**PATHOPHYSIOLOGY OF BLOOD SYSTEM**

The normal blood composition may change as a result of direct action of different injurious factors on the blood, or the changes may reflect the dysfunction's of various organs and tissues. Changes in the blood's biochemical composition and physicochemical properties, in its total volume, in blood cells and blood coagulability are distinguished.

Study of changes in the physicochemical properties of the blood is of diagnostic significance.

The specific gravity of the blood (normally 1.050-1.060) depends mainly on the number of erythrocytes, content of proteins and mineral substances (especially that of sodium chloride). Disturbances in protein metabolism particularly visibly affect the specific gravity of the blood. It increases in the pathological states that are connected with loss of water and hemoconcentration (for instance, in cholera), decreases in cases of blood dilution, that is, hydremia (for example, in various forms of qualitative starvation.

The viscosity of the blood (normally 5,if the viscosity of water is assumed to be unity) depends mainly on the number of blood cells, concentration of proteins, amount of colloidal substances, carbon dioxide saturation, etc. In pathology it may vary between 2 and 20. Anything that contributes to hemoconcentration increases the viscosity of the blood. It increases in polycythemia, leukemia, hyperproteinemia (especially hyperfibrinogenemia). Accumulation of carbon dioxide in the blood (hypercapnia) increases its viscosity. Therefore, viscosity of the venous blood is higher than that of arterial blood. The viscosity decreases in anemia, hydremia, hypoproteinemia, etc.

The surface tension of the blood (normally 57-58 dyna/cm) is measured by the strength required to separate the platinum ring which is in touch with the blood. Such substances as bile acids, soaps and certain metabolites reduce it. So, the surface tension of the blood decreases in jaundice, uremia, asphyxia, cancer, etc. In hypoproteinemia and hydremia it increases.

The osmotic pressure of the blood (normally 7.6-8.1 atm.) depends on the amount of ions and molecules of mineral substances. The osmotic pressure of the venous blood is somewhat higher than that of the arterial blood because the former contains more metabolites. Sodium ions play an important part in changes of osmotic pressure-hyperosmia (blood concentration of Na > 150 meq/l) and of hyposmia (blood concentration of Na < 135 meq/l). Increased carbon dioxide in the blood (respiratory, circulatory or metabolic disturbances) increases its osmotic concentration (owing to the increased dissociation of salts). Acute loss of water, excessive intake of sodium chloride in food, or disturbance of its excretion from the organism cause hyperosmia. In severe cases of hyperosmia dehydration in cells, rapid breakdown of proteins, muscular cramp are observed. Decreased osmotic pressure causes edema in cells which is especially dangerous in brain cells. In hypotonic solutions normal human erythrocytes can increase 46% of their volume and then hemolysis occurs.

The osmotic resistance of erythrocytes (normally the minimal resistance corresponds to the 0.4% and the maximal resistance-to the 0.34% NaCl solution) depends on their form, extent of maturity, composition of plasma. Ratio of erythrocyte's thickness to its diameter, that is, coefficient of sphericity (normally 0.27-0.28) influences greatly its osmotic resistance. In hereditary spherocytosis this index is increased, erythrocytes become like the sphere, their osmotic resistance is decreased. That is why this disease is accompanied by the hemolytic anemia.

The coefficient of sphericity is increased (osmotic resistance is decreased) also in hypercapnia (erythrocytes swell). In young erythrocytes (reticulocytes) this coefficient is low and they easily endure the decreased osmotic pressure, whereas to the end of their life the erythrocytes assume the form of sphere. In hypercholesterolemia the osmotic resistance of erythrocytes is increased. Because cholesterol settles on the membranes of erythrocytes and strengthens them.

The oncotic pressure of the blood (normally 0.03-0.04 atm, that is, 25-30 mm Hg) depends on the presence of proteins in it. So, the blood's oncotic pressure increases in hyperproteinemia and decreases in hypoproteinemia.

The osmotic and oncotic properties of the blood and tissues are particularly important in the genesis of oedemas.

ESR, that is, erythrocyte sedimentation rate (normally 3-9 mm/hour in men and 7-12 mm/hour in women) depends on the quantitative and qualitative composition of the plasma proteins, viscosity and density of the blood, number of erythrocytes, blood content of cholesterol and lecithin, , etc.

Inflammatory process, infectious diseases, malignant tumours, collagenoses, nephroses, the pathological states leading to breakdown of tissues are accompanied by increase of ESR. This is connected with changes in the ratio between plasma proteins. In normal conditions the erythrocytes' membranes are negatively charged and push away each other. Large-disperse proteins (globulin, fibrinogen), accumulating on their surface, reduce the erythrocyte charge and contribute to agglutination of the cells, which is conducive to their sedimentation. Physiologically ESR is increased in pregnancy.

Increased ESR is observed also in hyperchlesterolemia, decreased viscosity of the blood and number of erythrocytes (hydremia, anemia), increased osmotic pressure of the plasma (erythrocytes lose water, their volume is decreased and specific mass is increased).

Decreased ESR is observed in the following cases: increased blood content of lecithin and viscosity of the blood, polycythemia, dehydration, hypercapnia (a large amount of water penetrates into erythrocytes, and their specific mass decreases).

**Different pathological states cause changes in total volume of the blood. Normal total volume of the blood (4.5-6 litres) is called hypervolemia (polyemia or plethora) and its decrease-hypovolemia (oligemia).**

Depending on hematocrit (the per cent of cells in the blood), three forms of normovolemia, hypervolemia and hypovolemia are distinguished:

a) simple - with normal hematocrit (in men about 42%, in women - about 38%);

b) polycythemic - with increased hematocrit;

c) oligocythemic -with decreased hematocrit.

The simple normovolemia characterizes the normal state of the blood volume and ratio between the blood cells and plasma. The polycythemic normovolemia is observed in physiological conditions in persons living in highlands. The oligocythemic normovolemia occurs in different types of anemia.

The simple hypervolemia may arise for a short time following transfusion of large amounts of blood or as a result of ejection of blood from the blood depots in the beginning of strenuous work. The polycythemic hypervolemia (true plethora or true polyemia) is the main manifestation of erhythremia (Vaquez' disease). It is observed also in the diseases that are accompanied by the general oxygen deficiency (heart disease, respiratory insufficiency) and in persons living in highlands. The oligocythemic hypervolemia (hydremic plethora) may be due to retention of water in the blood stream as a result of certain diseases of the kidneys or disturbances in water metabolism, or diseases of the hematopoietic system. The attempts to produce oligocythemic hypervolemia experimentally by intravenous injections of physiological saline solutions have failed. Because the excess of fluid rapidly passed from the blood into the tissues and was gradually eliminated mainly through the kidneys.

The simple hypovolemia is observed for a short time directly after acute loss of blood (due to injuries of large vessels, ulcers, active forms of pulmonary tuberculosis or rupture of the fallopian tubes). The polycythemic hypovolemia (anhydremia) is characterized by appreciable concentration and increased viscosity of the blood. It is resulted from considerable loss of water by the organism (in cholera, dysentery, infantile diarrhea, intractable vomiting, extensive burns involving loss of a great deal of fluid with the exudate and evaporation from burned surfaces). The oligocythemic hypovolemia is observed in pernicious anemia (Addison-Biermer's anemia) as well as after a considerable blood loss in cases of increased passage of fluid from tissues into the vascular system.

One of the main causes of the decreased circulating blood volume is acute loss of blood. Going of blood out of the vascular lumen and cavity of the heart is called hemorrhage (bleeding). Accumulation of the blood which goes out of the vessel, in the intercellular space, is called apoplexy. The blood that is accumulated between the tissue elements which have not lost their morphological structure, is hemorrhagic infiltration. The mass of clotted blood accumulated in the damaged tissues is called hematoma.

Menstruations and normal labour are accompanied by the physiological loss of blood.

External and internal hemorrhages are distinguished. The external hemorrhages include hematemesis (black vomit) and melon (bloody stools) in ulcer and tumors of the digestive system, hemoptysis (blood spitting) in cavernous tuberculosis of lungs, metrorrhagia (pathological uterine bleeding), epistaxis (nasal bleeding). In the internal hemorrhages the blood is accumulated in the pericardial cavity (hemopericardium), pleural cavity (hemothorax) or peritoneal cavity (hemoperitoneum).

According to the character of the blood that is lost, the arterial (scarlet blood), venous (dark-red blood) and capillary (parenchymatous) hemorrhages are distinguished.

According to the mechanism of going of the blood out of vessels 3 types of hemorrhages are distinguished:

1) hemorrhage per rexin - from the vessel which is cut or torn;

2) hemorrhage per diabrosin - as a result of dissolving of the vascular wall in the area of the inflammatory process, ulcer or tumor;

3)hemorrhage per diapedesin - as a result of sharply increased vascular wall permeability.

The changes in the organism caused by loss of blood depend on a number of factors: rate of bleeding, amount of the blood that was lost, type of injury, rate of development of the organism's compensatory reactions, sex and age of the patient, general state of the organism before loss of blood (common cold diseases), blood coagulability, etc.

Loss of the 15-20% of the total amount of the blood does not cause severe changes in the healthy organism; a brief anemia may occur. It may be dangerous for life in hypothermia and in the organism that is weakened by diseases. Instant loss of 25-30% of the blood is dangerous for the life, and that of 50-60% is fatal (the death occurs as a result of paralysis of the respiratory center).

In the severe cases of blood loss extreme pallor, cooling of the skin, disorders in respiration and hemodynamics (microcirculatory changes, thready pulse, drop in arterial pressure, arrhythmia, cardiac failure), convulsions, loss of consciousness, involuntary micturition and defecation are observed. Hypoxia leads to the metabolic acidosis, disturbances in the activity of the central nervous system, and the vicious circle is formed. The pathological changes caused by the loss of blood are accompanied by the rapid (immediate) and protracted compensatory reactions.

The rapid compensatory reactions are connected with changes in the activity of the cardiovascular system (reflex spasm of peripheral vessels and redistribution of the blood, mobilization of the blood from depots and increase of the circulating blood volume, acceleration and strengthening of systoles, etc.) and increased blood coagulability.

The protracted compensatory reactions include recovery of the normal content of the plasma proteins (8-10 days after the loss of blood they become normal) and acceleration of the hemopoiesis. Hypoxia accelerates synthesis of erythropoietins which stimulate erythropoiesis. Hemopoiesis is stimulated also by the products of destruction of erythrocytes.

The neurohumoral and hormonal factors play a great part in the development of the organism's compensatory reactions. For instance, owing to the reflex stimulation of the vasomotor center, increased tonicity of the sympathetic nerve, hypersecretion of catecholamines and renin the tension of the peripheral vessels is increased, hypersecretion of the aldosterone and antidiuretic hormone cause delay of the water and chlorides in the organism.

Some hormones (thyroxin, ACTH, glucocorticoids) as well as the sympathetic nervous system, stimulate the erythropoiesis, whereas female sex hormones as well as parasympathetic nervous system, inhibited.

During loss of blood synthesis of thrombopoietins is accelerated, and several hours later the number of thrombocytes is increased twice.

In the blood cells quantitative and qualitative changes are observed. But qualitative changes rarely occur without concurrent qualitative changes.

**Increased number of erythrocytes is called erythrocytosis (polycythemia or erythremia). This may be absolute or relative.**

In the relative erythrocytosis the number of erythrocytes in a unit of blood volume is increased, though erythropoiesis is not accelerated and the total number of erythrocytes is not increased. This is connected with dehydration and hemoconcentration as a result of loss of water (in profuse perspiration, diarrhea, projective vomiting, cholera, poisoning) or rapid mobilization of the blood from depots.

The absolute erythrocytosis, that is, increase in the total number of erythrocytes as a result of accelerated erythropoiesis, may be primary and secondary (symptomatic).

The primary erythrocytosis is the main symptom of Vaquez disease or Vaquez-Osler disease (polycythemia vera or erythremia)- which is one of the diseases of the hematopoietic system of the tumoral character. In this disease the myeloid tissue is proliferated, and the number of all blood cells is increased: in 1 mcl of the blood 7-10 millions of erythrocytes, 9-15 thousands of leukocytes, from 400 thousands to 1 million of thrombocytes are found; hematocrit reaches 60-70%. The blood content of hemoglobin is increased (up to 180-200 g/l) relatively less than the number of erythrocytes, and therefore, the colour index is somewhat lowered. As a result of polycythemic hypervolemia and increased blood viscosity the blood pressure and the heart's work are increased, and the left ventricle is hypertrophied. Hyperemia in skin, mucous membranes and internal organs (especially in spleen and liver), increased vascular permeability, hemorrhages in tissues, microthrombi in the vessels of the microcirculatory system are observed. This disease is more frequent in men. Now it is regarded as a type of chronic leukosis of the myelocytic origin.

The secondary erythrocytosis is frequently connected with hypoxia and increased synthesis of erythropoietins (in the inhabitants of highlands, mountain - climbers, persons with the chronic diseases of the respiratory and cardiovascular system). Besides, it is observed in methemoglobinemia, hereditary erythrocytosis, in diseases connected with hypersecretion of ACTH and androgens (increased need in oxygen), in some tumors of the renal parenchyma.

**Reduction in the number of erythrocytes and hemoglobin concentration per unit of blood is called anemia.** In anemia colour (anisochromia), form (poikilocytosis) and size (anisocytosis) of erythrocytes may change, that is, their pathological forms appear. In the most cases of anemia in the blood hypochromic (colour index < 0.9) and hyperchromic (colour index > 1) erythrocytes appear, anisochromia (different colour of erythrocytes in one smear or in different part of one erythrocytes) or polychromatophilia (erythrocytes are stained not only with acid, as normally, but also with basic dyes) are observed.

Poikilocytes are sickle-shaped (drepanocytes), ball-shaped (spherocytes and microspherocytes), oval (ovalocytes), pear-shaped, target-shaped erythrocytes and those with rough surface (acanthocytes).

Anisocytes include unusually large (macrocytes, megalocytes) or small (microcytes, schizocytes) erythrocytes. Megalocytes (diameter >10 mcm) are hyperchromic ovalocytes, and schizocytes (diameter 2-3 mcm) are particles of decomposed erythrocytes.

At the period after loss of blood the number of reticulocytes (regenerative forms of erythrocytes) in the peripheral blood is increased. In the cases of poisoning and disturbances in the function of bone marrow the degenerative forms of erythrocytes are revealed in the blood. These include poikilocytes, anisocytes and the erythrocytes containing different inclusions, that is, denaturated hemoglobin particles (Heinz bodies), the remains of nuclei (Jolly bodies and Cabot's ring bodies), granules containing iron compounds (siderocytes), basophilic granules, , etc.

In the anemias, which are accompanied by acceleration of the hemopoiesis, immature forms of erythrocytes (erythroblasts, pronormocytes and normocytes) appear in the blood. In megalocytic anemia megalocytes and, from time to the time, megaloblasts (with a large pale nucleus) are found. Appearance of such cells in the blood denotes return to the embrional type of hematopoiesis. They are revealed in the blood of patients affected with pernicious anemia, severe sepsis, and tuberculosis.

Development of separate types of anemia are connected with different factors: loss of blood, weakened erythropoiesis, accelerated destruction of erythrocytes (erythrodiaresis). Etiologically anemia must be regarded as the symptom-complex observed in different diseases, which cause above-mentioned states.

As a result of decreased number of erythrocytes and their qualitative changes the respiratory function of the blood and oxygen supply of tissues are disturbed. In the organism pathological changes occur that are resulted from hypoxia. Anemia is accompanied by the organism's compensatory reactions directed to the improvement of the oxygen supply of tissues: acceleration of erythropoiesis, changes in the interstitial respiration, increased activity of the cardiovascular and respiratory systems, increased blood coagulability, etc.

Classification of anemia is based on different principles. Depending on the colour index normochromic, hypochromic and hyperchromic anemias are distinguished. According to the volume of erythrocytes anemia may be normocytic, microcytic and macrocytic.

Depending on the type of hemopoiesis two types of anemia are distinguished:

1. postembryonal (erythroblasic) anemia - in the peripheral blood the bone marrow cells are revealed which are characteristic of initial stages of crythropoiesis (erythroblasts, pronormocytes; basophilic, polychromatophilic and oxyphilic normocytes; reticulocytes);
2. embryonal (megaloblastic) anemia - in the peripheral blood megaloblasts and megalocytes are found which are characteristic of the hemopoiesis in the embryonal period.

According to the hemopoietic function of the bone marrow anemias may be:

1) regenerative - is accompanied by acceleration of the hemopoiesis;

2) hyporegenerative - is accompanied by weakened hemopoiesis;

3) aregenerative - erythropoiesis is stopped temporarily or completely.

**The pathogenic classification is more widely used:**

**1. Posthemorrhagic anemias.**

**2. Dyserythropoietic anemias, that is, anemias due to disturbances in hemopoiesis.**

**3. Hemolytic anemias.**

According to their clinical course anemias may be acute and chronic.

Posthemorrhagic anemias arise as a result of blood loss caused by various factors. They may be acute and chronic.

Acute posthemorrhagic anemia arises after single severe hemorrhage (wounds, pulmonary, gastrointestinal or renal hemorrhages, severe post-partum hemorrhages, etc.). Loss of 25% of the circulating blood volume causes hypoxia which especially severely influences the central nervous system. Several stages may be observed in the acute posthemorrhagic anemia:

I. Latent anemia- in the first several hours after loss of blood the number of erythrocytes and content of hemoglobin decrease evenly, colour index is normal. In blood smear the changes characteristic of anemia are not revealed.

II. Reflex compensation- owing to the reflex spasm of vessels arterial pressure is normal. Blood is mobilized from depots.

III. Hydremic compensation- 1-2 days after loss of blood a large amount of fluid passes from tissues into the blood which promotes approach of circulating blood volume to the normal level. Absolute as well as relative number of erythrocytes decrease progressively.

IV. Medullary (bone marrow) stage- 4-5 days after acute loss of blood hemopoiesis is accelerated, in the peripheral blood the cells appear that are characteristic of regenerative anemia, colour index is decreased. The mechanism of acceleration of regenerative processes in posthemorrhagic anemia are connected with increased synthesis of erythrocytes as a result of hypoxia and stimulation of hemopoiesis by the products of erythrocytes.

Chronic posthemorrhagic anemia is caused by repeated (even slight) loss of blood: gastrointestinal hemorrhage (peptic ulcer, hemorrhoids, cancer), metrorrhagia, hemophilia. To provide the normal hemopoiesis daily 5mg iron is required which is contained in 10 ml of blood. So, in the organism that loses on an average 10ml blood iron deficiency anemia develops. The number of erythrocytes in the blood is decreased, the number of reticulocytes is above the normal level, the degenerative form of erythrocytes appear (microcytosis, poikilocytosis, hypochromia).

Anemias due to disturbances in hemopoiesis are caused by the following factors:

1) deficiency of substances that are necessary for normal course of erythropoiesis-iron, trace elements (cobalt, copper, manganese), vitamin B12, folic acid, pyridoxine, riboflavin;

2) long protein deprivation;

3) factors exercising toxic action on the bone marrow-ionizing radiation, chemical toxic agents (benzene, arsenic and bismuth compounds), microbial toxins, antibiotics (chloramphenicol, streptomycin), preparations inhibiting metabolic processes (6- mercaptopurine, mercusal);

4) leukosis;

5) tumoral metastases into bone marrow;

6) disturbances in the neurohumoral regulation of the erythropoiesis- decreased synthesis of erythropoietins, formation of inhibitors acting against erythropoietins.

Anemias due to disturbances in hemopoiesis are divided into two groups:

1) anemias caused by deficiency of factors with hemopoietic action (iron deficiency anemia, vitamin B12 deficiency anemia, folic acid deficiency anemia, Addison-Biermer's anemia);

2) anemias that develop as a result of damage of bone marrow:

a) rare forms of anemia (the special forms of hypoplastic anemia) which are connected with absence (hereditary or acquired) of ability of the bone marrow to use antianemic factors (achrestic anemia, sideroachrestic anemia);

b) hypoplastic and aplastic anemias.

These two groups of anemias are not sharply limited. For instance, the severe forms of anemias belonging to the first groups also may cause dysfunction of bone marrow.

Iron deficiency anemia is more frequent. Its etiologic factors are the following:

1) low content of iron in nutrients (in babies that intake monotonous food); increased need of organism for iron (at the period of rapid grows, pregnancy, lactation);

2) disturbances in assimilation of iron in the digestive tract (achlorhydria, vitamin C deficiency, enteritis, small intestine and stomach resection, disturbances in synthesis of transferrin);

3) excessive sweating;

4) chronic loss of blood.

Under conditions of iron deficiency hyporegenerative and hypochromic anemia develops. One of the main manifestations of this disease is decreased content of iron in blood plasma (100 mcg/l against normal 1000 mcg/l). In the peripheral blood anisocytosis and poikilocytosis are observed; the number of reticulocytes is somewhat increased, but then decreased.

One of the special types of iron deficiency anemia is chlorosis (skin becomes pale tinged with green). Two types of this diseases are distingueshed:

1) early chlorosis- is observed in girls ages 15-20 (at the period of puberty) when the iron that is assimilateb by the organism can not satisfy it is increased needs (increase of estrogens, menstrual loss of blood);

2) late chlorosis- is observed in women at the age of 30-40 and older as a result of chronic loss of blood caused by dysfunction of ovaries, menopause, etc.; decreased gastric juice acidity participates as an additional factor in the development of this disease.

It is well known that Castle's intrinsic factor (which is synthesized in the mucous membrane of the stomach) is bound with Castle's extrinsic factor (vitamin B12) and promotes its absorbtion in the stomach and small intestine. Vitamin B12 accelerates activation of the folic acid (folate in the liver, that is, its conversion into tetrahydrofolic acid which accelerates differentation of the immature forms of erythrocytes (erythroblasts, pronormoblasts, normocytes). So, identity of clinic and hematologic manifestations of vitamin B12 deficiency anemia and folate deficiency anemia (that is, megaloblastic anemias) is connected with their influence on the hemopoiesis.

In Western countries vitamin B12 deficiency is usually connected with pernicious (Addisonian) anemia. True vegetarians like in India and breast- fed infants have dietary lack of vitamin B12. Gastrectomy by lack of intrinsic factor and small intestinal lesions (involving distal ileum where absorption of vitamin B12 occurs) may cause deficiency of this vitamin. Vitamin B12 deficiency may be caused by tapeworms parasitizing in intestines, which assimilate vitamin B12. In some cases it is observed also in pregnant women. Vitamin B12 deficiency takes at least 2 years to develop when the body stores are totally depleted.

Folate deficiency arises suddenly since the body's stores of folate are relatively low which can last for up to 4 months only.

Patients with tropical sprue are often deficient in both vitamin B12 and folate. Combined deficiencies of vitamin B12 and folate may occur from severe deficiency of Vitamin B12 because of the biochemical interrelationship with folate metabolism.

In addition to deficiency of vitamin B12 and folate, magaloblastic anemia's may occasionally be inducad by other factors: many drugs which interfere with DNA synthesis, acquired defects of hemopoietic stem cells, rarely - congenital enzyme deficiencies.

Pathogenesis of vitamin B12 deficiency and folate deficiency anemias is connected with disturbance in synthesis of DNA in erythroblasts and normocytes, delay of mitosis and differentiation in these cells. Normoblastic erythropoiesis is replaced by megaloblastic erythropoiesis. Under these conditions up to 50% of cells are destructed immediately in the bone marrow (in norm - no more than 20%). This causes decreased number of erythrocytes passing from bone marrow into blood vessels.

Deficiency of vitamin B12 and folate cause clinical manifestations that may be present singly or in combination and in varying severety: macrocyting megaloblastic anemia (onset of which is insidious and gradually progressive), glossitis (smooth, beefy, red tongue), neurologic manifestations (degeneration of the spinal cord, peripheral neuropathy-numbness, paraesthesia, weakness, ataxia, poor finger coordination, diminished reflexes). Mild jaundice, angular stomatitis, purpura, melanin pigmentation, symptoms of malabsorption, weight loss, anorexia may be observed. In microscopic blood picture in peripheral blood megalocytes and single megaloblasts are revealed.These are easily hemolyzed and cause still more decrease in number of erythrocytes. Jolly bodies, Cabot's ring bodies, erythrocytes with basophilic granulation, poikilocytosis and anisocytosis (with a large number of macrocytes), excessively segmented neutrophils are revealed. Anemia is accompanied by leukopenia and thrombopenia. Owing to comparatively large size of cells the megaloblastic anemias are of hyperchromic type (colour index is 1.3-1.5), though the total amount of hemoglobin is low. Because the number of erythrocytes is decreased to an even greater degree (in 1 mol of blood to 2 millions of erythrocytes). Up to the time when vitamin B 12 was used, Addision-Biermer's anemia, as a rule, resulted in death and therefore, was called pernicious (malignant) anemia. This disease was first described in 1855 by Addison as a chronic disorder of middle-aged and elderly individuals of either sex in which intrinsic factor secretion ceases owing to atrophy of the gastric mucosa. The average age at presentation is 60 years but rarely it can be seen in children under 10 years of age (juvenile pernicious anemia). Pernicious anemia is seen most frequently in individuals of Northern European descent and American blacks and is uncommon in South Europeans and Orientals.

As for pathogenesis of the pernicious anemia there is evidence to suggest that the atrophy of gastric mucosa is caused by an autoimmune reaction against gastric parietal cells. Weakness of these cells may be inherited.

The following evidences exist in support of immune abnormalities in pernicious anemia:

1. The incidence of pernicious anemia is high in-patients with other autoimmune diseases (Graves'disease, myxoedema, thyroiditis, vitiligo, diabetes, and idiopathic adrenocortical insufficiency).

2. Patients with pernicious anemia have abnormal circulating autoantibodies (anti-parietal cell antibody in 90% cases, anti-intrinsic factor antibody in 50 % cases).

3. Relatives of patients with pernicious anemia have an increased incidence of the disease or increased presence of autoantibodies.

4. Corticosteroids have been reported to be beneficial in curing the disease both pathologically and clinically.

5. Pernicious anemia is more common in patients with agammaglobulinemia supporting the role of cellular immune system in destruction of parietal cells.

In achrestic (Gr. achrestes - useless, vain) anemia (Israels - Wilkinson syndrome) vitamin B12 content in blood plasma is more than normal, but bone marrow cannot use it. This results in disturbance in erythropoiesis: since erythroblasts cannot use vitamin B12, erythropoiesis continues by the erythroblastoid way which is characteristic of the embryonal development. The number of erythrocytes in peripheral blood is decreased down to 2-1 millions. There are many macrocytes and megalocytes among them, and therefore, colour index is more than 1.

In sideroachrestic (Greek, sideros-iron) anemias bone marrow cannot use combinations of iron. Hereditary and acquired disturbances of enzyme systems participating in the synthesis of the hemoglobin's prosthetic group (heme) form the basis of these diseases. They are accompanied by hemosiderosis, that is, a large amount of iron is accumulated in liver, pancreas, cardiac muscle, bone marrow, kidneys, adrenal and thyroid glands, and their anatomic-functional properties are disturbed. Changes in the peripheral blood are similar to those characteristic of iron deficiency anemia.

Hypoplastic and aplastic anemias result from the severe dysfunction of the bone marrow. ''Bone marrow failure'' is the term used for primary disorders of the bone marrow, which result in impaired formation of the erythropoietic precursors and consequent anemia. It includes aplastic anemia and other primary bone marrow disorders (pure red cell aplasia, myelodysplastic syndromes, myelophthisic anemia).

Aplastic anemia is defined as panmyelophthisis (Gr. pan-completely, myelos-bone marrow, phthisis-exhaustion, fading) or pancytopenia (simultaneous presence of anemia, leukopenia and thrombocytopenia) resulting from aplasia of the bone marrow. The underlying defect appears to be sufficient reduction in the number of hemopoietic stem cells, which makes them unable to divide and differentiate. Based on the etiology, aplastic anemia is classified into 2 main types: primary and secondary. Primary aplastic anemia includes:

1) congenital form called Fanconi's anemia which is often associated with other congenital anomalies (skeletal and renal abnormalities, sometimes-mental retardation);

2) immunologically mediated acquired form, which is caused by suppression of hemopoietic stem cells by immunologic mechanisms. Secondary aplastic anemia may be caused by a variety of industrial, physical, chemical, iatrogenic and infectious causes.

Ehrlich's syndrome (hypoplastic anemia) is also one of the main types of the anemias connected with hereditary factors.

Hemolytic anemias are defined as anemias resulting from increase in the rate of red cell destruction, that is, erythrodiaeresis prevails over erythropoiesis. Normally, effete erythrocytes undergo lysis at the end of their life-span of 120 days within the cells of reticuloendothelial system in spleen and elsewhere( extravascular hemolysis),and hemoglobin is not liberated into the plasma in appreciable amounts. The red cell life- span is shortened in hemolytic anemia, that is, accelerated hemolysis occurs. The premature destruction of erythrocytes in hemolytic anemia may occur by 2 mechanisms:

1) erythrocytes undergo lysis in the circulation and release their contents into plasma(intravascular hemolysis); the plasma hemoglobin rises substantially and part of it may be excreted in the urine(hemoglobinuria);

2) erythrocytes are taken up by cells of the reticuloendothelial system where they are destroyed and digested(extravascular hemolysis); plasma hemoglobin level is barely raised. Extravascular hemolysis is more common. Spleen is enlarged, jaundice and hemociderosis develop.

In hemolytic anemias blood content of products of erythrocytes' destruction is increased, erythropoiesis is accelerated. This results in increased number of reticulocytes and polychromatophile erythrocytes in the peripheral blood. Jaundice is caused by increased content of free (indirect) bilirubin. Accelerated erythrodiaeresis leads to the compensatory hyperplasia of the bone marrow. Hemolytic anemias are broadly classified into 2 main categories:

I. Acquired hemolytic anemias caused by variety of extrinsic environmental factors (extra-corpuscular).

II. Hereditary hemolytic anemias which are usually the result of intrinsic red cell defects (intracorpuscular).

Depending on the etiologic factors the following types of the acquired hemolytic anemias are distinguished:

1. Immunohemolytic anemias-occur due to antibody production by the body against its own erythrocytes:

a) autoimmune hemolytic anemias caused by warm antibody and cold antibody (cold agglutinin disease, paroxysmal cold hemoglobinuria), in malignant tumors, lupus erythematosus, etc.

b) isoimmune hemolytic anemias in which isoantibodies or alloantibodies are acquired by blood transfusions, pregnancies and in hemolytic disease of newborn;

c) drug-induced immunohemolytic anemias caused by α-methyl-dopa; penicillin; quinidine, etc.

2. Microangiopathic hemolytic anemias - are caused by mechanical trauma to erythrocytes in circulation and are characterized by schizocytosis (in karate players, patients with prosthetic cardiac valves or artificial grafts, hypertension, eclampsia, disseminated cancers, transplant rejection, hemangioma, hemolytic-uremic syndrome, disseminated intravascular coagulation).

3. Hemolytic anemias from direct toxic effects (malaria, bartonellosis, pneumococci, staphylococci, copper, lead poisoning, snake and spider bites, extensive burns). For instance, to reproduce hemolytic anemia in experiment, rabbit is administered phenylhydrazine.

4. Hemolytic anemia in splenomegaly, which exaggerates the damaging effect to which erythrocytes are exposed.

5.Acquired red cell membrane abnormalities -spur cell anemia (in severe cirrhosis, neonatal hepatitis), paroxysmal nocturnal hemoglobinuria.

In hereditary hemolytic anemias as a result of hereditary disturbances, erythrocytes lose their elasticity and are hemolyzed by macrophages of spleen and liver (hence splenomegaly and hepatomegaly). The hereditary diseases that are accompanied by the hereditary anemia, are divided into 3 groups:

1. Erythrocytopathies.

2. Erythrocytoenzymopathies.

3. Hemoglobinopathies (hemoglobinoses).

Erythrocytopathies or hereditary abnormalities of red cell membranes include hereditary spherocytosis (microspherocytic hemolytic anemia) and hereditary ovalocytosis or elliptocytosis (ovalocytic hemolytic anemia). Since the osmotic resistance of spherocytes and ovalocytes is low, they circulate in blood vessels no more than 12-14 days.

Erythrocytoenzymopathies are connected with hereditary disturbances in enzyme system of erythrocytes, especially deficiency of glucose-6-phosphate dehydrogenase (which catalyzes oxidation of glucose by the way of pentose monophosphate) and some other enzymes of glycolysis in erythrocytes. These diseases become worse after intake of some drugs (quinine, primaquine, paraaminosalicylic acid), vicia faba species of beans (fabism), under the influence of infectious agents, acidosis. The number of erythrocytes is sharply decreased, hemoglobinuria and jaundice are observed.

Hemoglobinopathies are connected with hereditary disturbances in hemoglobin molecule (more than 300 types of these disorders are known). They are divided into two groups:

1) qualitative disorders of hemoglobin- drepanocytosis (sickle-cell anemia), hemoglobinoses of C,D,M types;

2) quantitative abnormalities of polypeptide globin chain synthesis(α-and β- thalassemias).

Thalassemias (Gr. thalassa-the sea) were first described in people of mediterranean countries from where the name "Mediterranean anemia".

**Pathological changes in leukocytes also may be quantitative and qualitative.** The quantitative changes include decrease (leukopenia), increase (leukocytosis) in the number of leukocytes, changes in the differential blood count. In some hereditary and acquired diseases changes occur in the morphological and biochemical properties of leukocytes and qualitatively changed degenerative forms of leukocytes appear in the peripheral blood. Both quantitative and qualitative changes are observed in leukosis (leukemia) which is independent disease of the hematopoietic system.

Qualitative changes are frequent in neutrophils and monocytes. In neutrophils the following changes are observed:

1. Toxic granulation of cytoplasm-includes coagulated proteins which are formed under the influence of severe infectious and toxic agents.

2. Vacuolization of cytoplasm - is the sign of the fatty degeneration of cells (when the smear is fixed by spirit the fat is dissolved and in it's place empty spaces remain which do not accept colouring matters): It occur in severe sepsis, abscess, radiation sickness.

3. Dohle bodies-are small, round or oval patches in the cytoplasm, which are mostly seen in bacterial infectious.

4. Botkin-Gumprecht shadows, that is, the remains of lymphoblasts, prolymphocytes and lymphocytes that are distracted in the process of preparing of blood smear, are observed in chronic lymphoid leukemia.

5. Anisocytosis-leukocytes of different size are revealed.

6. Karyopyknosis-granulations of granulocytes disappear, nucleus is swollen.

7. Hypersegmentation-may be connected with constitutional familial properties in healthy persons. It is observed also in vitamin B12 and folate deficiency anemias, radiation sickness.

8. Appearance of immature or decomposed leukocytes in the peripheral blood.

9. Pelger-Huet anomaly -is an inherited disorder in which majority of neutrofils has decreased number of nuclear segments (2-3) and coarsely staining chromatin. The nuclei appear rod-like, dumb-bell or spectacle-like.

10. Nuclear shift of neutrophils-is important qualitative change of neutrofils in the peripheral blood.

The ratio of the aggregate number of juvenile (metamyelocytes) and band (stab) neutrophils (1-%+2-5%) to the number of segmented neutrophils (51-67%) is called nuclear shift index (in norm 0.06-0.08). Increased number of nonsegmented neutrophils (myelocytes, metamyelocytes, band cells) in the peripheral blood leads to increased nuclear shift index. This is called shift to the left. This index is decreased as a result of increased number of the segmented and hypersegmented neutrophils. This is called shift to the right. Increased number of neutrophils in the blood (neutrophilia) is usually accompanied by the shift to the left. This is connected with increased regenerative ability of the bone marrow. Two types of the shift to the left are distinguished:

a) regenerative -the number of juvenile and band cells as well as the total number of neutrophils is increased;the nuclear shift index is increased up to 0.25-0.45;

b) hyperregenerative-besides increased number of juvenile and band cells, in the blood younger forms of neutrophils (myelocytes) are revealed (in severe infectious and septic processes when the number of leukocytes in 1 mcl of the blood reaches 20-30 thousands); frequently this weakens the myeloid tissue and soon the number of leukocytes is decreased.

The shift to the right is connected with weakened granulopoiesis.

Depending on the type of the pathogenic agent the total number of leukocytes, as well as the number of their different forms may be decreased. According to the developmental mechanisms of leukopenia its following types are distinguished:

1. Leukopenia resulted from diminished leukopoietic function of the hemopoietic organs - is observed in the following cases:

1. chronic poisoning by benzene, tetraethyl lead, etc.;
2. intake of large doses of cytostatic preparations;
3. influence of X-rays and radioactive rays (these cause lymphopenia);
4. autoallergic reactions damaging hematopoietic organs;
5. metastatic spreading into bone marrow of tumors of other localizations;
6. poisoning by grain-crops soiled with mould fungi of toxic action;
7. infectious diseases (abdominal typhoid, grippe, etc.).

2. Leukopenia resulted from rapid destruction of leukocytes-is caused by antilymphocytic antibodies which are often formed under the influence of drugs of allergen and hapten nature (amidopyrine, phenacetin, antibiotics, sulfanilamides). Sometimes in the immunocompetent cells of the person to whom the donor's blood was transfused, antilymphocytic isoantigens are synthesized which cause leukopenia after repeated blood transfusion.

3. Leukopenia resulted from unequal distribution of leukocytes in blood vessels - is observed in subcutaneous vessels during transfusion shock and anaphylactic shock when a large number of leukocytes is accumulated in dilated capillaries of lungs, liver and intestine. This type of leukopenia is soon replaced by leukocytosis.

To produce leukopenia in experiment, small doses of benzene are injected to rabbits, or rats are exposed to the influence of X-rays.

Agranulocytosis, that is, sharp decrease of the number of granulocytes (especially that of neutrophils) in the blood occurs as a result of severe disturbances in the function of the bone marrow. It is frequently accompanied by anemia and thrombocytopenia. Organism's resistance to the pathogenic microorganisms is sharply weakened. One of the severe complications of the agranulocytosis is ulceronecrotic angina.

Lymphocytopenia (decreased absolute number of lymphocytes) is observed in radiation sickness, miliary tuberculosis, lymphogranulomatosis, lymphosarcomatosis. Glucocorticoids, immunodepressants, cytostatic substances also decrease the number of lymphocytes in the blood. Long lymphopenia decreases the organism's resistance to the infectious diseases, and probability of development of malignant tumors is increased.

The acute period of the myocardial infarction, stress situations, administration of ACTH into the organism are accompanied by eosinopenia. Monocytopenia is observed in severe cases of sepsis.

The total number of leukocytes and differential blood count differ depending on periods of age. In newborns and pregnant women (at the second half of the pregnancy) the physiological leukocytosis is observed. The physiological leukocytosis 2-3 hours after the intake of food and during intensive physical work is connected with mobilization of the blood from depots. The same is the mechanism of leukocytosis in emotions, pain, epileptic attacks, shock, operative trauma. Leukocytosis connected with redistribution of the blood is not accompanied by changes in the differential blood count.

Some chemical and infectious agents, products of destruction of injured tissues and leukocytes accumulated in the inflammatory foci accelerate leukopoiesis and cause pathological leukocytosis.

During leukocytosis frequently the absolute and relative number of different forms of leukocytes are also changed-eosinophilia, basophilia, neutrophilia, monocytosis, lymphocytosis are distinguished.

Eosinophilia is observed in allergic diseases, helminthic invasion, periarteritis nodosa, lymphogranulomatosis, period of recovery after infectious diseases, hypofunction of adrenal cortex.

Basophilia is the rare form of leukocytosis (in chronic myeloleukosis, erythremia, chronic ulcerative colitis).

Neutrophilia is observed in suppurative infectious processes (abscess, peritonitis, pneumonia), carboxyhemoglobinemia, at the initial stage of radiation sickness, in the damage and necrosis of tissues (myocardial infarction, gangrene), as a result of administration of heterologous proteins into the organism. Changes in the activity of the central nervous system caused by different factors (trauma, narcosis, tumors of the brain, cerebral hemorrhages) are also accompanied by neutrophilia.

Monocytosis is the main sign of the chronic monocytic leukosis, but sometimes the chronic infectious processes (infectious mononucleosis, syphilis, chronic septicemia, lingering septic endocarditis, malaria, measles, pox, acute period of pulmonary tuberculosis) are also accompanied by monocytosis.

Lymphocytosis is one of the main symptoms of the chronic lympholeukosis. It is observed also in syphilis, epidemic parotiditis, infectious mononucleosis, wooping cough, chronic period of pulmonary tuberculosis). Infectious mononucleosis is often accompanied by the leukemoid reactions of the lymphocytic type.

In experiment leukocytosis is produced by administration of large doses of benzene to rabbits.

**Hemoblastoses (Gr. haima-blood, blast-growth, sprout, osis-pathological process, disease) are tumors arising from hemopoietic cells.** Being neoplasms, they come into the group of diseases making up the "number 2 killer "(after the cardiovascular diseases). As a cause of death the hemoblastoses are in the first place among all diseases of the blood.

Two varieties of tumors are referred to hemoblastoses: leukoses (leukemias) and hematosarcomas. Leukoses (Gr. leukos- white (cell), osis-pathological process, disease) are tumors diffusely affecting hemopoietic tissue of the bone marrow, where as hematosarcomas originate from hemopoietic cells that are found out of the bone marrow. As distinct from leukoses, hematosarcomas are characterized by local growth up to the stage of metastatic spreading. But leukoses and hematosarcomas may turn into one another. Unlike the leukocytosis, which is only the symptom of other diseases, leukosis is independent disease of the hematopoietic system. The leukoses are a group of disorders characterized by malignant transformation of blood -forming cells. As distinct from the usual pathological leukocytoses, leukoses are characterized by systemic changes in the hematopoietic organs with considerable, progressive and stable increase in the number of leukocytes, reaching several hundred thousand per 1 mcl and appearance of immature forms of leukocytes (myelocytes, myeloblasts, lymphoblasts, etc.) in the blood.

Proliferation of leukemic cells takes place primarily in the bone marrow, and in certain forms, in the lymphoid tissues. Ultimately, the abnormal cells appear in the peripheral blood raising the total white cell count to high level. In addition, features of bone marrow failure (anemia, thrombocytopenia, neutrpenia) and involvement of other organs (liver, spleen, lymphnodes, meninges, brain, skin , etc.) occur.

There are forms of leukosis in which number of leukocytes in the blood is normal or even low (aleukemic leukosis). These forms are also characterized by disturbed processes of leukocyte formation in the bone marrow and other hematopoietic organs.

There are several theories explaining the etiology of leukosis:

1. Viral theory-is due to the fact that leukoses of hens and cattle are contagious. The viruses causing leukosis in hens and mammals (mouse, cat, dog, etc.) are used in experiment. Recently it has been established that a human retrovirus called human T-cell lymphotropic virus is causative for human T-cell leukosis and lymphoma.

2. Genetic theory- there is high concordance rate among identical twins if acute leukosis develops in the first year of life. Families with excessive incidence of leukosis have been identified. Acute leukosis occurs with increased frequency with a variety of congenital disorders (Down's, Klinefelter's, Fanconi's syndromes, etc.).

3. Radiation theory-it is presumed that the ionizing radiation injures the chromosomes of the hematopoietic system cells and converts them into tumoral cells. It is possible to cause experimental leukosis in mice and rats using X-rays. Percentage of acute leukosis and chronic myelosis is 11-18 times more in Hiroshima and Nagasaki (survivors of the atomic bomb explosions) than in other cities of Japan.

4. Theory of chemical carcinogenesis- benzene and other aromatic hydrocarbons are associated with the development of acute myeloblastic leukosis. Treatment with certain drugs (alkylating agents, other chemotherapeutic agents) is also associated with increased incidence of this disease.

Pathogenesis of leukosis is explained by the clonal theory. According to this theory the mutagenous agents (ionizing radiation, chemical carcinogenic substances) cause mutation in non-differentiated cells of the hematopoetic system. Initially the change occurs in the genotype of one cell which then is reproduced, and a large numbers of malignant cells, that is, leukemic clone is formed. These replace the normal blood cells. In the process of reproduction they may be subjected to new mutations. So, the process acquires multiclonal character. Precursors of the pathological leucocytes gradually spread into the entire bone marrow, spleen, lymph nodes, liver. So, the new zones of the leukemic infiltration are formed. The leukemic cells do not submit to the organism's regulating mechanisms.

A number of clonal cytogenetic abnormalities have been reported in association with various forms of acute and chronic leukoses. The most consistent chromosomal abnormality is Philadelphia (Ph) chromosome seen in chronic myeloid leukoses involving reciprocal translocation of chromosome 22 to the long arm of chromosome 9.

As the leukemic cells accumulate in the bone marrow, they suppress normal hemopoetic stem cells, partly by physically replacing the normal marrow precursors.

Leukoses are classified on the basis of cell types predominantly involved - into myeloid and lymphoid, and on the basis of the natural history of the disease - into acute and chronic. The incidence of both acute and chronic leukoses is higher in man than in women.

According to the total number of leukocytes in the peripheral blood and the number of pathological cells the following variants of leukoses are distinguished:

1. leukemic leukoses-from 25 thousands to several hundreds of thousands (even to the million) of leukocytes in 1 mcl of the peripheral blood;
2. subleukemic leukemia-15-25 thousands of leukocytes in 1 mcl of blood;
3. aleukemic leukoses- the leukocyte count is normal or even subnormal;
4. leukopenic leukosis - the number of leukocytes is decreased, but pathological forms are revealed among them.

Acute leukoses are characterized by predominance of undifferentiated leukocyte precursors of leukemic blasts. Acute leukemias may be derived from the myeloid stem cells (acute myeloblastic leukemia) or from the lymphoid stem cells (acute lymphoblastic leukoses).

According to the FAB (French, American, British hematologists) classification a leukosis is acute if the bone marrow consists of more than 30% blasts. Acute myeloblastic leukoses are divided into 7 subtypes (Ml to M7) and acute lymphoblastic leukoses into 3 subgroups (L1 to L3).

The changes of the blood cells and bone marrow cells in acute leukoses are called "leukemic disparity": the number of blast forms of the leukocytes in the blood is sharply increased and few mature leukocytes are revealed; the number of transitional cells between them is few(sometimes they are not revealed in the smear).Leukemic infiltration is formed in spleen, liver, kidneys, lymphnodes, brain, meninges. The type of acute leukoses depends on the cells whose proliferation prevails in the hemopoiesis.

Acute myeloblastic leukosis and acute lymphoblastic leukosis share many clinical features. In approximately 25% of patients with AML preleukemic syndrome with anemia and other cytopenias is usually present for a few months to years prior to the development of overt leukosis.

Clinical manifestations of acute leukoses are divided into 2 groups:

1)manifestations due to bone marrow failure anemia (pallor, lethargy, dyspnea), bleeding (due to thrombacytopenia), infectious, fever;

2) manifestations due to organ infiltration - pain and tenderness of bones(for instance, sternal tenderness),lymphadenopathy and enlargement of tonsils, splenomegaly, hepatomegaly, gum hypertrophy, chloromas (tumor forming masses in the skin or orbit due to the local infiltration of the tissues by leukemic cells), meningeal involvement (raised introcranial pressure, headache, vomiting, blurring of vision, diplopia; sudden death may occur from massive introcranial hemorrhage) , etc.

Chronic leukoses are the hematological malignancies in which the predominant leukemic cells are initially well-differentiated and easily recognizable as regards to their cell type. Chronic leukemias are divided into 2 main types: chronic myeloid (granulocytic) leukoses and chronic lymphocytes leukoses. Less common variants include: chronic easinophilic, chronic basophilic, chronic monocytic, chronic neutrophilic and chronic lymphosarcoma cell leucoses. An unusual chronic lymphoproliferative variant is hairy cell leukosis.

Peak incidence of chronic myeloid (myelogenous) leukosis is observed in the 3rd and 4th decades of life. Its distinctive variant in children under 3 years of age is called juvenile chronic myeloid leukosis. Both sexes are affected equally. An increased incidence of both acute myeloblastic leukosis and chronic myeloid leukosis was observed years later in Japanese atomic bomb survivors.

Some of the common presenting manifestations of the chronic myeloid leukosis are: features of anemia(weakness, pallor, dyspnea, tachicardia), symptoms due to hypermetabolism(weight loss, lassitude, anorexia, night sweats), splenomegaly, bleeding tendencies, less commonly-gout, visual disturbance, neurological manifestations, priapism.

Chronic lymphocytic leukoses is predominantly disease of the elderly (over 50 years of age)with a male preponderance (male-female ratio 2:1). Common presenting manifestations are the following: features of anemia (weakness fatigue, dyspnea), enlargement of superficial lymphnodes, splenomegaly and hepatomegaly, hemorrhagic manifestations(in cases with thrombocytopenia), infectious, occasional features-mediastinal pressure, tonsillar enlargement and joint pains.

Hairy cell leukosis is an unusual and uncommon form of chronic leukosis in which presence of abnormal mononuclear cells with hairy cytoplasmic projections in the bone marrow, peripheral blood and spleen is characteristic. Hairy cell leukosis occurs in the older males. Clinically it is characterized by the manifestations due to infiltration of reticuloendothelial organs (bone marrow, liver, spleen) and hence its previous name is reticuloendotheliosis.

**Leukemoid [Gr. leukos-white (cell), haima- blood, aides-similar] reactions are typical pathological processes which are characterized by considerable increase of number of different immature forms of leukocytes (up to normal, non-tumoral blast cells) and increase of total number of leukocytes (as a rule, but not always) in the peripheral blood.** They are named "leukemoid" because outer changes in the hemopoietic tissue and in the peripheral blood in these reactions resemble those in leukoses. But the leukemoid reactions never are transformed into that leukosis which they remind from the "hemopoietical" point of view. In spite of confusing blood picture, the clinical features of leukemia (splenomegaly, lymphadenopathy, hemorrhages) are usually absent, and the features of underlying disorder causing the leukemoid reaction are generally obvious. In most cases the leukemoid picture of the blood is the reaction of the organism to agents of the biological character ( viruses, rickettsia, microorganisms, parasites) as well as to action of biologically active substances that are released in immunogenic and allergic processes, in decomposition of tissues ( in particular, that of tumors), in hemolysis of erythrocytes, etc. Hence the leukemoid reactions are one of symptoms of other diseases, mostly those of infectious (varicella, infectious mononucleosis, adenoviral processes) and allergic (allergic dermatitis, rheumatism, lupus erythematosus) character, as well as that of tumoral growth.

The developmental mechanism of leukemoid reactions is connected with reactive focal hyperplasia of different normal sprouts of leukopoietic tissue, stimulation of leukopoiesis and elimination of a great number of immature leukocytes from the hemopoietic tissue into the blood. This is conditioned by increase of content and activity of leukopoietic factors or decrease of agents inhibiting division and stimulating maturation of cells (keylons).

According to the cellular composition myelocytic, monocytic, lymphocytic and mixed (lymphomonocytic, myelomonocytic) forms of the leukemoid reactions are distinguished.

Depending on the total number of leukocytes in the unit of the blood volume, the leukemoid reactions are divided into: leukopenic (less than 4 . 109/l), leukocytic (10 - 80 . 109/l) and reactions with the normal leokocyte count. Frequently the leukemoid reactions are accompanied by increase of the number of mature forms of leukocytes and that of their functional (including phagocytic) activity. This leads to increase of specific and non-specific (in particular, anti-infectious) resistance of the organism.

However, in the cases of prevalence of immature forms of leukocytes in the blood, resistance of the organism may be decreased.

The myeloproliferative disorders are a group of neoplastic proliferation of multipotent hemopoietic stem cells. Besides their common stem cell origin, these disorders are closely related, occasionally leading to evolution of one entity into another during the course of the disease.

Myeloproliferative disorders include 4 disorders: chronic myeloid leukosis, polycythemia vera, myeloid metaplasia with myelosclerosis and essential thrombocytosis.

**Pathological changes in thrombocytes (blood platelets) may be, as in other blood cells, quantitative.and qualitative.** The number of thrombocytes may be decreased (thrombopenia) or increased (thrombocytosis). Sometimes these quantitative changes are accompanied by qualitative changes, as in thrombasthenia.

Thrombopenia is observed in anemias and leukemias, especially in severe forms of these diseases (pernicious and aplastic anemias), in certain severe infectious diseases (scarlet fever, smallpox, dysentery, sepsis); it also results from the action of physical and chemical agents ( ionizing radiation, poisoning with benzene, thorium, quinine). Thrombopenia and hemorrhagic phenomena are noted in certain affections of the diencephalon and hypophysis. Thrombopenia is usually accompanied by hemorrhages from the gastrointestinal mucosa and extravasations into the skin and mucous membranes.

Thrombocytosis is observed in various infectious diseases (cholera) and after removal of the spleen where they are (like the erythrocytes) normally destroyed.

In thrombasthenia the properties of the platelets are altered, for instance, they lose their agglutinating ability. Some cases show pycnosis or anisocytosis of the platelets.

In the pathology of hemostasis changes in the vascular-thrombocytic hemostasis and coagulation disorders are distinguished.

Vascular bleeding disorders or vascular purpuras may be caused by inherited or acquired defects in blood vessels. They are mild and characterized by petechiae, purpuras or ecchymoses confined to the skin and mucous membranes. Majority of the standard screening tests of hemostasis including the bleeding time, coagulation time, platelet count and platelet function are usually normal. Vascular purpuras arise from damage to the capillary endothelium, abnormalities in the subendothelial matrix or extravascular connective tissue that supports the blood vessels or from formation of abnormal blood vessels.

A few examples of hereditary vascular disorders are the following :

1. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)- begins in childhood and is characterized by abnormally telangiectatic (dilated) capillaries which develop particularly in the skin, mucous membranes, internal organs and are the source of frequent episodes of bleeding from nose and gastroitestinal tract.

2. Inherited disorders of connective tissue matrix - include Marfan's syndrome, Ehler-Danlos syndrome, pseudoxanthoma elasticum, all of which have inherited defect in the connective tissue matrix and thus have fragile skin vessels and easy bruising.

The following acquired conditions are associated with vascular purpuras:

1. Henoch-Schonlein ( anaphylactoid ) purpura - is a self - limited type of hypersensitivity vasculitis occurring in children and young adults. Circulating immune complexes are deposited in the vascular wall. The hypersensitivity vasculitis produces purpuric rash on the extensor surfaces of arms, legs, on the buttocks, as well as hematuria, colicky abdominal pain due to bleeding into the gastrointestinal tract, polyarthralgia and acute nephritis. But all coagulation tests are normal.

2. Hemolytic - uremic syndrome - is a disease of infancy and early childhood in which there is bleeding tendency and varying degree of acute renal failure. The disorder remains confined to the kidney where hyaline thrombi are seen in the glomerular capillaries.

3. Simple easy bruising (devil's pinches) - is a common phenomenon in women of childbearing age group.

4. Scurvy - vitamin C deficiency results in defective collagen synthesis which causes skin bleeding as well as bleeding into muscles, and ocassionally into the gastraintestinal and genitourinary tracts.

5. Infectious (septicemia, severe measles, scarlet fever, grippe,)-cause vascular hemorrhages either by causing toxic damage to the endo-thelium or by disseminated intravascular coagulation (DIC).

6. Drug reactions - certain drugs (quinine, barbiturates, sulfanilamides, antibiotics, etc.) form antibodies and produce hypersensitivity (or leukocytoclastic) vasculitis responsible for abnormal bleeding.

7. Steroid purpura - long-term steroid therapy or Cushing's syndrome may be associated with vascular purpura due to defective vascular support.

8. Senile purpura - atrophy of the supportive tissue of cutaneous blood vessels in old age may cause senile atrophy especially in the dorsum of forearm and hand.

Blood coagulation disorders manifest themselves in the form of slowing of blood coagulation and bleeding tendency (hemorrhagic diatheses) or increased (accelerated) blood coagulation. Decreased blood coagulability may be caused by quantitative and qualitative changes of thrombocytes, hereditary deficiencies of clotting factors in the blood plasma, increased quantity of the natural anticoagulants, activation of the fibrinolysis system.

Werlhof's disease or idiopathic (immune) thrombocytopenic purpura is characterized by immune destruction of platelets and normal or increased megakaryocytes in the bone marrow.

Many commonly used drugs (quinine, sulfonamides, anticancer drugs,digitoxin, etc.) cause thrombocytopenia by depressing megakaryocyte production.

Thrombocytopathies include several hereditary diseases connected with defective platelet aggregation and adhesion: von Willebrand's disease,Glanzmann-Naegeli disease(thrombasthenia),Bernard-Soulier syndrome, etc.

The clinical manifestations of Willebrand's disease and Glanzmann-Neageli disease are similar: frequent subcutaneous hemorrhages, nasal, uterine bleeding are observed; clotting time is increased.

Von Willebrand's disease is due to defect in von Willebrand's factor which comprises the larger fraction of factor VIII-VWF complex circulating in the blood.

In Glanzmann-Neageli disease there is failure of primary platelet aggregation due to inherited deficiency of two platelet membrane glycoproteins. Acquired defects of platelet functions include aspirin therapy, uremia, liver disease, multiple myeloma, Waldenstrom's macroglobulinemia and various myeloproliferative disorders. Prolonged use of aspirin leads to easy bruising and abnormal bleeding time. Because aspirin inhibits the enzyme cyclooxygenase, and thereby suppresses the synthesis of prostaglandins which are involved in thrombocyte aggregation as well as release reaction.

Deficiency of each of the thirteen known plasma coagulation factors has been reported, which may be inherited or acquired. The type of bleeding in coagulation disorders is different from that seen in vascular and thrombocytic abnormalities. Instead of spontaneous appearance of petechiae and purpuras, the plasma coagulation defects manifest more often in the form of large ecchymoses, hematomas and bleeding into muscles, joints, body cavities, gastrointestina1 and urinary tracts.

The most common inherited coagulation disorders are the sex (x)-linked inherited disorders-classic hemophilia (hemophilia A) due to deficiency of factor VIII and Christmas disease (hemophilia B) due to deficiency of factor IX.

As distinct from the true hemophilias, inheritance of the hemophilia - like syndromes is not connected with sex and they are observed in men as well as in women. These include hypoproaccelerinemia (deficiency of factor V), hypoproconvertinemia (deficiency of factor VII), Stuart-Prower disease (deficiency of factor X), hemorrhagic diathesis connected with deficiency of factor XI (hemophilia C).

Sinse vitamin K serves as cofactor in formation of VI vitamin K- dependent coagulation factors synthesised in the liver, in diseases connected with hepatic function disorders and vitamin K deficiency hypoprothrombinemia is observed and besides, synthesis of factors VII, IX, X, proteins C and S is disturbed.

Hypofibrinogenemia and afibrinogenemia may be resulted from disturbed synthesis of fibrinogen in liver, excessive fibrinolytic activity of the blood , etc. Ionizing radiation, infectious and toxic agents cause dysfibrinogenemia, that is, the fibrinogen with changed molecule structure and physicochemical properties is synthesized.

Unchecked and excessive fibrinolysis may be sometimes the cause of bleeding. The causes of primary pathological fibrinolysis leading to hemorrhagic defects are:

l) deficiency of α2-plasmin inhibitor following trauma or surgery;

2) impaired clearance of tissue plasminogen activator such as in cirrhosis of liver.

At times it may be difficult to distinguish primary pathological fibrinolysis from secondary fibrinolysis accompanying disseminated intravascular coagulation.

Increased (accelerated) blood clotting may be caused by the following factors:

l) increased number and activity of thrombocytes;

2) increased blood content of procoagulants;

3) decreased fibrinolytic activity of the blood;

4) increased blood content of the natural anticoagulants.

Injury to the vessels and slowing of the blood current may lead to increased functional activity of thrombocytes.Aggregation and adhesion of thrombacytes is increased under the influence of catecholamines (emotions,traumata.diseases accompanied by acute pain).The number of thrombocytes is increased in erythremia.

Accelerated formation of active thromboplastin causes conversion of the greater part of the prothrombin into thrombin.Thrombin,in its turn accelerates conversion of fibrinogen into fibrin,activates other coagulation factors in the blood and causes aggregation of thrombocytes. So,greater part of the coagulation factors is consumed, microaggregates and microthrombi are formed which circulate in the vessels. As a result of decreased fibrinogen content,the blood does not coagulate. This is called disseminated intravascular coagulation DIC or defibrination syndrome or consumption coagulopathy.

Abruptio placentae,amniotic fluid embolism, massive trauma, metastatic malignancies, certain infectious, sepsis, shock, leukosis, severale burns, some diseases of internal organs (acute glomerulonephritis) may be complicated by DIC.

One of the main causes of the accelerated blood coagulation is decrease of natural anticoagulants and fibrinolysin in the blood. Alcholic intoxication, atherosclerosis.diabetes mellitus, hypertensive desease are accompanied by decreased fibrinolysin activity in the blood.

When increased blood coagulability is accompanied by the weakened fibrinolytic activity, the probabelity of formation of thrombi in the organism is increased. This is called prethrombosis state. It is observed in atherosclerosis, hypertensive disease, diabetes mellitus, obesity, rheumatism, etc.