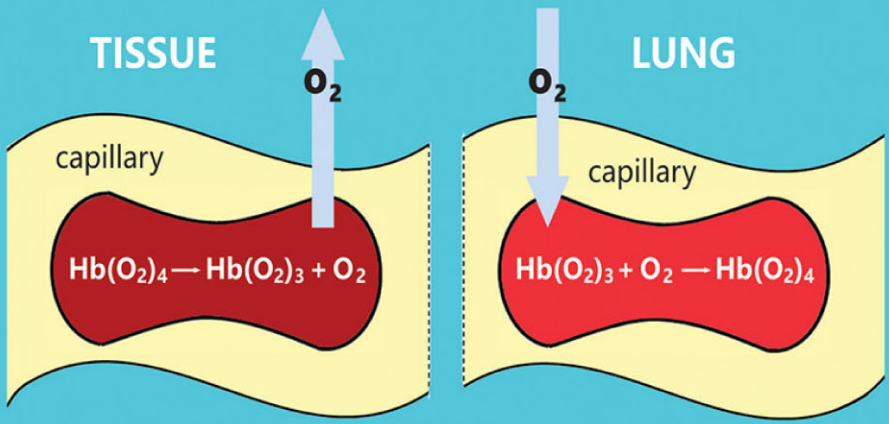
Нормальная физиология

Normal physiology



Для иностранных студентов учреждений высшего образования
For foreign students of higher education institutions

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Представлен теоретический материал об основных физиологических закономерностях и процессах организма человека, приведены физиологические термины и определения, вопросы для самоконтроля, ситуационные задачи.

Для изучения (на английском языке) нормальной физиологии иностранными студентами медицинских учреждений высшего образования, может быть полезна всем, кто изучает данную дисциплину.

This textbook is designed to study (in English) normal physiology by international students of medical higher education institutions and can be used by others who study this discipline as well.

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Chapter 1

BLOOD PHYSIOLOGY

The internal environment is a group of fluids (blood, lymph, interstitial fluid, etc.) that directly participate in metabolic processes and in the maintenance of the body's homeostasis. The internal environment is characterized by a relative constancy of composition and conditions. "The fixity of the internal environment is the condition for free life" (C. Bernard, 1813–1878). It is provided by various mechanisms. They include not only the physiological processes that maintain the stable state of the organism but also the mechanisms of regulation that, in certain limits, change these states.

There are the following types of the internal environment:

- Intracellular;
- Extracellular:
  - extravascular (interstitial fluid, joint fluid, pleural fluid, cerebrospinal fluid, etc.);
  - intravascular (blood, lymph).

General characteristics

Blood as a tissue of the internal environment has a number of features: its components are synthesized outside it; the main portion of the blood tissue is liquid; it moves constantly. In 1939, G.F. Lang introduced the concept of the blood system, which includes blood circulating in vessels, the organs of blood formation, destruction and regulatory apparatus.

There is also another concept: erythron – an aggregation of erythrocytes of peripheral blood, organs of erythrocyte formation (erythropoiesis) and organs of erythrocyte destruction.

Blood functions:

- transport (nutrition, transport of gases, excretion, water and salt balance, osmotic concentration, acid and base balance (pH);
- regulation;
- defense;
- thermoregulation;
- homeostasis.

These functions reflect the contribution of the blood system to the homeostasis formation. Thereby the main blood parameters are rigid homeostatic constants (Table 1.1).

Table 1.1. **Main parameters of the blood system of a healthy adult**

Parameters	Gender	Range, units
Hemoglobin	M F	130–160 g/L 120–140 g/L
Erythrocytes	M F	$(4.0–5.0)\cdot10^{12}$/L $(3.9–4.7)\cdot10^{12}$/L
Average erythrocyte volume		75–95 μm^3
Average erythrocyte diameter		7.2–7.5 μm
Hematocrit ratio (*Ht* or *Hct*)	M F	40–48 % 36–42 %
Color index		0.85–1.05
Average Hb content in 1 erythrocyte		27–33 pkg
Reticulocytes		0.2–1.0 %
Platelets		$(180–320)\cdot10^9$/L
Leukocytes		$(4.0–9.0)\cdot10^9$/L
Erythrocyte sedimentation rate (ESR)	M F	2–10 mm/h 2–15 mm/h
Total blood volume in the organism		6–8% of total body weight
Blood density		1.050–1.064 g/cm^3
Plasma density		1.024–1.030 g/cm^3
Blood cells density		1.089–1.097 g/cm^3
Blood pH – arterial – venous		7.37–7.45 7.34–7.43
Plasma osmotic pressure		5,780 mmHg/7.6 atm
Plasma oncotic pressure		25–35 mmHg
Total plasma protein		65–85 g/L
Blood ions concentration		0.9–0.95 %
Blood viscosity		5 cP
Plasma viscosity		1.7 cP

The blood volume in the body is 6–8% of total body weight, i.e. 4–6 L in an average man. Most of the blood moves constantly, about 30% of its volume is in a deposited state.

Blood depots (venules and veins):

- spleen;
- liver;
- lungs;
- skin.

Blood plasma properties

Blood consists of plasma of a pale yellow color and formed elements (erythrocytes or red blood cells, leukocytes or white blood cells, thrombocytes or platelets). Plasma from which fibrinogens have been removed is called serum. **Hematocrit** is the ratio of formed elements volume (mostly red blood cells) to the total volume of blood (Figure 1.1). Its value is 40–48% for men and 36–42% for women. This blood parameter can vary significantly depending on the conditions of the internal and external environments.

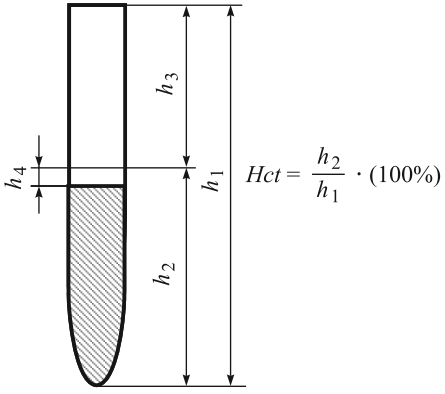

Figure 1.1. Hematocrit ratio determination:
h_1 – blood volume; h_2 – formed elements volume; h_3 – plasma volume; h_4 – leukocytes volume

Plasma is composed of (90–92%) water, (6.5–8.5%) proteins and (about 2%) organic and inorganic substances (Table 1.2). Due to the latter, the osmotic pressure of plasma is formed (5,780 mmHg or 7.6 atm). The simplest blood substitute is a 0.95% solution of NaCl (normal saline). This isotonic solution has the same osmotic pressure as plasma, but its compo-

sition is much simpler, contains only one component (NaCl). There are other plasma substitutes (Ringer's solution, Tyrode's solution), which in their composition are closer to plasma and can be named physiological salt solutions (Table 1.3).

Table 1.2. **Plasma composition in the fasting state**

Component	Level	Component	Level
Water	900–910 g/L	Uric acid	179–476 μmol/L
Proteins	65–85 g/L	Creatinine	44–150 mmol/L
Albumins	38–50 g/L	Sodium	135–145 mmol/L
α_1-globulins	1.4–3.0 g/L	Potassium	3.3–4.9 mmol/L
α_2-globulins	5.6–9.0 g/L	Total calcium	2.23–257 mmol/L
β-globulins	5.4–9.0 g/L	Free (ionized) calcium	1.15–1.27 mmol/L
γ-globulins	9.0–16.0 g/L	Magnesium	0.65–1.1 mmol/L
Fibrinogen	2.0–4.0 g/L	Chlorides	97–110 mmol/L
Total bilirubin	3.4–22 mmol/L	Total iron	9.0–31.0 mmol/L
Lipids	2.0–4.0 g/L	Total copper	11.0–24.3 mmol/L
VLDL	0.8–1.5 g/L	Hydrocarbonate (HCO_{3-})	23.0–33.0 mmol/L
IDL	0.2–0.75 g/L	Phosphate (PO_4^{3-})	0.8–1.2 mmol/L
LDL	3.2–4.5 g/L	Sulfate (SO_4^{2-})	0.4–0.6 mmol/L
HDL	2.7–4.3 g/L	Ammonia	19.0–43.0 mmol/L
Triglycerides in the fasting state	<2.85 mmol/L	Residual nitrogen	14.0–28.0 mmol/L
Glucose	3.3–5.5 mmol/L		

Note: VLDL – very low – density lipoproteins; IDL – intermediate – density lipoproteins; LDL – low – density lipoproteins also called "bad cholesterol"; HDL – high density lipoproteins also called "good cholesterol".

Various substances dissolved in the plasma determine its **osmotic pressure** – the force of water movement across a selectively permeable membrane towards a greater concentration of solutes. Solutions with osmotic pressure of 7.6 atm (5,780 mmHg) are called ***isotonic***, with a higher osmotic pressure – ***hypertonic***, with a lower osmotic pressure – ***hypotonic***. Changes in the osmotic pressure of the blood plasma can lead to edema.

Table 1.3. **Composition of the main physiological salt solutions**

Solution	NaCl	KCl	$CaCl_2$	$NaHCO_3$	$MgCl_2$	NaH_2PO_4	Glucose
Isotonic	9.5	–	–	–	–	–	–
Ringer's	6.5	0.14	0.1	0.2	–	–	–
Ringer-Locke's	9.0	0.42	0.24	0.15	–	–	1.0
Tyrode's	8.0	0.2	0.2	1.0	0.1	0.05	1.0

Note: concentration is given in g/L comparing to the isotonic solution.

Erythrocytes in hypotonic solutions swell and are destroyed (osmotic hemolysis), and in hypertonic solutions they shrink. **Hemolysis** is the destruction of the erythrocyte membrane which is accompanied by the release of hemoglobin into the blood plasma, which turns red and becomes transparent ("laky blood"). Hemolysis may occur either within the body or outside (in a test tube) from a number of reasons.

Types of hemolysis:

- osmotic;
- chemical;
- biological;
- mechanical;
- temperature (cold, warmth).

The protein content of the plasma is 65–85 g/L. Using the method of electrophoresis (placing in a medium with a gradient of a constant electrical field), plasma proteins are divided into a number of fractions: albumin, α_1-globulin, α_2-globulin, β-globulin, γ-globulin. Albumin is a relatively low molecular weight protein; it determines the value of the oncotic pressure of the plasma (its contribution is 80%), has a large total surface area, due to which it binds many substances (bilirubin, urobilirubin, fatty acids, bile salts, some exogenous products like penicillin, mercury). Globulins consist of various proteins. α_1-globulins are mainly glycoproteins (up to 2/3 of the whole plasma glucose is bound to it), α_2-globulins are haptoglobulins (mucoproteins); these include, in particular, ceruloplasmin, binding up to 90% of all copper contained in the plasma, thyroxin-binding protein, B_{12}-binding globulin, bilirubin-binding globulin, cortisol-binding globulin. β-Globulins include proteins that transfer lipids and polysaccharides; up to 70% of all plasma lipids are a part of lipoproteins. They also include transferrin, which primary transfers iron. γ-Globulins are antibodies that perform a specific defense function. Almost any inflammatory process is accompanied by an increase in their content.

The plasma contains microelements (trace elements), the main part of which is associated with proteins (metalloproteins: ceruloplasmin, cobalamin – a component of vitamin B_{12}, thyroxine-binding protein – thyroxine contains iodine). In addition, plasma contains fibrinogen, a soluble precursor of fibrin. This protein is involved in blood clotting. Oncotic pressure or colloid osmotic pressure is a part of the osmotic pressure of plasma, exerted by proteins (25–30 mmHg). Its value is very important for transcapillary fluid exchange.

Blood formed elements

Blood formed elements are morphologically and functionally differentiated blood cells. These include erythrocytes (red blood cells containing hemoglobin), leukocytes (white blood cells: granulocytes – eosinophils, basophils, neutrophils, and agranulocytes – monocytes, lymphocytes), as well as thrombocytes (platelets). The lifetime of the main blood cells is represented in Table 1.4.

Table 1.4. **Lifetime of the main blood cells**

Formed elements	Time of cells compartmentalization		
	Bone marrow	Bloodstream	Tissues
Erythrocytes	7.5 days	100–120 days	–
Monocytes	55 days	12 hours	–
Leukocytes (granulocytes)	14 days	less than 24 hours	1–2 days
Thrombocytes	5 days	up to 10 days	–

Erythrocytes properties

Erythrocytes are nonnucleated cells having the shape of a biconcave disk with a diameter of 7.2–7.5 μm and a thickness of 2.1 μm (Figure 1.2). In adults, the size of red blood cells decreases a little with age. The total surface area of all adult human erythrocytes is approximately 3,800 m^2 (1.5 thousand times greater than the body surface area). The area of the erythrocyte is almost 2 times larger than that of a sphere of the same volume.

To determine the number of erythrocytes in the blood, the counting method in Goryaev's chamber is used, as well as various photometric methods. Highly efficient automated blood cell counters are widely used in clinics.

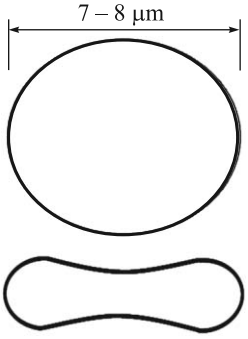

Figure 1.2. Shape and size of erythrocytes

An increase in the number of red blood cells is called **erythrocytosis**, and the decrease is called **erythrocytopenia**. Their absolute number in the blood of the body is $(25–30)\cdot10^{12}$ cells. True (absolute) erythrocytosis is an increase in the number of erythrocytes due to their enhanced formation; the arrival of cells from the depot or decreased plasma volume leads to the relative erythrocytosis. The absence of a nucleus significantly reduces intracellular oxygen consumption (more than 200 times). Providing oxygen to the whole body, the erythrocytes themselves consume a minimal amount of it.

One of the integrative indicators of the functional state of erythrocytes is the erythrocyte sedimentation rate (ESR), which characterizes the sedimentation of blood erythrocytes when adding an anticoagulant substance. Determination of ESR is performed by measuring the height of the plasma column in mm above the red blood cells settled in a vertically placed capillary for 1 hour under standard conditions. Measurement of ESR is performed using the Panchenkov's apparatus. For men, the value of this parameter is 1–10 mm/h, for women – 2–15 mm/h. The sedimentation phenomenon is determined by the functional state of the erythrocyte, its charge, the protein composition of the plasma. A number of physiological states are characterized by a higher value of ESR (pregnancy, physical work). In newborns, the value is lower (1–2 mm/h). In many inflammatory states, infectious and other pathological processes, the value of this parameter increases.

Rheological properties of blood

Blood viscosity is a physico-chemical property of blood, mediated by internal friction. In the state of motion, the flow of liquid can be considered as a series of cylindrical layers moving with respect to each other with different velocities. The unit of viscosity measurement is Pa·sec (in the SI system) or poise – P (in the CGS system). 1 poise is 0.1 Pa·sec. In medicine, the most common for the evaluation of viscosity has become a unit of centipoise (cP). The viscosity of water at 20.3 °C is 1 cP. The viscosity of blood plasma is about 1.7 cP and the viscosity of whole blood is 5 cP. Therefore blood viscosity mainly depends on the concentration of plasma proteins and cells number (hematocrit ratio). Blood is an unusual, non-

Newtonian fluid, i.e. its rheological properties can not be described by Newton's law of viscosity (Figure 1.3). These blood properties are primarily due to the aggregation of erythrocytes and their deformability.

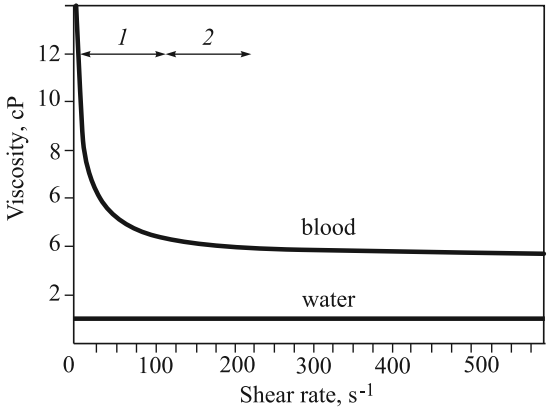

Figure 1.3. Blood rheological properties:
1 – erythrocytes aggregation; *2* – erythrocytes deformability

Fåhræus-Lindqvist effect is a decrease in the viscosity of blood when moving in small diameter vessels (less than about 100 μm). The physiological meaning of this phenomenon is that it significantly reduces heart work for blood movement through small-diameter vessels which have a large total area.

Erythrocytes aggregation is a reversible process of the formation of three-dimensional complexes and intercellular red blood cells structures. Erythrocytes interact with each other, touching the flat surfaces, stick to each other; thus, forming a rouleau or "stack-of-coins". This phenomenon is also called the "sludge effect" or "blood sludge". The process of erythrocyte aggregation is carried out with the participation of various high-molecular proteins, which form a kind of "bridge" between the cells. The increase in the concentration of such proteins as fibrinogen, α_1-, α_2-, β-globulins, immunoglobulins induces erythrocytes aggregation. This phenomenon is observed during blood stasis or at very low shear forces.

The mechanical properties of red blood cells are also of particular importance. **Erythrocytes deformability** is the ability of these cells to change their shape under the influence of an external force. Erythrocytes are capable to elongate 2–3–fold during deformation. The nonnucleated

erythrocytes of humans and other mammals are capable of deforming more than nucleated erythrocytes (e.g., birds). Discoid erythrocyte passes easily through capillaries with a diameter of 3 μm.

Hemoglobin

Hemoglobin is a molecule consisting of protein globin (2α- and 2 β-chains) and 4 pigment groups (heme), which are capable of reversible binding molecular oxygen.

Hemoglobin has multiple functions:

- transport of oxygen from the lungs to the tissues;
- carriage of carbon dioxide from tissues to the lungs as carbaminohemoglobin;
- buffering of hydrogen ions formed in the erythrocyte from the conversion of carbon dioxide into bicarbonate;
- nitric oxide metabolism.

The hemoglobin level in the blood can vary. In women, it is lower (120–140 g/L) than in men (130–160 g/L). One erythrocyte contains roughly 400 million molecules of hemoglobin.

There are different types and compounds of hemoglobin depending on its functional state (Table 1.5). Various abnormal and pathological forms of hemoglobin, differing in amino acid composition, are also known. Hemoglobin, combined with oxygen, is called ***oxyhemoglobin*** (gives the blood a bright red color). The process of its binding to O_2 is called oxygenation, and its removal from oxyhemoglobin molecule is deoxygenation. Non-oxygenated hemoglobin is called ***deoxyhemoglobin***.

Combination of hemoglobin with oxygen:

$$\underset{\text{(desoxy-)}}{Hb} + 4O_2 \rightarrow \underset{\text{(oxy-)}}{Hb(O_2)_4}$$

The binding of the hemoglobin protein and oxygen proceeds in steps. Each new O_2 molecule attachment to one of four iron-binding sites changes the shape or conformation of hemoglobin molecule, which provides positive cooperativity of the oxygen-binding properties of hemoglobin. Therefore, it is easier to bind a second and third O_2 molecule to hemoglobin than the first molecule.

In 2019, the 118th Nobel Prize in Physiology or Medicine was awarded to W.G. Kaelin Jr, Sir P.J. Ratcliffe, and G.L. Semenza for studying the physiological mechanisms of adaptation to changes in the oxygen content to the environment, for studying the mechanisms of how cells react to

oxygen or its deficiency in the body, in particular, for studying the role of the HIF-1α (Hypoxic-inducible factor 1α) in these processes.

Table 1.5. **Hemoglobin types and compounds**

Types	HbP – primitive (embryonic), first 12 weeks of pregnancy
	HbF – fetal, 12–36 weeks of pregnancy
	HbA – adult HbA_1 – 96–98% HbA_2 – 1.5–3%
Compounds	Hb – reduced or desoxyhemoglobin
	HbO_2 – oxyhemoglobin
	$Hb(CO_2)$ – carbhemoglobin
	Hb(CO) – carboxyhemoglobin
	MetHb – methemoglobin
	SNO-Hb – nitrosohemoglobin
	$HbFe^{2+}NO$ – nitrosilhemoglobin

Blood oxygen capacity (oxygen carrying capacity) is the maximum amount of O_2 that can be transported by 1 L of blood with complete saturation of hemoglobin with O_2. Normally, the oxygen capacity of the blood is 180–220 ml O_2 in 1 L of blood. Its calculation may be carried out according to the following formula:

$$Blood\ \ oxygen\ \ capacity = \mathrm{Hb} \cdot 1.36\ \ \mathrm{ml}\ \ \mathrm{O_2}/\mathrm{g},$$

where, Hb – hemoglobin concentration (g/L); 1,36 ml O_2/g – Hüfner's constant (the in vivo maximum oxygen-carrying capacity of 1 g of hemoglobin).

Hemoglobin can also bind to carbon dioxide, forming carbhemoglobin or carbaminogemoglobin, with carbon monoxide – carboxyhemoglobin. Carbaminohemoglobin plays an important role in the formation of the acid-base balance of the body and elimination of carbon dioxide. The affinity of CO to hemoglobin is 300 times greater than the affinity of oxygen. When the content of CO in the air is 0.1%, most of it (about 80%) binds to hemoglobin, which leads to severe poisoning. Normally, carboxyhemoglobin level in the body is 1%, and in smokers – up to 3%. Binding NO to hemoglobin is one of the main ways of eliminating this compound, which, as recently established, plays an important mediator role in the body, in

particular, mediating the relaxation of smooth muscle vessels. In addition, NO, interacting with hemoglobin, forms various NO-Hb derivatives: methemoglobin, nitrosylhemoglobin, and S-nitrosohemoglobin, which play the role of allosteric regulators of hemoglobin functional activity at the level of each tetramer subunit.

There are different types of hemoglobin depending on the age. The most abundant hemoglobin of the body is A (adult), its alpha chains consist of 141 amino acids, and beta chains – from 146 (HbA1 – 96–98%, HbA_2 – 1.5–3%). The fetus has hemoglobin P (embryonic, the first 12 weeks of development) and F (fetal, 12–36 weeks of fetal life). Hemoglobin F instead of beta chains contains gamma chains and has a greater affinity for oxygen than hemoglobin A (in the fetus oxygen content is relatively small). After birth, hemoglobin F is replaced. In some diseases, the content of this hemoglobin in adults can increase.

The **color index** shows the degree of red blood cells saturation by hemoglobin, i.e. characterizes the ratio between the number of erythrocytes and hemoglobin level. Its normal range is 0.8–1.05 (***normochromia*** or normochromic erythrocytes). At a value less than 0.8 the condition is called hypochromia, above 1.05 – hyperchromia. Its calculation may be carried out according to the following formula:

$$Color\ index = \frac{Hb \cdot 3}{Er*},$$

where, Hb – hemoglobin concentration, g/L; *Er** – the first three digits of the erythrocytes number.

Erythropoiesis

The lifespan of erythrocytes in the circulatory system in adults is 100–120 days, about 1% of these cells ($(0.05–0.08)\cdot10^{12}$/L) are renewed daily. The number of erythrocytes in the body is determined by the rate of their formation and destruction. The immediate precursors of erythrocytes are reticulocytes – cells with residues of ribonucleic acids, mitochondria, and other organelles that form in the bone marrow. Their content ranges from 0.2 to 1.0%. The number of reticulocytes is an indicator of erythropoiesis activity. In the spleen and bone marrow macrophages perform erythrophagocytosis, accumulating iron in the form of hemosiderin and ferritin, which can be reutilized by erythroblasts. At the end of the life cycle of red blood cells, they are phagocytosed by reticular cells, histocytes, macrophages, and polynucleated leukocytes. As a result of this process, the hemoglobin molecule and membrane are decomposed with the formation of low-molecular compounds.

Erythropoiesis is activated by adrenocorticotropic hormone (corticotropin), somatotropin, thyroxine, and androgens. These factors, except growth hormone, stimulate erythropoiesis through an increase in the rate of erythropoietin formation, additionally, androgens can directly stimulate the bone marrow. Inhibition of erythropoiesis is provided by estrogens. It is also known that some parts of the central nervous system affect erythropoiesis: irritation of the posterior parts of hypothalamus increases the formation of erythropoietin, and the destruction of supraoptic nuclei of the hypothalamus inhibits erythropoiesis.

Erythropoiesis regulators:

♦ activators (male sexual hormones, erythropoietin, tropic hormones of the adenohypophysis, adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropic hormones, somatotropin, pituitary, and placental prolactin, thyroid hormones, insulin, vitamins (B_{12}, B_6, ascorbic acid), trace elements, activation of the sympathetic division of the ANS);

♦ inhibitors (female sexual hormones, glucagon, erythrocyte chalones, activation of the parasympathetic division of the ANS).

In the regulation of erythrocyte number, an important role belongs to **erythropoietin** – a glycoprotein, synthesized mainly in the kidneys and stimulating erythropoiesis (Figure 1.4). It appears in the blood during hypoxia. It is activated by a special Hypoxia Inducible Factor (HIF-1).

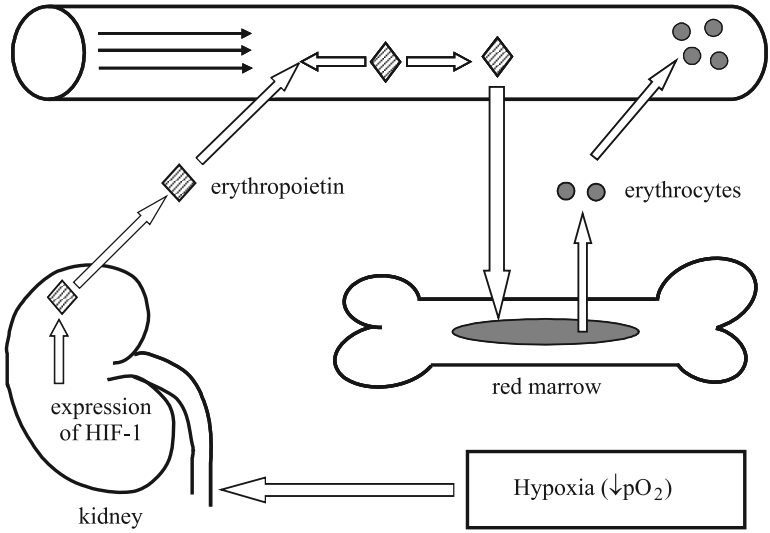

Figure 1.4. Erythropoiesis activation in hypoxia via the mechanism of Hypoxic-Inducible Factor-1 and erythropoietin formation

Leukocytes properties

Leukocytes (white blood cells) are colorless blood cells that have nuclei and do not contain hemoglobin. The functions of leukocytes in the body are different. They provide phagocytosis, which is an important component of the body defense system against infection. The increase in the number of leukocytes is called ***leukocytosis***. It is observed under normal conditions during physical exertion, emotional stress, pain stress, after food intake, during pregnancy (***physiological leukocytosis***).

The functions of leukocytes in the body are different. The phenomenon of adhesion is characteristic for leukocytes and is realized with the participation of cell adhesion molecules: integrins, selectins, etc.

Adhesion is the interaction of cells with each other and subsequent attachment to endotheliocytes, proceeded by expression of complementary adhesive molecules. ***Integrins*** is a family of membrane-bound protein receptors of the extracellular matrix providing cell adhesion (e.g., fibronectin, laminin). Leukocytes are capable of amoeboid movement (movement speed – up to 40 μm/min).

Apoptosis (from Ancient Greek **apo** – "off, from, away" and **ptosis** – "a falling in or upon") is the physiological process of programmed cell death, accompanied by a set of characteristic cytological signs (markers of apoptosis) and molecular processes.

Diapedesis is the migration of leukocytes from the vascular bed through the interendothelial space into the surrounding tissue.

The blood defense function is realized through specific and nonspecific (humoral and cellular) mechanisms. When re-meeting the antigen, the immune defense mechanisms react more quickly.

The complement system is a cytolytic complex formed from plasma proteins and ensuring the process of the antigen-antibody reaction. This system of proteolytic enzymes provides the humoral protection of the body against the action of foreign agents (a component of both inborn and acquired immunity). It includes about 20 interacting components: C1 (a complex of three proteins), C2, C3, ..., C9, factor B, factor D, and a number of regulatory proteins. Its activation is realized in three ways: classical, alternative, and lectin pathways. The first is realized with the participation of antibodies, while others can be activated by antigens without antibodies. Antibodies (***immunoglobulins***) are γ-globulins of blood, interacting with certain antigens and neutralizing microorganisms and foreign proteins.

A special role in the defence processes belongs to ***cytokines***, i.e. proteins, produced by cells and performing the function of intercellular mediators in the immune response (e.g., interleukins). In 1980, antimicro-

bial peptides were isolated from rabbit alveolar macrophages, which were called ***defensins***. These antimicrobial peptides are the important components of the immune system. This family of low-molecular (4,000 Da), rich in cysteine cationic peptides, kill bacteria, fungi and enveloped viruses. The main depot of α-defensins in the body are neutrophils.

Phagocytosis (from Ancient Greek **fago** – "eat away", **kutos** – "cell" and wois – "process") is the capture and elimination of microorganisms or foreign solid substances by leukocytes (one white cell can phagocytize up to 15–20 bacteria). The phenomenon of phagocytosis was discovered by I.I. Mechnikov in 1883, for that discovery he was awarded the Nobel Prize in 1909.

According to the presence of specific colored granules in leukocytes, they are divided into granulocytes (neutrophils, basophils eosinophils) and agranulocytes (lymphocytes, monocytes). Granulocytes make up about 50–70% of all leukocytes. By the method of fixation and dyeing of granules, they are subdivided into neutrophils, eosinophils, and basophils. The leukocytic formula shows the percentage distribution of various forms of white blood cells (Table 1.6).

Table 1.6. **Leukocytic formula**

Parameters	Normal range, unit of measurement
Neutrophils: myelocytes	0 %
Neutrophils: metamyelocytes	0 %
Neutrophils: stab neutrophils	1–6 %
Neutrophils: polymorphonuclear (PMN)	47–72 %
Eosinophils	0.5–5 %
Basophils	0–1 %
Lymphocytes	19–37 %
Monocytes	3–11 %

Neutrophils are the most numerous fractions of granulocytes (93–96%). They are polymorphonuclear (PMN) cells. Mature neutrophils have a moderately compact nucleus of a band or polymorphonuclear shape. Their granules are 5–8 nm spherical formations and contain acidic phosphatase, glucuronidase, phospholipase, neuraminidase, cathepsin, phagocytin, lysozyme, and other active substances. Neutrophils provide nonspecific protection of the body. These are the most numerous white

blood cells. The circulation time in the vascular bed is small (up to 8 hours). The main part of them is deposited in the bone marrow (about 60%), lungs, spleen and other tissues (about 40%), and the peripheral blood contains only about 1%. Approximately half of the granulocytes are in large vessels, and half are sequestered in capillaries (marginal granulocyte pool). Neutrophils that have migrated into tissues do not usually return to the vascular bed (the tissue phase is final). In acute infectious diseases, their number increases rapidly. Neutrophils phagocytize bacteria and the products of their decay.

Eosinophils (2–4% of total leukocytes number) are also capable of phagocytosis, but they have lower bactericidal activity than neutrophils (their granules contain less peroxidase). Eosinophils are characterized by a daily rhythm of changes in their number. At night, their quantity is the greatest, and in the morning is the smallest, 30% less than the average daily level, which is due to the change in the glucocorticoids level in the adrenal cortex. After circulation in the blood, eosinophils migrate into tissues, where they stay for about 80 days. In the tissues, eosinophils number is about 100 times greater than in the bloodstream. In allergic reactions, the number of eosinophils increases significantly (eosinophilia). They are involved in other immune responses.

Basophils remain in the vessels for several hours, their number is small (about 1%), the circulation time is about 24 hours, they contain heparin and histamine. They are the source of the formation of a number of physiologically active substances: heparin, histamine, kallikrein, etc. In general, the functions of basophils are similar to the functions of mast cells (they play an important role in allergy, anaphylaxis, wound healing, angiogenesis, immune tolerance, defense against pathogens, blood-brain barrier function and interaction with the neuroimmune system).

Agranulocytes include lymphocytes and monocytes. *Lymphocytes* are the main cellular elements of the body's immune system, recognizing foreign antigens and producing antibodies against them. They provide mechanisms of cellular and humoral specific immunity (Figure 1.5). They are formed in lymph nodes, tonsils, spleen, thymus, Peyer's patches, appendix, bone marrow. There are short-lived (lifespan of several days, in peripheral blood, account for up to 30%) and long-lived (170 days) lymphocytes. From "zero" lymphocytes, depending on the site of differentiation, *T-cells* (thymus gland) and *B-cells* (lymphoid nodes, in birds – bursa) with different structural and functional organization are formed, providing mechanisms of specific cellular and humoral immunity.

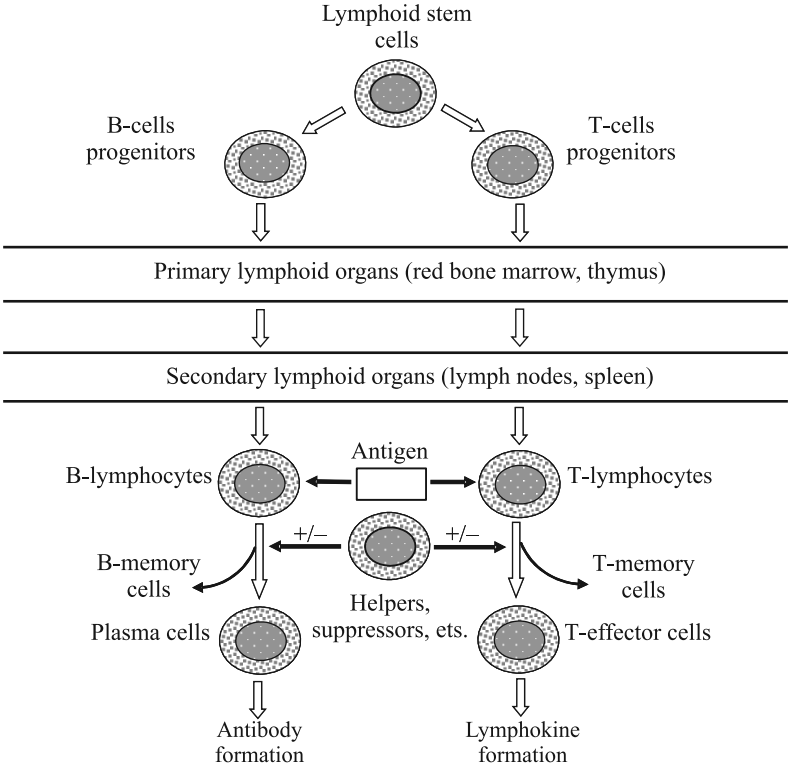

Figure 1.5. Mechanisms of specific cellular and humoral immunity

In bursa and other lymphoid tissues, B-lymphocytes that determine humoral immunity are formed, i.e., form specific antibodies in response to antigenic stimulation. The interaction of leukocytes with antigenic substance leads to the complex processes from the side of macrophages, activation of *B-lymphocytes*, their differentiation, resulting in the formation of various immunoglobulins (JgG, JgA, JgM, etc.). B-lymphocytes are able to form a complex of "antigen-antibody", which provide elimination of the foreign factor.

Lymphocytes maturating in the thymus are called *T-lymphocytes*. They determine the specific cellular immunity. Upon contact with the antigen, proliferation (multiplication) of cells capable of interacting with it occurs and as a result of this interaction, the antigen is destroyed. There are several subpopulations of T-cells: T-killers or cytotoxic T-cells (kill bacteria),

T-helpers (promoting killer activation), T-suppressors (depressing cellular immunity), delayed-type hypersensitivity effector $CD4^+$ T-cells (release humoral mediators, lymphokines, that direct the immune system response by signaling between other cells). They include a macrophage activation factor, a macrophage migration inhibition factor, chemotactic factors for neutrophils, eosinophils, basophils. There are also lymphocytes that recognize foreign antigens and give a signal to the beginning of an immune response – cells of immunological memory.

The mechanisms of nonspecific humoral immunity include:

- complement system;
- kinin system (kinin–kallikrein system);
- properdin system;
- lectins, plakins, etc.

Monocytes are the largest in size leukocyte cells (up to 20 μm). These cells are formed in the bone marrow. Their number is 3–11% of all leukocytes. They are larger than other blood cells (mature cell diameter is 16–20 μm). They are called "scavengers of the body". Through the formation of a number of cytokines (interleukins, interferons, etc.) they are involved in both immune and hemostasis systems functioning (coagulation, fibrinolysis). Having stayed for 2–3 days in the vessels, monocytes move to the surrounding tissues, transforming into tissue macrophages. They participate in the mechanisms of specific immunity. During maturation, monocytes are transformed into tissue macrophages and acquire specific properties depending on the tissue in which they are located. Once monocytes have left the bloodstream, they can never enter the blood again (like neutrophils). Monocytes stay in circulation for around 72 hours. Macrophages participate in inflammatory processes (phagocytosis, the release of physiologically active substances, interaction with plasma and tissue factors) and in the immune response.

It is necessary to bear in mind that the percentage distribution of various forms of white blood cells (leukocytic formula) in infectious diseases can vary significantly. This can serve as a good criterion for diagnosing multiple diseases.

Leukocytes play a key role in immune response.

The characteristics of the main mechanisms of blood immunity are presented in Figure 1.6.

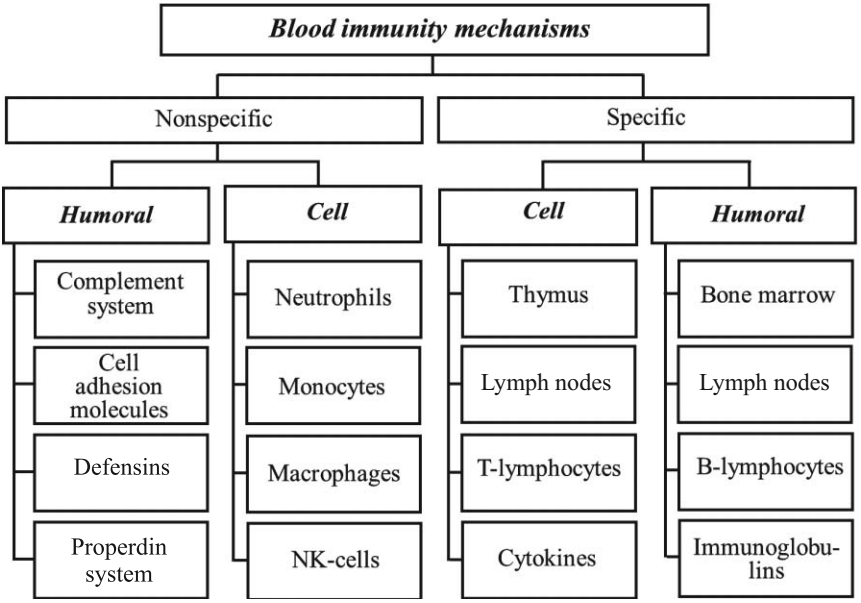

Figure 1.6. Blood immunity mechanisms

Thrombocyte properties

Thrombocytes (platelets) are blood plates that perform an important role in the hemostasis processes. Their number is $(180–320)\cdot10^9$/L. They have an irregular shape and a diameter of 1–4 μm. The circulation time in the blood is 5–11 days. Their destruction occurs in the liver, spleen, and lungs. The number of platelets grows during digestion, pregnancy and intense muscular activity. Their number during the day is higher than at night.

Thrombocytes functions:

- hemostatic – adhesion and aggregation leading to the formation of a thrombus in the vessels of microcirculation and participation in fibrinolysis;
- angiotrophic – affecting the structure and condition of the vessels of the microcirculatory bed and feeding the endothelial cells of the capillaries;
- regulation of vascular tone (via secreting vasoconstrictors: serotonin in granules, etc.);
- a source of platelet coagulation factors;

♦ a source of thromboxane A_2, which causes platelet aggregation and spasm of blood vessels;

♦ initiation of reparative processes in the damaged vascular wall;

♦ bactericidal and phagocytic-like activity;

♦ containing endotoxin-binding substances and interacting with bacteria, endotoxins, viruses, fungi, and parasites.

Thrombocytes have a key role in blood coagulation, bleeding stoppage, vessels trophicity and also participate in the mechanisms of nonspecific immunity of the body. About 70% of the platelets are in the peripheral blood, the rest are in the spleen. Platelets contain a number of specific factors involved in blood clotting (platelet coagulation factors). The most important are platelet thromboplastin (released when platelets are destroyed, have the structure of a phospholipid), thrombostenin (causes retraction of a platelet clot), a vasoconstrictor factor (platelet-adsorbed serotonin) and a platelet aggregation factor (PAF). In addition, platelets contain prostacyclin (anticoagulant effect) and thromboxanes (procoagulant effect), which change significantly the intensity of platelets aggregation.

Hemostasis system

The **hemostasis system** is a set of factors that ensure the liquid aggregate state of blood under normal conditions and its coagulation in case of vessel wall damage, as well as fibrinolysis and the recanalization of vessels after vessel wall damage area healing. Hemostasis is provided by several interacting components: blood vessel wall, platelets, plasma clotting factors, anticoagulant factors, and fibrinolysis mechanism. Thanks to the functioning of this system, the basic functions of blood and normal blood circulation are provided, as it prevents the blood from passing through the vessel wall and maintains normal physico-chemical properties of the blood.

Structural and functional components of hemostasis system:

♦ vessel wall;

♦ thrombocytes;

♦ plasma clotting factors (see Table 1.7 for details).

The vascular endothelium is the main source of formation of many physiologically active substances acting on vascular smooth muscle cells. Given its unique position between the circulating elements of the blood and the surrounding tissue (in the capillaries), the endothelium acts as an integrator and transmitter of signals through the synthesis of various vasoconstrictor, vasodilator and remodeling factors. The endothelium is considered as an endocrine-paracrine organ, which is not only a structural barrier between blood and surrounding tissues but also a multifunctional system that plays an essential role in hemodynamics. Endothelial cells are