided into central (the thymus and bone marrow) and peripheral lymphoid organs, such as lymph nodes, the spleen and gut-associated lymphoid tissue (tonsil, Peyer's patches, and appendix).

The thymus is the central organ for differentiation of T (thymus-dependent) lymphocytes. Stem cells migrating to the thymus in early fetal life are influenced by humoral factors, such as thymosin and thymopoetin. On leaving the thymus, these T cells migrate throughout the body and preferentially seed specific T cell areas within the lymph nodes, spleen, appendix, and intestinal Peyer's patches. The thymus is a rather mature organ after birth. Its maturation continues till 12-15 years. After 15 years the thymus function decreases; this is called physiological involution. If involution takes place early due to action of pathological factors (stress and severe diseases), this is called accidental (convertible) involution.

- The structure of lymph nodes resembles that of the thymus. It consists of a capsule, paracortical (T-dependent) areas and germinal (thymus-not-dependent) centres. This is a place for synthesis of antibodies. A delay of antigens and tumor cells and destruction of erythrocytes occur here.
- The spleen is formed in the 5^{th} week of the intrauterine development, but its maturation is over some years after birth. The function of the spleen in immunity resembles that of lymph nodes.
- The intestinal lymphoid tissue is formed from the 9^{th} till the 20^{th} week of gestation. The lymphoid tissue of the intestines takes part in the formation of tolerance to food allergens.
- The tonsils are laid in the 22^{nd} week of gestation, but develop till the period of sexual maturity. The lymphoid tissue of the intestines and respiratory tract is of great value for local defense, synthesis of antibodies and differentiation of lymphocytes.

Immunity may be divided into two types: innate (non-adaptive, non-specific) and adaptive.

The innate immune system consists of the following parts.

1. Natural barriers:

– anatomical barriers (the skin and mucous membranes);

– mechanical removal (cough, diarrhea, vomiting, the discharging of urine, sweat, saliva, tears);

– biochemical barriers (lysozyme, acidity of stomach juice, fatty acids of sebaceous glands, biochemical changes due to high temperature, the hormonal status, etc.).

2. Cells of the innate immune system:

– macrophages phagocytize and kill bacteria; they produce antimicrobial peptides and inflammatory cytokines;

– natural killer (NK) cells kill foreign and host-affected cells;

– neutrophils phagocytize and kill bacteria; they produce antimicrobial peptides;

– eosinophils kill invading parasites;

– mast cells and basophils release inflammatory cytokines in response to antigens;

– epithelial cells produce anti-microbial peptides; tissue-specific epithelia produce mediator of local innate immunity, e.g. lung epithelial cells produce surfactant proteins that bind and promote clearance of lung-invading microbes.

3. Humoral (plasma) factors:
   – complement system;
   – blood coagulation system (plasma factors);
   – properdin;
   – acute phase proteins (C-reactive protein);
   – interferon.

Lysozyme is a termostable factor, present in lymphocytes, blood plasma, tear, saliva, mucous secretions of the respiratory and intestinal tracts. It plays an important part in local immunity. It causes lysis of Gram-positive microbes. The quantity of lysozyme in newborns versus adults is higher.

Phagocytosis is the main function of cells of the innate immune system. Phagocytosis consists of several stages: activation, chemotaxis, adhesion, absorption of antigen into cytoplasma-forming vacuoles, lysis. All phagocytes may be divided into two groups: macrophages (monocytes, NK) and microphages (neutrophils, eosinophils, basophils). Phagocytosis in newborns is not perfect. The function of absorption is advanced, but lysis is underdeveloped. The function of digestion (maturation of cation protein in phagocytes) is formed only to 6 months. Except for that, some microbes (Haemophilus influenzae, Klebsiella pneumoniae) cannot be destroyed by phagocytosis in early childhood. This is the cause of a high frequency of pneumonia and its severe course with complications and serious prognosis in this age period. Other microbes (Staphylococci, Gonococci) keep an ability to multiply in the protoplasm of phagocytes and cause destruction of phagocytes.

The complement system is a series of plasma enzymes, regulatory proteins and proteins that are activated in a cascading fashion, resulting in cell lysis. There are two arms of the complement system activation: by classic and alternative complement pathways. Both lead to cleavage and activation of C3. The latter is a protein whose activation fragments, when bound to target surfaces such as bacteria and other foreign antigens, are critical for opsonization (coating by antibody and complement) in preparation for phagocytosis. The classic complement pathway is activated by interaction of antigen and antibody to form immune complexes. The classic pathway is a rapid and efficient manner to activation of terminal complement components.

- In contrast, activation of the alternative complement pathway is slower and less efficient. In addition to the role of complement in opsonization of bacteria and cell lysis, several complement fragments are potent mediators of immune cell activation. C3a and C5a bind to receptors on mast cells and basophils, resulting in release of histamine and other mediators of anaphylaxis. C5a is also a potent chemoattractant for neutrophils and monocytes-macrophages. The complement system activity in newborns is low (50% versus in adults), but it increases very fast during the first month and at the age of 1 month it is equal to the level of adults.

- The level of properdin (a protein for activation of the alternative way of the complement system) is low at once after delivery, but it increases very fast during the first week and its level during all periods of childhood is high.

- Interferon (IFN) is produced by leukocytes (macrophages, lymphocytes), dendritic and epithelium cells in response to viral infections. IFN in turn activates NK cells to kill virally infected cells and activates monocytes-macrophages to recruit antigen-specific T and B cells to respond to viral infections. There are 3 types of INF: INF-α is synthesized by B lymphocytes; INF-β is synthesized by fibroblasts; INF-γ is synthesized by O and T lymphocytes. The newborn is characterized by a high ability to synthesize INF, but then this ability decreases till 1 year. After 1 year it increases and reaches its maximum level by the age of 12-18 years.

• The adaptive immune system is characterized by antigen-specific responses to antigen and, compared to innate immunity which occurs immediately (1 to 2 days), generally takes several days or longer to materialize. A key feature of adaptive immunity consists in memory for the antigen, so that subsequent antigen exposures lead to more rapid and often more vigorous immune responses. The adaptive immune system consists of dual limbs: cellular and humoral immunity.

- Adaptive immunity is found only in the vertebrates and is based on the generation of antigen receptor T and B lymphocytes by germ-line gene rearrangements that occur during the development of each person.
  • Mature T lymphocytes constitute 70 to 80 % of normal peripheral blood lymphocytes. T cells are the primary effectors of cell-mediated immunity, with subsets of T cells maturing into CD8+ cytotoxic T cells capable for lysis of virus-infected or foreign cells and CD4+ helper T cells, which are regulatory cells for immunity by the production of cytokines. In addition, T cells regulate erythroid cell maturation in bone marrow, and through cell contact play an important part in activation of B cells and induction of Ig isotype switching.

Mature B cells comprise 10 to 15 % of human peripheral blood lymphocytes. On their surface, B cells express intramembranous immunoglobulin (Ig) molecules that function as B cell receptors for antigen in a complex of Ig-associated. The primary function of B cells consists in production of antibodies. B cells also are highly efficient at antigen processing. Their antigen-presenting function is enhanced by a variety of cytokines. B-lymphocyte development can be divided into antigen-independent and antigen-dependent phases. Antigen-independent B cell development occurs in the primary lymphoid organs, including the fetal liver and bone marrow. Antigen-dependent B cell maturation is driven by the interaction of antigen with the mature B cell, leading to memory B cell induction, Ig class switching, and plasma cell formation. Antigen-dependent stages of B cell maturation occur in the secondary lymphoid organs, including lymph nodes, spleen, and gut Peyer's patches.

Immunoglobulins are products of differentiated B cells and mediate the humoral immune response. The primary functions of antibodies are to bind specifically to antigen and bring about the inactivation or removal of the offending toxin, microbe, parasite, or another foreign substance from the body. All immunoglobulins have the basic structure of two heavy and two light chains. Immunoglobulin isotype (G, M, A, D, E) is determined by the type of Ig heavy chain present. IgG and IgA isotypes can be divided further into subclasses (G1, G2, G3, G4, and A1, A2), based on specific antigenic determinants on Ig heavy chains.

IgG comprises approximately 75 to 85 % of the total serum immunoglobulin. IgG antibodies are frequently predominant antibodies made after challenge of the host with antigen (the secondary antibody response). The ability to synthesize antibodies arises in the intrauterine period. IgG may be synthesized from 5 months of gestation. But the fetus is in sterile conditions, that is why the levels of all its own Igs are not high. They may increase only after antigen stimulation due to some intrauterine infection. But maternal IgG is actively transported across the placenta and found in the fetal intravascular and extravascular spaces. Maternal IgG provides passive immunity against generalized infections. Blood group antibodies are also in the IgG class and therefore can freely cross the placenta to cause haemolytic disease of the newborn.

IgM is the first immunoglobulin to appear in the immune response (the primary antibody response). It is the initial type of antibodies made by neonates. IgM may be synthesized from 3 months of gestation. The IgM molecule is the largest of all immunoglobulins, therefore it cannot cross the placenta. If IgM is found in the fetus or neonate it must be of a fetal origin and prove the existence of a congenital infection.

IgA comprises only 7 to 15 % of the total serum immunoglobulin but is the predominant class of immunoglobulins in secretions (tears, saliva, nasal secretions, gastrointestinal tract fluid and human milk) and plays an important part in local immunity. IgA may be synthesized from 7 months of gestation. IgA is the second largest group of immunoglobulins and it cannot cross the placenta. Its presence in human breast milk lowers the incidence of enteric infections in breastfed infants. IgA can be found in saliva of neonates after several days of life.

IgD is found in small quantities in serum. It is a marker for mature B cells.

• IgE, which is present in serum in very low concentrations, involves mast cells and basophils in activation. Antigen cross-linking of IgE molecules on basophil and mast cell surfaces results in release of mediators of the immediate hypersensitivity response (allergy, antiparasite responses).

Cytokines are soluble proteins produced by a wide variety of hematopoietic and nonhematopoietic cells. They are critical for both normal innate and adaptive immune responses. Cytokines exert their effects by influencing gene activation that results in cellular activation, growth, differentiation, functional cell-surface molecule expression, and cellular effector function. In this regard, cytokines can have dramatic effects on the regulation of immune responses and pathogenesis of a variety of diseases. Indeed, T cells have been categorized on the basis of the pattern of cytokines, that they secrete, and it results in either humoral immune response (TH2) or a cell-mediated immune response (TH1).

Several responses by the host's innate and adaptive immune systems to foreign microbes culminate in rapid and efficient elimination of microbes.

There are five general phases of host defences:

1) migration of leukocytes to sites of antigen localization;

2) antigen nonspecific recognition of pathogens by macrophages and other cells of the innate immune system;

3) specific recognition of foreign antigens mediated by T and B lymphocytes;

4) amplification of the inflammatory response with recruitment of specific and nonspecific effector cells by complement components, cytokines, kinins, arachidonic acid metabolites and mast cell-basophil products;

5) macrophage, neutrophil, and lymphocyte participation in destruction of antigen with ultimate removal of antigen particles by phagocytosis or direct cytotoxic mechanisms.

The clinical examination of patients suffering from immune disorder includes:

questioning (complaints, case history, family history, side effects of vaccination, serum and blood transfusion);

physical examination –

– visual examination (assessment of physical development, condition of the skin, mucous membranes and skeleton, presence of ataxia, etc.) to reveal signs of immunological insufficiency;

– palpation (the spleen, liver and lymph nodes,);

– auscultation (to reveal infections from the respiratory and cardiovascular systems, which can be clinical manifestations of the immune system disorders).

Paraclinical methods of investigation

• Clinical assessment of immunity requires investigation of the four major components of the immune system that participate in host defence and in the pathogenesis of autoimmune diseases: (1) humoral immunity (B cells); (2) cell-mediated immunity (T cells, monocytes); (3) phagocytic cells of the reticuloendothelial system (macrophages), as well as polymorphonuclear leukocytes; and (4) complement.

Semeiology of the immune system diseases

Clinical problems that require an evaluation of immunity include chronic infections, recurrent infection, unusual infecting agents and certain autoimmune syndromes. Immunodeficiency disorders may be primary and secondary.

Primary immunodeficiencies may be either congenital or manifested later in life and are currently classified according to the mode of inheritance and whether the genetic defect affects T cells, B cells or both.

Secondary immunodeficiencies are those, which are not caused by intrinsic abnormalities in development or function of T and B cells. Their examples are: AIDS, immune deficiency associated with malnutrition, protein-losing enteropathy, intestinal lymphangiectasia, hypercatabolic states such as occur in myotonic dystrophy, lymphoreticular malignancy. Secondary immunodeficiencies may be permanent or transient.

Examples of T-cell immunity deficiency:

- Di-George's syndrome is probably caused by an embryologic field defect that often results in thymic abnormalities (immune defects), heart malformations, facial anomalies, parathyroid deficiency (convulsion) and urinary tract abnormalities.
- Nezeloff's syndrome, a cartilage-hair hypoplasia, a bone dysplasia, is associated with short-limbed dwarfism and immune deficiencies similar to Di-George's syndrome.
- Antibody deficiencies result in recurrent or chronic bacterial infections (sinopulmonary infection, otitis media, meningitis and bacteraemia), frequently with organisms such as Str. pneumoniae and Haemophilus influenzae and Staphylococci; and nodular lymphoid hyperplasia. Infestation with the intestinal parasite Giardia lamblia is a frequent cause of diarrhea in antibody-deficient patients.

Examples of B-cell immunity deficiency:

X-linked Bruton's agammaglobulinaemia includes all classes of immunoglobulin deficiency. Typical for agammaglobulinemia are recurrent bacterial infections. There may be growth failure, but usually there is no lymphadenopathy or splenomegaly. Skin disorders and later pulmonary dysfunction are frequent.

Selective deficiencies of immunoglobulins

- Selective deficiency of immunoglobulin A is characterized by recurrent respiratory infections and diarrhea. Autoimmune diseases are associated, but many children are asymptomatic. Serum and secretory IgA disorders may be distinguished, but they are usually not isolated defects.
- Selective deficiency of immunoglobulin M. These patients have a high risk of rapid hematogenous spread of bacterial infections.

Combined immunodeficiency disease (T and B cell associated deficiency):

The most severe form of immune deficiency occurs in infants, who lack both cell-mediated and humoral immune functions. Individuals with severe combined immunodeficiency are susceptible to the whole range of infectious agents including organisms not ordinarily considered pathogenic. Multiple infections with viruses, bacteria and fungi occur, often simultaneously. Combined immunodeficiency disease may be a mild or severe disorder leading to death within several years of birth. The type of infections that occur depends on the combination and degree of T and B cell defect. Common are gastroenteritis, hepatitis and skin manifestations.

- Wiscott-Aldrich syndrome, an X-linked recessive disorder, is characterized by thrombocytopenia, otitis, pneumonia and eczema during the first 6 months of life. Hepatosplenomegaly and lymphadenopathy are common. Serum IgG and IgE are markedly elevated.
- Ataxia-telangiectasia is characterized by ataxia, ocular and cutaneous telangiectases, chronic sinopulmonary disease, endocrine abnormalities and neurological disorders.
- Disorders of phagocyte function are frequently manifested by recurrent skin infections, often due to Staphylococcus aureus, abscesses of the subcutaneous tissue and lungs, purulent arthritis and osteomyelitis.
- Deficiencies of early and late complement components are associated with autoimmune phenomena and recurrent Neisseria infections.

Acquired immune deficiency syndrome, or acquired immunodeficiency syndrome (AIDS), is a disease of the human immune system caused by the human immunodeficiency virus (HIV). This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumors. HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a HIV-containing bodily fluid, such as blood, semen, vaginal fluid, and breast milk. This transmission can be due to anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, exchange between mother and baby during pregnancy, childbirth, breast feeding or other exposure to one of the above bodily fluids. AIDS is now a pandemic disease.

Thank you for attention.