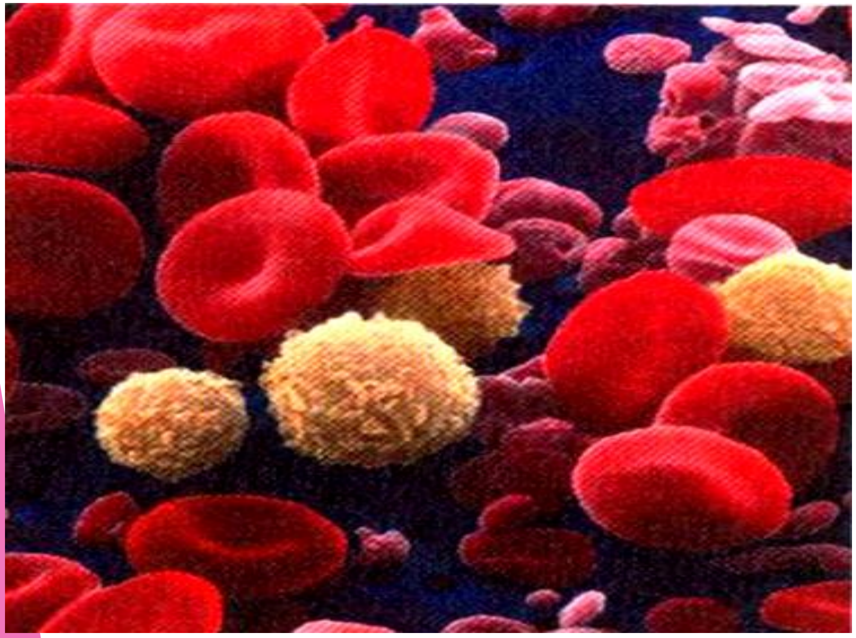
GOMEL STATE MEDICAL UNIVERSITY

Normal and Pathological Physiology Department

PHYSIOLOGY OF BLOOD



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Lecture plan

1. The concept of the blood system. Basic functions of blood. Composition and volume of blood.

2. Blood plasma.

3. Physical and chemical properties of blood. Buffer systems of blood.

4. Erythrocytes, their structure, properties and functions.

5. Hemoglobin, its structure, behavior, varieties, compounds, and function.

6. Hemolysis and its varieties.

7. Erythrocyte sedimentation rate

8. Leukocytes, their classification, features, and functions

9. Thrombocytes, their structure, behavior, and functions

1. The concept of the blood system

Blood along with interstitial fluid and lymph is an important component of an organism`s internal environment, the relative constancy of which, including physical and chemical parameters (pH, osmotic pressure, temperature, etc.), is a prerequisite for the organism`s vital activity. The changes of the physical and chemical properties of blood, which are important mechanisms in the pathogenesis of many diseases, are used for their diagnostics, assessment of the efficacy of treatment and prognosis.

The blood system, as proposed by G. F. Lang (1939), **includes**:

1. ***Blood* (in the blood vessels).**

2. ***Organs of hemopoiesis*** (red bone marrow, lymph nodes, spleen, thymus gland).

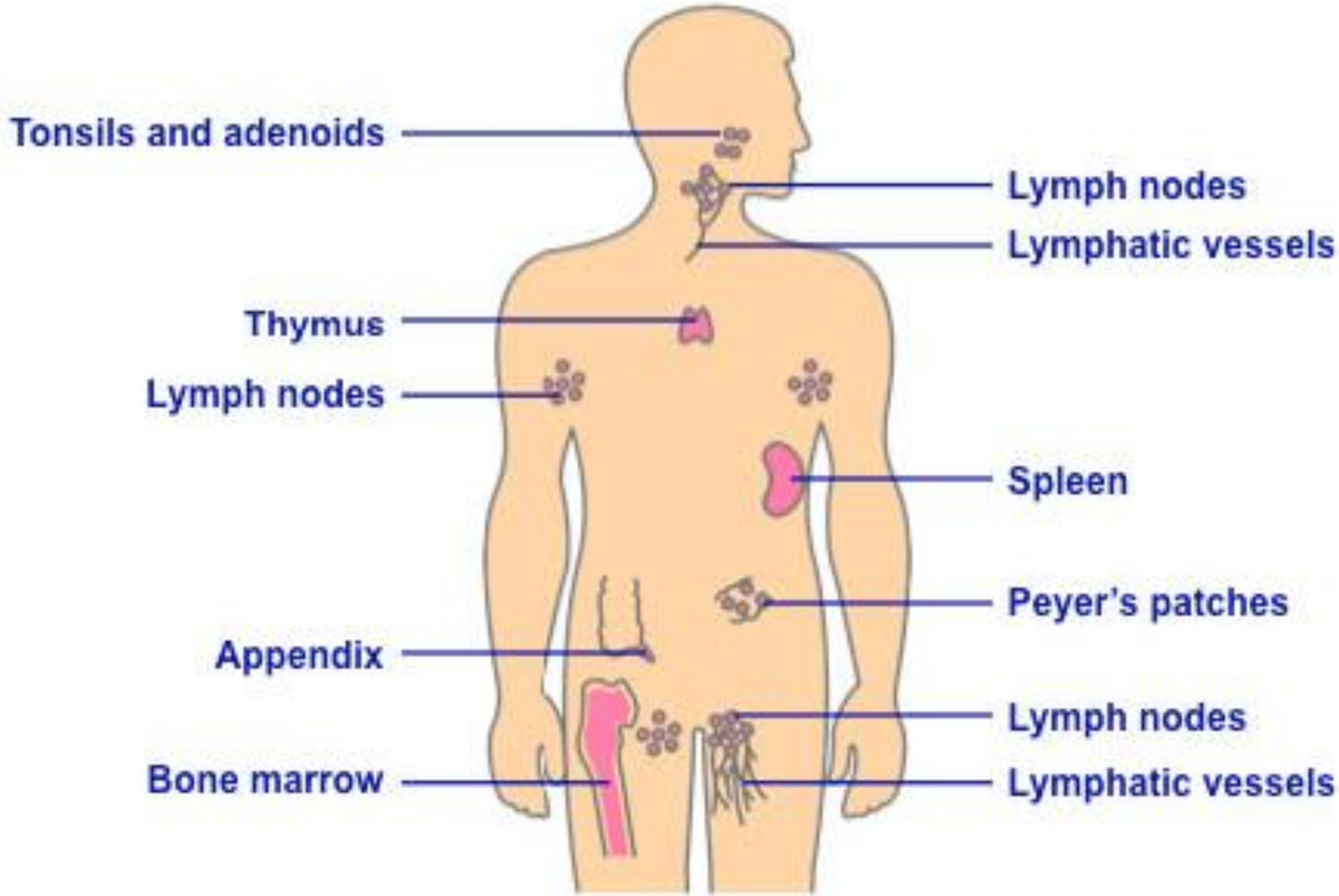
3. ***Organs of blood destruction*** (liver, bone marrow, spleen).

4. ***Neurohumoral apparatus***.

The main site in the human body where blood cells are manufactured is *the* ***red bone marrow***. Also, here the destruction of cells (erythrocytes), iron recycling, Hb synthesis, and maturing of B-lymphocyte populations, being the factors of humoral immunity, occur.

The production of T-lymphocytes takes place in the ***thymus gland***. Besides, the spleen, lymph nodes, and other lymphoid formations (Peyer's plaques, tonsil, appendix, etc.) take part in the development of the immune components (Figure).

Lymphocytopoiesis, Ig synthesis, destruction of erythrocytes, leucocytes, thrombocytes, the deposition of blood are carried out in *the* ***spleen***.



Fugure — Main organs of hemopoiesis

Basic functions of blood

1. *Transportation* (transition of various substances).

2. *Respiratory* (transition of oxygen from the respiratory organs to tissues, and CO_2 in the reverse direction).

3. *Trophic or nutritional* (transition of nutrients from the digestive truct to cells and the use of blood components by the cells of tissues and organs for plastic and energy needs).

4. *Excretory* (transition of waste and harmful substances to the excretory organs: the end products of metabolism, excessive mineral and organic substances formed during metabolism or ingested with food).

5. ***Temperature control*** (blood is warmed up in the internal organs, where a lot of energy is formed, and is cooled down at the upper layers of the body).

6. ***Homeostatic*** (along with interstitial fluid and lymph, blood forms the internal environment and participates in the maintenance of its constancy).

7. ***Provides the water-salt exchange*** between blood and tissues.

8. ***Protective*** (blood contains the factors of humoral and cell-mediated immunity: antibodies, phagocytes, coagulation factors, interferon, T- and B-lymphocyte populations, etc.).

9. ***Correlative*** (blood transfers biologically active substances which provide interconnections among various organs and tissues thus ensuring that the organism functions as a whole).

10. ***Maintenance of constant acid-base balance*** due to the buffer system.

Composition and volume of blood

Blood consists of ***plasma*** and *the* ***formed elements***: **erythrocytes, leucocytes, thrombocytes** (platelets) (Figure).

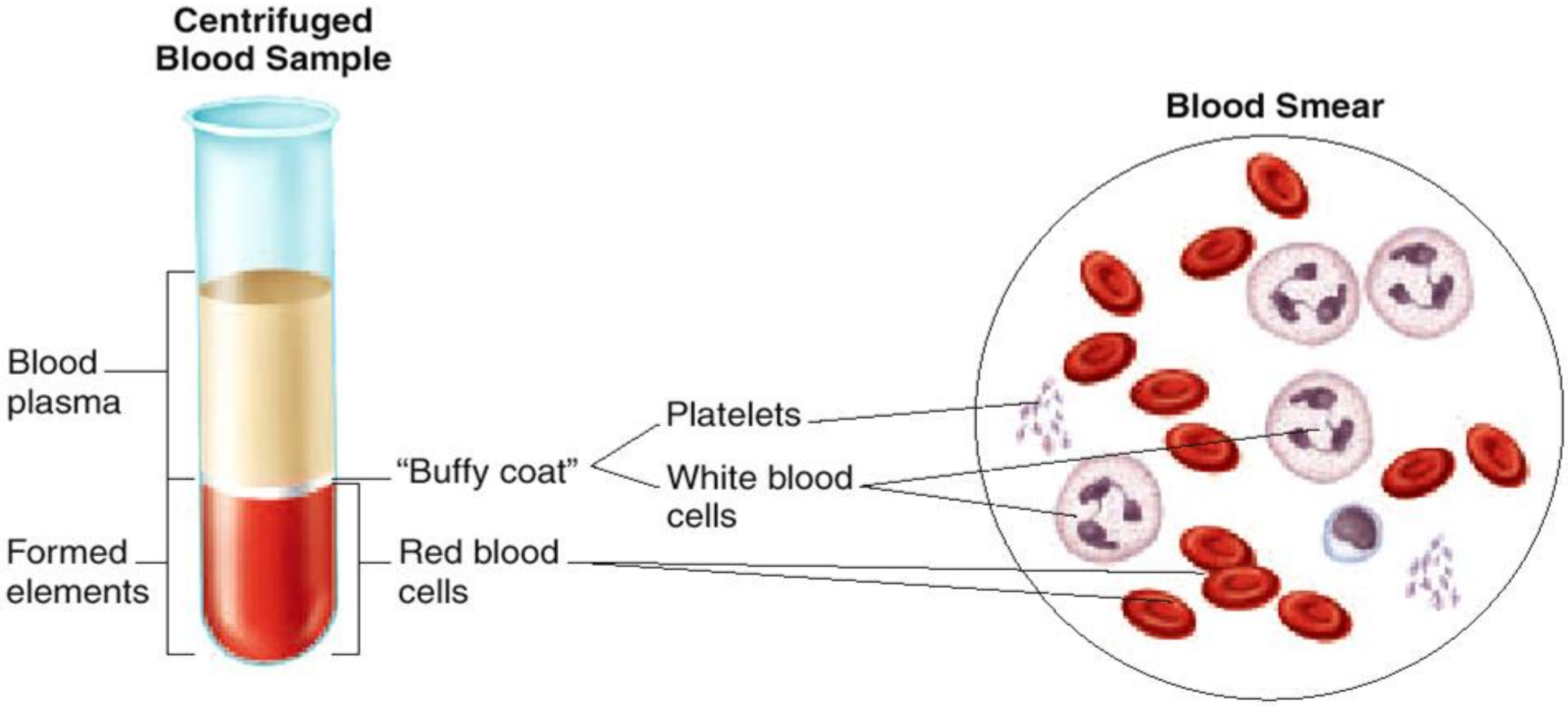
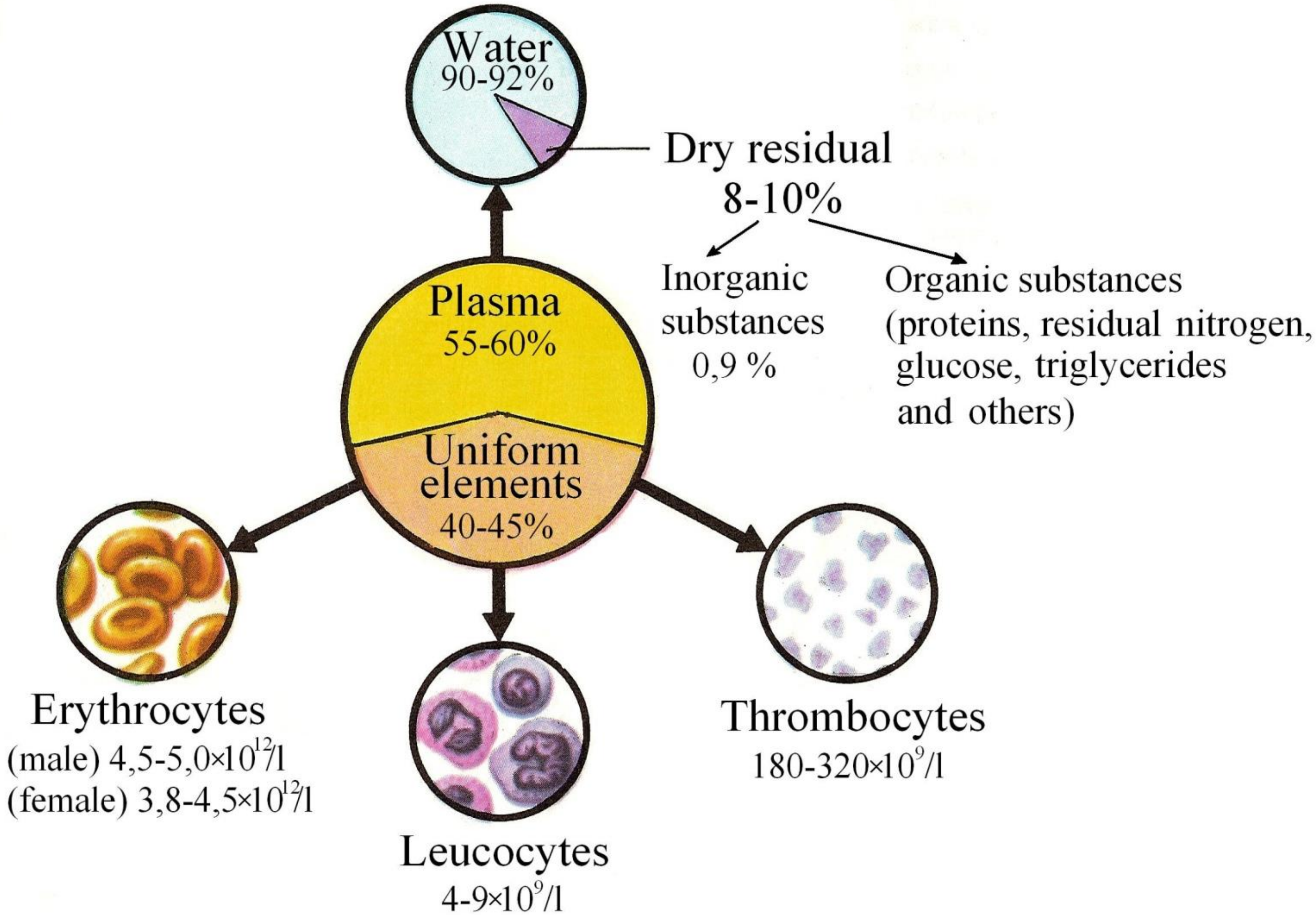


Figure — Blood composition



The composition of blood

Between the counts of the formed elements and plasma there is a certain interrelation which is called the **hematocrit value** (Figure). The hematocrit measures the count of red blood cells (RBCs) compared to the total blood count (red blood cells, white blood cells, platelets, and plasma).

In norm, the **erythrocyte** count **in males** constitutes **42–52 %**, **plasma** count — **48–58 %**. To transform it into SI (International System of Units), the obtained number is multiplied by 0.01. The normal value for **males** is **0.42–0.52**, for **females — 0.37–0.47**. **In newborns**, the hematocrit is **10 % higher**.

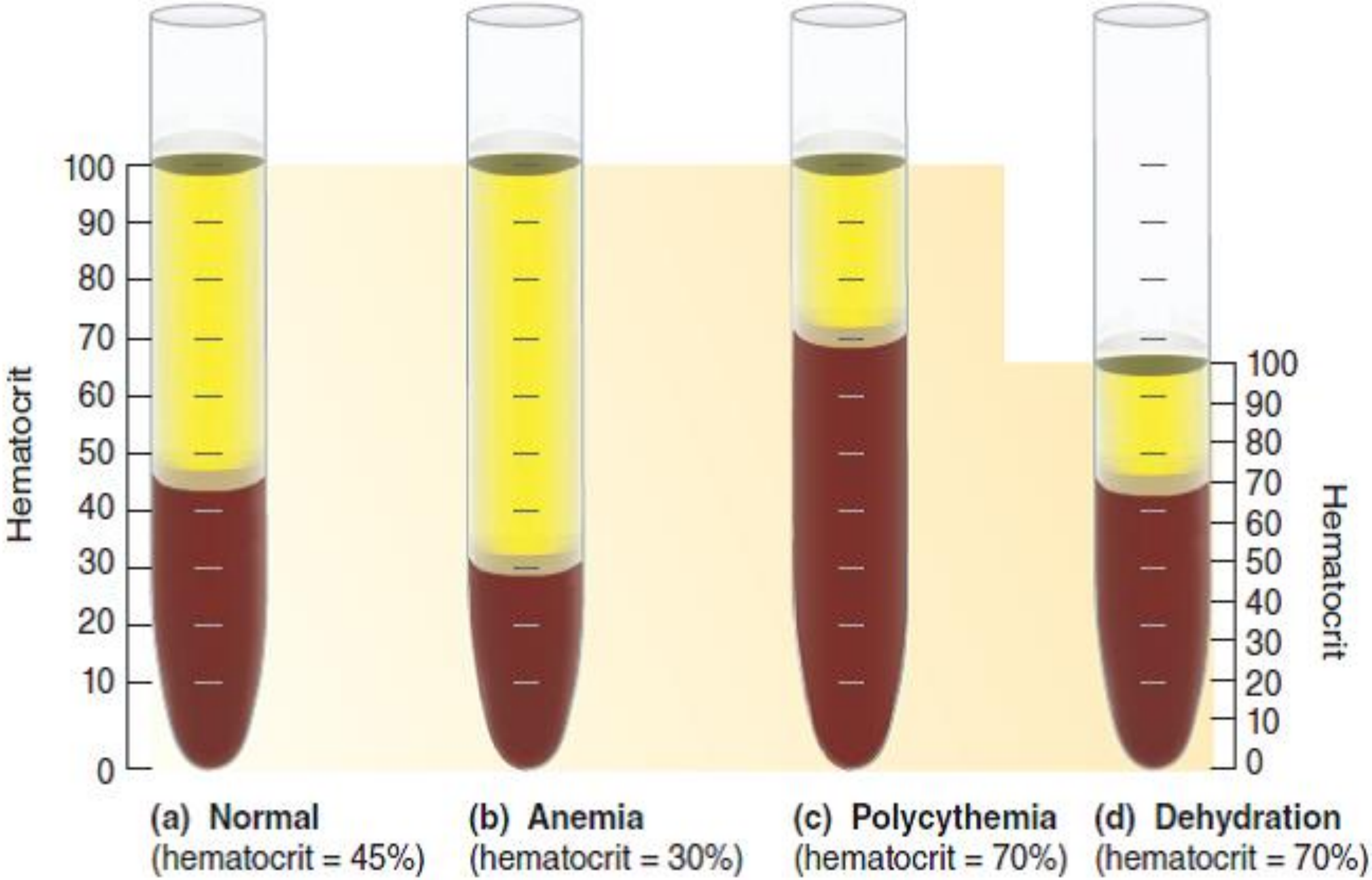


Figure — Hematocrit values under various circumstances

Blood volume

In adults, the **absolute blood volume** is approximately **4.5–6 liters**. Its relative content corresponds to **6–8% of body weight (in newborns — 15 %).**

The normal total blood volume is called *normovolemia*. There are **simple, oligocythemic, and polycythemic types** of normovolemia (Table).

- ***Simple* normovolemia** is the normal interrelation between the volume of the formed elements and plasma.
- ***Oligocythemic* normovolemia** can be observed in anemia as a result of blood loss when the volume of blood is restored due to its fluid part (transition of the interstitial fluid into the blood vessels), and the number of the formed elements is not yet restored.
- ***Polycythemic* normovolemia** can be observed during transfusion of small amounts of erythrocytic mass.

Increased blood volume (hypervolemia, plethora) is observed:

1. After administration of a large amount of blood.

2. During intensive hemopoiesis (increased erythrocyte count).

3. Due to water retention in the body (kidney diseases).

4. After an excessive water intake.

Decreased blood volume (hypovolemia) is caused by:

1. Acute blood loss.

2. Anemia.

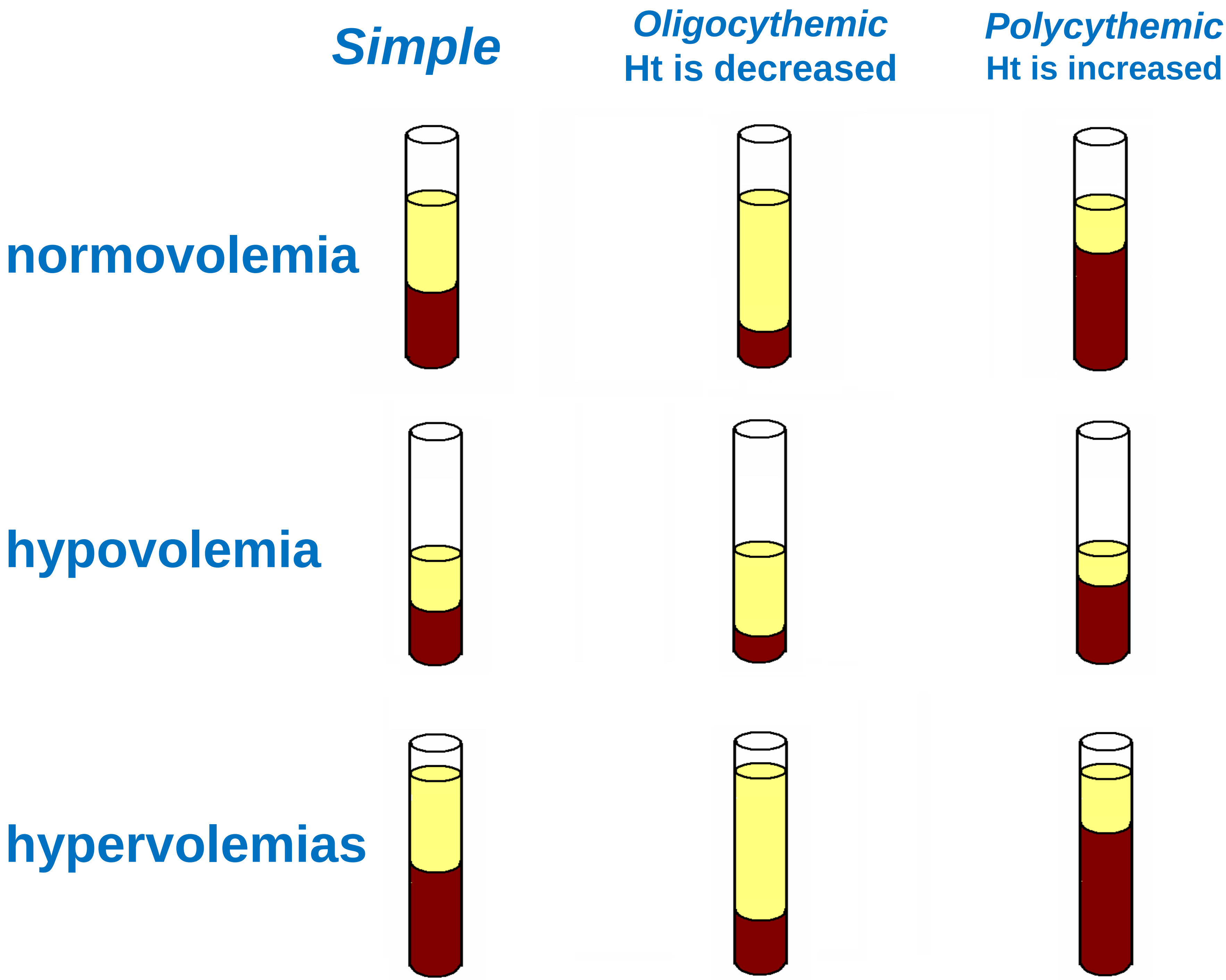
3. Body fluid loss (body dehydration), e. g., in profuse diarrhea, continuous vomiting.

Kinds of hypervolemia:

- ***Simple*** — proportional increases of the volumes of the formed elements and plasma (in hemotransfusion). The hematocrit value is normal.
- ***Oligocythemic*** — increased blood volume due to an increase of its fluid part (administration of blood-substituting fluids, kidney dysfunction). The hematocrit value is low.
- ***Polycythemic*** — increased blood volume due to an increased number of the formed elements (compensatory character in populations living in mountainous areas). The hematocrit value is low.

Kinds of hypovolemia:

- ***Simple*** — proportional decreases of the volumes of the formed elements and plasma (it is short-term in acute hemorrhages). The hematocrit value is unchanged.
- ***Oligocythemic*** — decreased blood volume due to a decreased number of the formed elements after blood loss (when the volume of blood is restored owing to the interstitial fluid getting into the blood vessels). The hematocrit value is low.
- ***Polycythemic*** — decreased blood volume due to a decrease of the fluid part of blood (blood clotting in dehydration, e. g., in profuse diarrhea, continuous vomiting, hyperhidrosis). The hematocrit value is high.



Simple
Oligocythemic
Ht is decreased
Polycythemic
Ht is increased
normovolemia
hypovolemia
hypervolemias

By the degree of its participation in the circulation, there is ***deposited blood (45–50 %)*** and ***circulating blood*** **(50–55 %).**

The depots of blood:

Liver*.* A large amount of blood is deposited here (up to 20% of its total volume) but is not excluded from the total blood flow completely (opposed to the spleen).

Spleen. In the spleen up to 500 mL (10–16 %) of blood can be deposited (excluded from the blood flow).

Skin. Blood is deposited in the capillaries and veins (about 10 %), which is connected with thermoregulation.

Lungs. Blood is deposited due to the change of the volume of the arteries and veins.

Venous system (regarded as the depot of the fluid part of blood containing a significant amount of lymph).

Lymph in the lymphatic **vessels** may be regarded as the depot of the fluid part of blood.

Deposited blood can transfer into circulating blood due to:

- An emotional state.
- A physical strain.
- Low oxygen (hypoxia).
- Hemorrhages.

Value of the depots of blood. The ability of organisms to increase the mass of circulating blood becomes vital in concrete conditions which require urgent satisfaction of the organism`s oxygen need (in mountaineering, physical exercise and other states connected with high oxygen consumption).

Hemorrhages and their effects. For a healthy person a single loss of **1/3 or even 1/4 of the volume of circulating blood is life-hazardous** (low blood pressure, hypoxia). **A sudden loss of 50 % blood leads to death**, a slow loss (within a few days) of this amount of blood is not lethal, as in this situation there is enough time for the organism to mobilize the compensatory mechanisms directed to the stabilization of blood pressure and elimination of hypoxia.

Babies and newborns are especially sensitive to hemorrhages (compensatory mechanisms are not yet well developed). The sensitivity to hemorrhages increases in narcosis, hypothermia, pain, and shock.

2. Blood plasma

Blood plasma is a colloid-polymeric solution of organic and inorganic substances (electrolytes, nutrients, proteins, hormones, etc.) with an addition of dissolved blood gases.

Colloidal components are proteins and their compounds. Plasma is the fluid portion of blood (its volume is approximately **2.8–3.0 L**).

The composition of plasma: **$H_2$0 (90–92 %)**, being a solvent, and **solid (dense) residue (8–10 %),** which includes dissolved substances such as salts and low-molecular organic compounds.

Composition of blood plasma

Dry residual

Water
(90–92%)

Organic components

Proteins:
- albumins;
- globulins;
- Fibrinogen.

Glucose.
Triglycerides.
Cholesterol.
Urea.
General bilirubin.

Inorganic components:

Gases:
- O_2,
- nitrogen,
- CO_2

Mineral substances:
- Na^+,
- K^+,
- Ca^{2+},
- chlorides, phosphates, hydrocarbonates

I. ***Organic part*:**

Proteins (albumins, globulins, fibrinogen) — **65–85 g/L.**

1. ***Albumins*** **(35–55g/L).**

- They form 80 % of the colloid-osmotic pressure (high concentration, a relatively small size of molecules).
- They participate in the regulation of water-salt balance.
- They transport many substances (bilirubin, fats acids, exogenous substances, including drugs — antibiotics, sulfanilamids, mercury, and others).
- They bind hormones (for example, thyroxine).
- They are a protein reserve.

2. **Globulins** ***(20–35g/L)*** — α_1 -, α_2 -, β_1 – β_2 - and *Y*-fractions:

α-globulin — thyroxinbinding protein;

— transcobalamin (B_{12});

— cortisolbinding protein.

ß-globulin – is a transferring agent of lipids, lipoids, and polysaccharides:

— transport of Cu, Fe (transferrin).

Y-globulins — (IgA, IgD, IgE, IgG, IgM) perform immune functions and are better known as antibodies or immunoglobulins. The agglutinins of blood are related to this fraction.

3. ***Fibrinogen*** **(*2–4 g/L*)** — participates in blood coagulation.

Formation of proteins:

a) albumins, fibrinogen are produced in the liver;

b) globulins are produced in the bone marrow, spleen, lymph nodes, cells of the mononuclear phagocytic system.

The role of plasma proteins:

- They exert a part of the osmotic pressure, so-called the colloid-osmotic pressure of plasma protein, or oncotic pressure (1/200 of the osmotic pressure).
- They maintain pH (buffering action).
- They maintain blood viscosity (important for blood pressure).
- They prevent erythrocyte sedimentation (stabilization).
- They participate in blood coagulation (fibrinogen, etc.).
- They perform the factors of immunity (immunoglobulins).

The role of plasma proteins:

- They transport substances which are poorly soluble in water (transport of hormones).
- They perform the nutrient (plastic) function.
- They regulate the concentration of free ions, for example, Fe^{++} (transferrin).
- They may inhibit the action of some proteases (antitrypsin — inhibitor of trypsin).
- They regulate metabolic functions (protein hormones, enzymes).
- They provide redistribution of water between tissues and blood (1 g of albumin binds 0.35 g of water and during swelling it can bind up to 18 mL of water). In hypoproteinemia (decrease of protein to 55 g/L) — edemas occur. Hunger edemas, for example, are caused by starvation.

Glucose. Glucose concentration in adults:

Whole blood — 3.30–5.55 millimole/L.

Plasma — 3.30–6.10 millimole/L.

Glucose concentration in newborns — 1.70–4.20 millimole/L.

The blood glucose test is commonly used to diagnose diabetes mellitus.

Not protein nitrogen-containing substances (polypeptides, amino acids, urea, urinary acid, creatine, creatinine, bilirubin, etc.). Not protein (residual) nitrogen — 14.3–28.5 millimole/L.

Urea is the end product of protein metabolism which is transported to the organs of excretion. The blood urea nitrogen test is used mainly for diagnosis of renal disorders. The normal concentration of **urea** in the blood ranges **2.5–8.3 millimole/L.**

General bilirubin — **3.4–20.5 micromole/L.** Bilirubin is an orange-yellow pigment which is produced after the breakdown of hemoglobin and is excreted by the liver. High bilirubin blood level results in the yellow pigmentation of the skin and sclera, which is known as jaundice (icterus). The evaluation of the bilirubin concentration may be used to diagnose liver diseases, hemolytic anemia.

Cholesterol and **triglycerides** are present in the blood mainly in the forms of lipoproteins and chylomicrons. **Triglycerides** — **0.55–1.65 millimole/L. Cholesterol** — **3.0–6.2 millimole/L.**

Also, plasma contains hormones, vitamins, and enzymes.

II. ***Inorganic part***: **gases** (O_2, nitrogen, CO_2) and **mineral substances**.

Mineral substances — **0.9 %** (ions of potassium, sodium, chlorine, calcium, HCO^-, HPO^-, etc.). The basic cations of plasma are Na^+, K^+, Ca^{++}, which play an important role in the maintenance of the osmotic pressure, redistribution of water between blood and tissues, blood coagulation, excitability and contraction of cells, etc. The basic anions of plasma are Cl^-, sodium hydrogenums HCO^3, phosphates, which play an important role in the regulation of pH, acid-base balance, excitability of cells, etc.

3. Physical and chemical properties of blood

The osmotic pressure is formed mainly by dissociated salts and is equal to 290 ± 10 mosm/L. The osmotic pressure has an important value in the maintenance of the concentrations of various substances dissolved in the body fluids and promotes distribution of water among blood, cells, and tissues.

There are

- **isotonic,**
- **hypotonic,**
- **and hypertonic solutions** depending on the value of the osmotic pressure.

***An isotonic* solution** is a solution whose osmotic pressure *is equal* to that of blood (e.g., **0.85 % NaCl solution**). **Erythrocytes placed in such a solution do not change**, as the osmotic pressure in them is the same as in the solution (Figure). This solution is called physiological. It is used as a blood-substituting solution, solvent for many medications for parenteral administration. **Over 60 % of the osmotic pressure of blood is provided by NaCl**. Totally, inorganic substances provide 96 % of the osmotic pressure.

A hypotonic solution is a solution whose osmotic pressure *is lower* than that of blood (for example, **0.3 % NaCl solution**). **Erythrocytes placed in such a solution swell and burst** (i.e., get hemolyzed) as a result of transition of water into cells, as the osmotic pressure in erythrocytes is higher than in the solution (Figure).

A hypertonic solution is a solution whose osmotic pressure *is higher* than that of blood (for example, **2 % NaCl solution**). **Erythrocytes placed in such a solution, shrink** as a result of the output of water from the cell, as the osmotic pressure in erythrocytes *is lower* than in the solution (Figure).

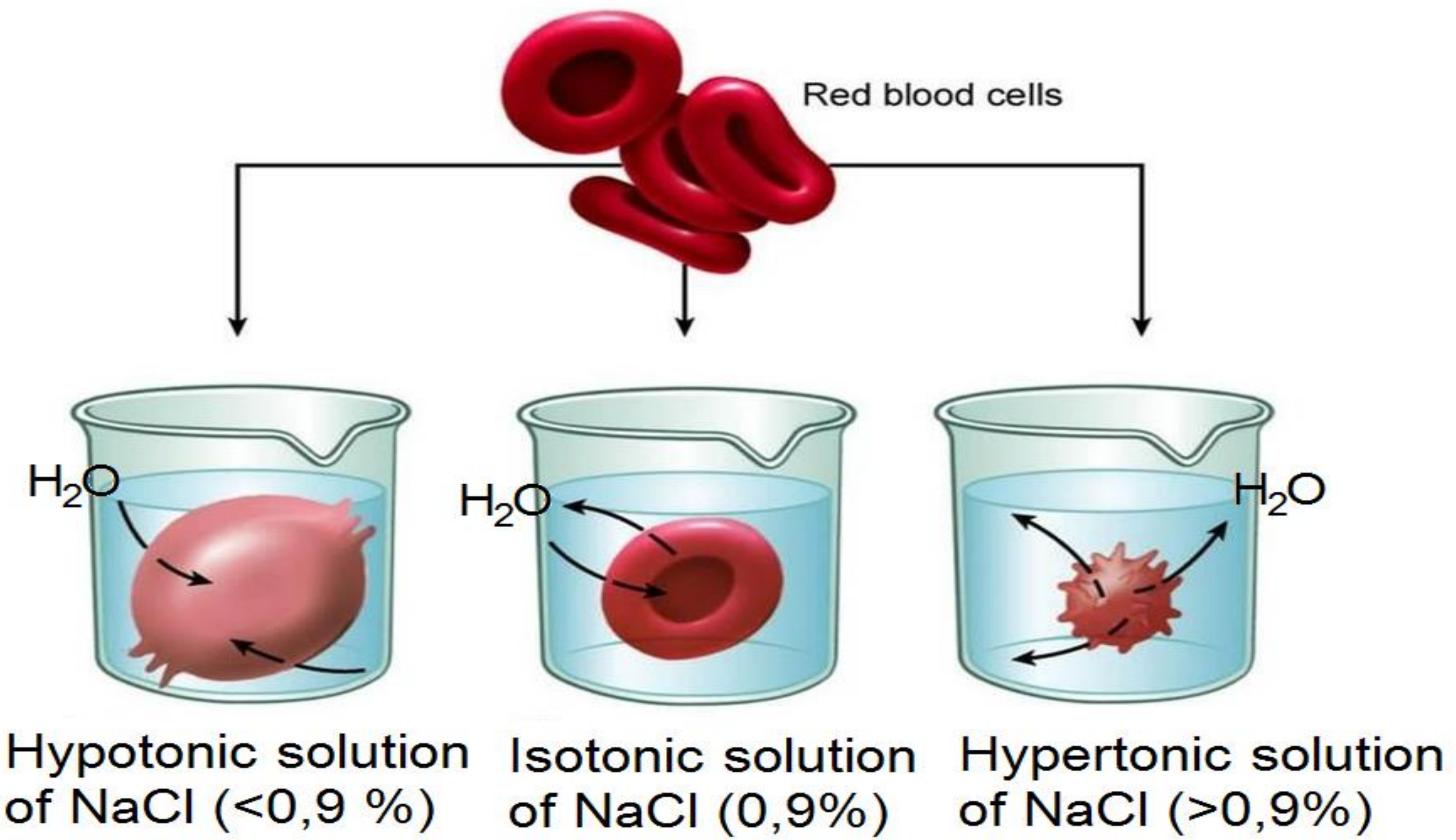


Figure — The state of erythrocytes in solutions with different NaCl concentrations

(in the hypotonic solution there is osmotic hemolysis)

The human osmotic pressure is rather constant. The excretory organs (kidneys, perspiratory glands) participate in its neurohumoral regulation. The osmotic pressure changes are perceived by special osmoreceptors located both on the periphery (in the endothelium of the blood vessels) and in the center (in the hypothalamus).

Oncotic pressure. The osmotic pressure formed by proteins is called oncotic (due to their ability to draw H_2O).

The portion of the osmotic pressure formed by proteins is 25–35 mm Hg, which approximately makes 1/200 of the total osmotic pressure of plasma.

More than 80 % oncotic pressure is caused by albumins due to small sizes of their molecules and their high number (as compared with fibrinogen and globulins).

The oncotic pressure is important for:

1. **The formation of the interstitial fluid.**
2. **The formation of lymph.**
3. **The formation of urine.**
4. **The adsorption of H_2O in the intestines.**
5. **The redistribution of H_2O between blood and tissues.**

Proteins have a big size of molecules and, therefore, are unable to pass through the endothelium of capillaries (they remain in the blood flow). They keep a certain amount of water in the blood.

Blood viscosity:

— **whole — 4.5–5 (water viscosity is accepted as 1.0);**

— plasma — 1.7–2.2.

High blood viscosity is caused by:

— body dehydration (profuse diarrhea, continuous vomiting);

— high count of the formed elements in the blood (polycythemia, leukosis);

— accumulation of CO_2*;*

— increased content of proteins, especially fibrinogen.

High blood viscosity leads to the slow blood flow and high hydrodynamical peripheral resistance in the blood vessels, which forces the heart to work harder to pump the blood, increasing the risk for heart problems.

Blood viscosity depends on the number of erythrocytes (Table). High counts of red blood cells and particles lead to high blood thickness.

Table 2.3 — Dependence of blood viscosity on the erythrocyte count

Number of erythrocytes	Blood viscosity
4.5×10^{12}/L	5.0
6.7×10^{12}/L	6.4
7.4×10^{12}/L	8.1
9.3×10^{12}/L	20.9

Low blood viscosity is caused by:

— body hydration (intake of too much water, water retention in kidney diseases),

— anemias, hypoproteinemias,

— decreased rate of blood coagulation (under the influence of administered heparin).

Low blood viscosity leads to the accelerated blood flow.

The relative density (specific gravity) of blood depends on the content of proteins, salts, and erythrocytes. The **relative density of whole blood** changes within rather narrow limits **(1.050–1.060)**, **plasma (1.025–1.034)**, and **relative density of erythrocytes** is higher than that of whole blood and plasma **(1.090).**

The reaction of blood (acid-base balance). The active reaction of blood (pH) is caused by the interrelation of hydrogen (H^+) and hydroxyl (OH^-) ions. It is one of the rigid parameters of homeostasis.

— **the pH of arterial blood is 7.37–7.45;**

— the pH of venous blood is 7.34–7.43 (it has more carbonic acid);

— the pH inside cells is 7.0–7.2 (acidic metabolic products).

— the pH ranges compatible with life are 7.0–7.8. But a long-term pH shift of 0.1–0.2 can be hazardous for life. Any pH shift, first of all, influences the activity of enzymes.

Despite the fact that CO_2, lactic acid, and other acidic components constantly get into the blood, which may affect its pH level, the active reaction (pH) remains constant. It is provided by the buffer properties of blood and activity of the excretory organs (excretion of CO_2 by the lungs, excretion of acidic and containment of alkaline products by the kidneys).

Buffer systems of blood

The buffer systems (also buffer solutions or buffer mixtures), are solutions which maintain the constancy of the concentration of hydrogen ions, both after addition of acids or alkalis, and their dilution. They consist of a mixture of weak acids with salts of these acids and strong alkali. Due to the buffer systems, the active reaction of blood (pH), the major parameter of the constancy of the internal environment, is maintained.

The buffer systems of blood:

1. *Bicarbonate* (H_2CO_3+$NaHCO_3$) and (H_2CO_3+$KHCO_3$). Acidic components which come into the blood cooperate with bicarbonate ones. Coming into the blood, the alkaline components cooperate with H_2CO_3, thus forming the salt and H_2O (removed by the excretory organs).

2. *Phosphate* (NaH_2PO_4+Na_2HPO_4) NaH_2PO_4 has the property of an acid and reacts with alkaline components, and Na_2HPO_4 having the properties of alkalinity reacts with the acidic components.

3. *Protein*. It is caused by the amphoteric properties of plasma proteins. In an acidic medium they behave like alkali, in an alkaline medium — like acids, binding acids in the former, and alkalis in the latter.

4. *Hemoglobin*. Low Hb is an acid which is weaker than H_2CO_3 and thus gives it its K^+ ions, attaching H^+ and becoming a low-dissociated acid.

Shifts of the active reaction of blood either to **acidic *(acidosis)*** and to **alkaline *(alkalosis)*** sides are possible (Figure).

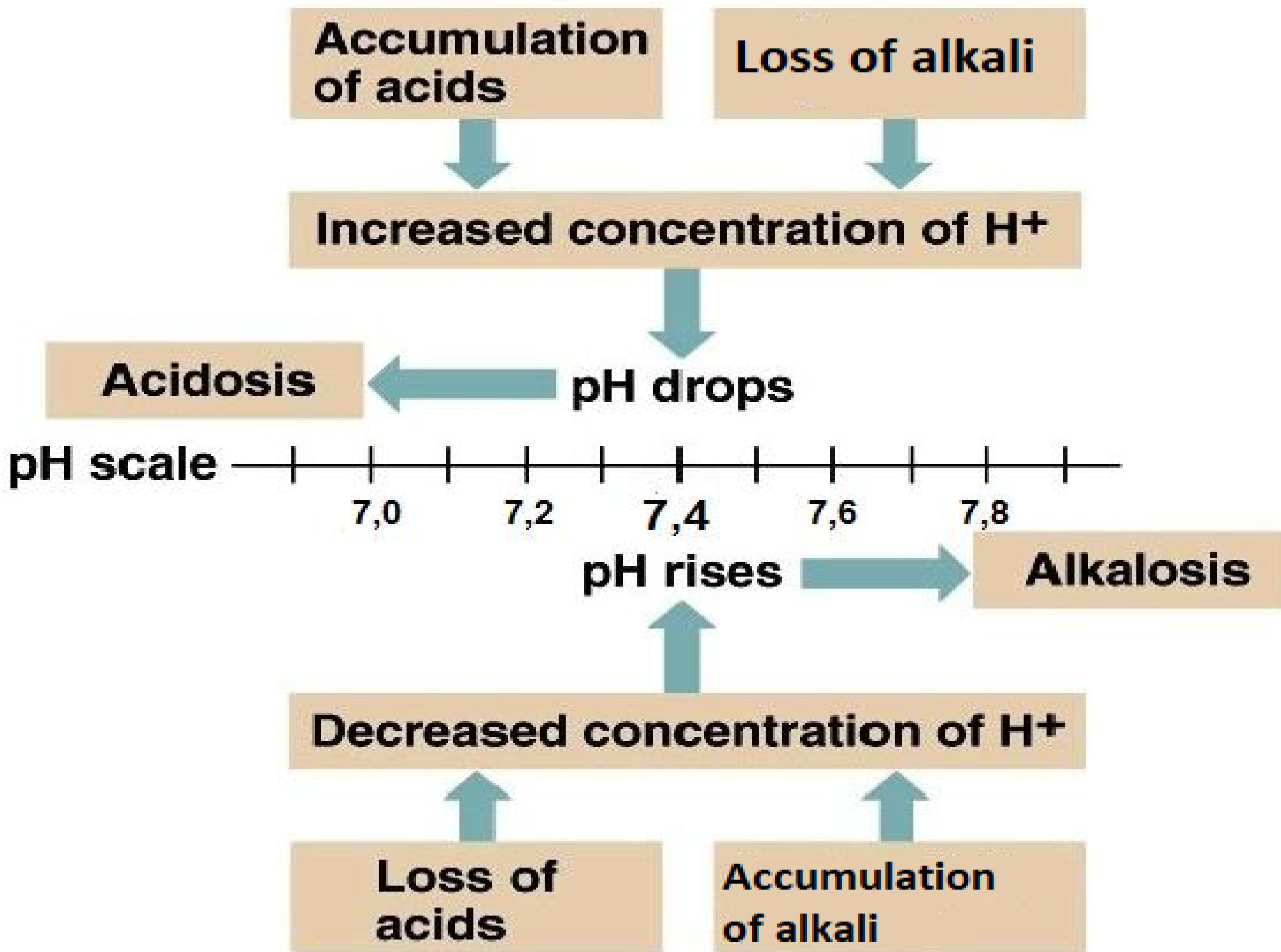


Figure — Acidosis and alkalosis

By the degree of its intensity, **acidosis** can be **compensated and non-compensated**.

In ***compensated acidosis*** the accumulation of acids in the blood results only in the depletion of the alkaline reserve without pH changes. Despite the chemical and functional shifts in the body, the pH is maintained due the action of the buffer systems. Due to the exhaustion of the alkaline reserve and failure of the protective mechanisms, the pH is shifted outside the limits, and ***non-compensated acidosis*** develops.

By their origin there are:

1. Gaseous acidosis and **gaseous alkalosis**.

2. Non-gaseous acidosis and **non-gaseous alkalosis**.

Gaseous (respiratory) acidosis refers to high levels of the acid (H_2CO_3) in the blood. Its common causes are:

1. Malfunction of external respiration.

2. Circulatory insufficiency.

3. Inhalation of air (admixture) with an increased concentration of CO_2.

Gaseous (respiratory) alkalosis is a medical condition in which **hyperventilation** elevates the blood pH beyond the normal range (7.34–7.45) with a concurrent reduction of carbon dioxide in the arterial levels (mountain sickness, excessive artificial respiration).

Non-gaseous (metabolic) acidosis is caused by excess accumulation of acidic products. Its common causes are:

1. Excessive formation of acidic products in dysbolism (diabetes, starvation).

2. Affected excretion of acidic products from the body (nephrites).

3. Alkali loss (in profuse diarrhea, fistulas of the intestines).

4. Excessive administration of mineral substances (poisoning by acetic acid).

Non-gaseous (metabolic) ***alkalosis*** is caused by excess accumulation of alkaline products. Its common causes are:

1. Administration of a big amount of alkaline products into the body (baking soda, alkaline water abuse).

2. Loss of a large amount of gastric juice (in continuous vomiting, stomachal fistula).

3. Hyperproduction of glucocorticoids or treatment with the preparations of adrenal hormones.

4. Erythrocytes, their structure, properties, and functions

The erythrological system is a physiological system including erythrocytes circulating in the blood, organs of their production and destruction, incorporated into the system of neuroendocrinological regulation.

In humans and mammals, erythrocytes **do not contain nuclei.** The absence of nuclei presumes that erythrocytes consume 200 times less oxygen for their own needs than nucleus-containing representatives (erythroblasts, normoblastes).

The size of erythrocytes: diameter — 7.7 micrometers (μm), thickness — 2.2 μm (Figure).

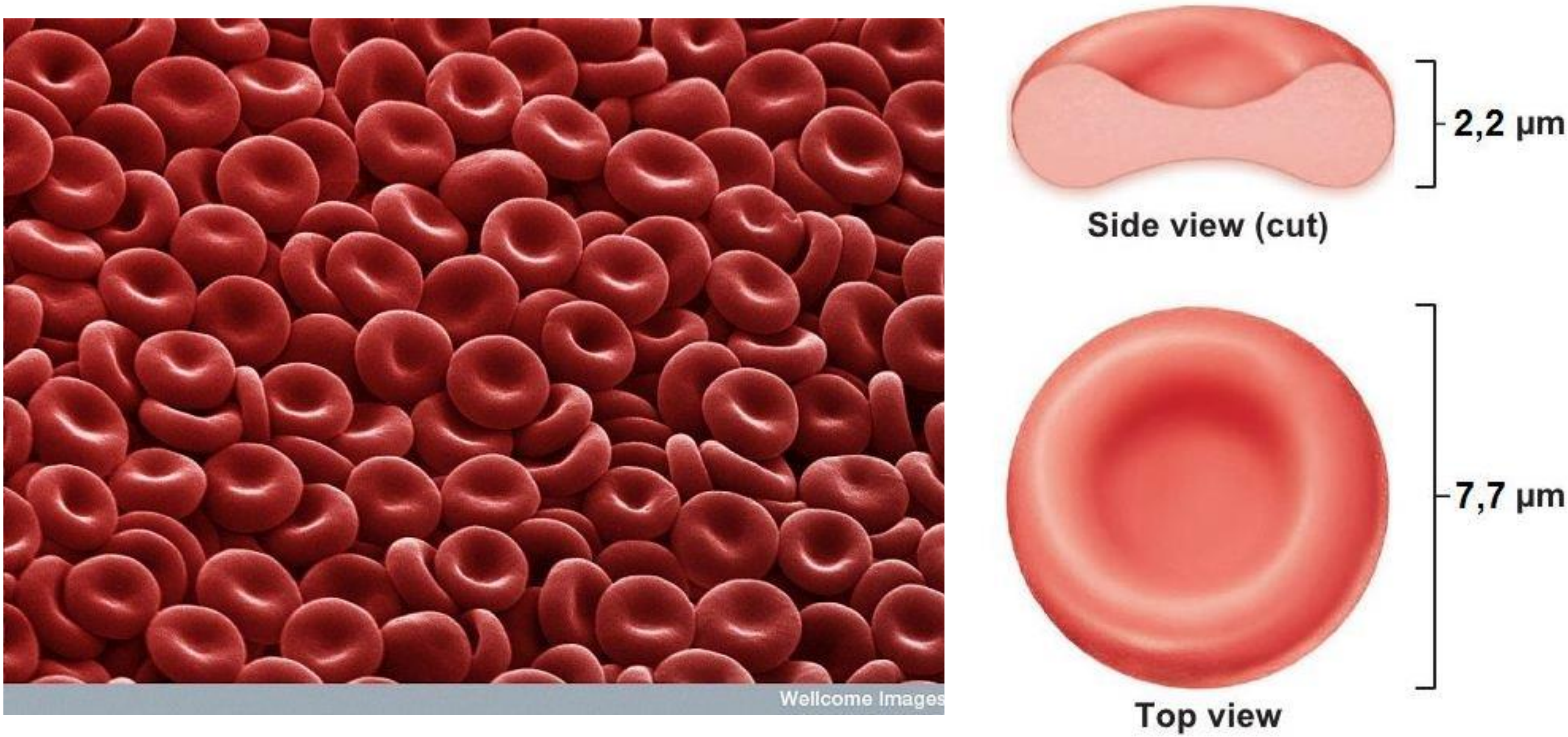


Figure — The shape and size of erythrocytes

One important feature of erythrocytes is that they are biconcave disks: plump at their periphery and very thin in the center.

The biconcave shape of erythrocytes:

- It provides a greater surface area (by 20 %) in comparison with the same diameter of a sphere.
- It performs one of the basic functions — transition of O_2 and CO_2.
- It increases the ability for reversible deformation (plasticity) during the passage through narrow and bent capillaries.

In some pathology (anemia), there are erythrocytes of **various shapes (crescent, pear-shaped, etc.) named *poikilocytosis***, and also of **various sizes — *anisocytosis*** (Figure).

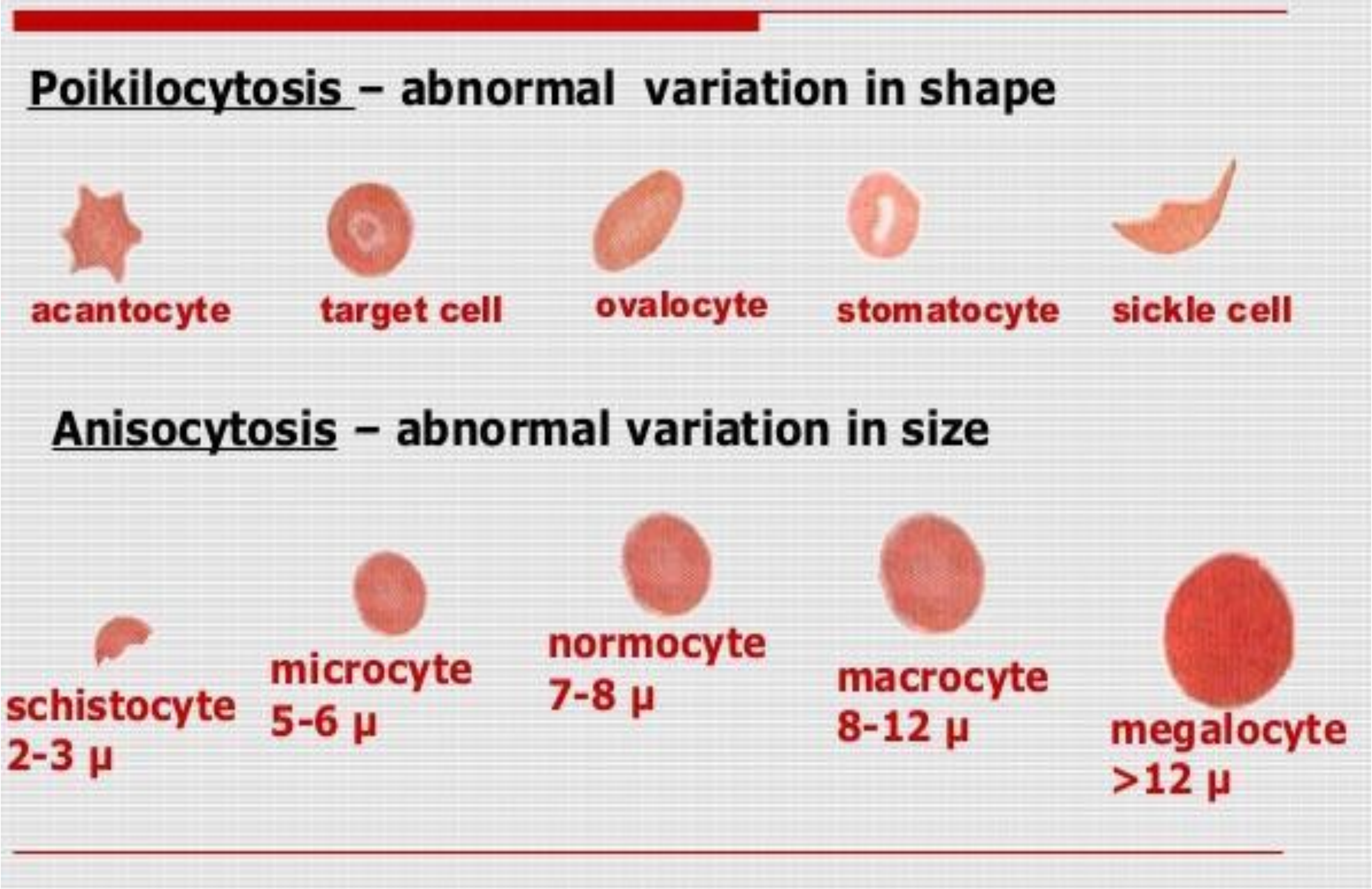


Figure — Poikilocytosis and anisocytosis

Erythrocytes consist of **the skeleton of the cell — stroma**, and the upper layer — **membrane**. The thickness of the membrane is 10 nanometers.

The membrane of the erythrocyte consists of **4 layers:**

- External, which is formed by glycoproteins.
- Average 2 layers — bi-lipid layers.
- Internal layer — protein.

The chemical composition of erythrocytes: 60 % — H_2O, 40 % — dry sediment (almost 90 % of which is hemoglobin (Hb)).

The functions of erythrocytes:

- **Transition of O_2 and CO_2** (participation of hemoglobin).
- **Protection** (absorption of harmful substances, production of antibiotic — eritrin).
- **Regulation of the water-and-salt exchange.**
- **Transition of nutrients.**
- **Participation in the regulation of erythrogenesis.**
- **Creative.** It presumes the transition of macromolecules ensuring information links of the body (see «Main Functions of Blood»).
- **Participation in the regulation of acid-base balance** (hemoglobin buffer).
- **Participation in blood coagulation** (erythrocytes contain thromboplastin, released during their destruction. The presence of destroyed erythrocytes in the blood induces hypercoagulation and thrombus formation. Along with it, they are heparin bearers being anticoagulants).

The erythrocyte count in the blood:

— **in males — 4.5–5.1 × 10^{12}/L;**

— **in females — 3.7–4.7 × 10^{12}/L**.

A condition characterized by an increased number of red blood cells is called erytrocytosis.

A condition characterized by a decreased number of erythrocytes is called erythropenia. Erythropenia is observed in anemia (in combination of low Hb).

The life span of erythrocytes is 130 days.

The production of erythrocytes occurs in the red bone marrow (160 × 10^6 cells are produced per minute), and their destruction — in the spleen, liver, red bone marrow.

5. Hemoglobin, its structure, behavior, varieties, compounds, and functions

One of the major functions of blood is the transmission of oxygen to organs and tissues and transport of carbonic gas (CO_2).

The important role in this process is played by erythrocytes due to the presence of the red blood pigment — **hemoglobin**.

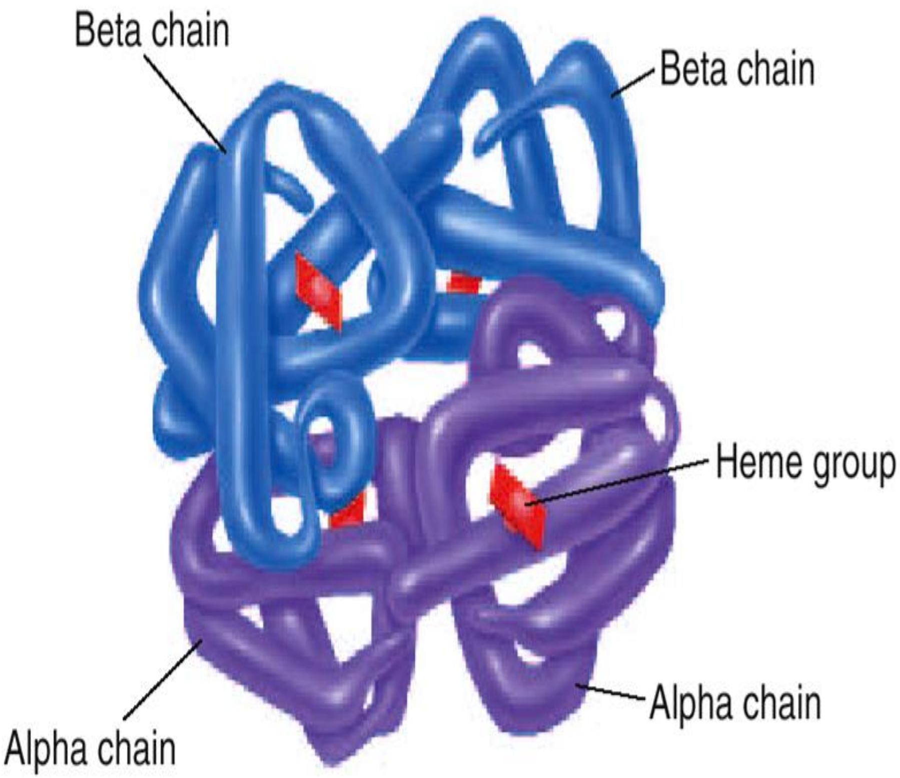
The advantages of Hb localization in erythrocytes:

- **it provides low blood viscosity;**
- **it reduces the oncotic pressure, preventing water loss in tissues;**
- **it prevents** Hb loss during blood filtration in nephrones.

Hemoglobin is a chromoproteid consisting of a protein called globin (96 %) and the prosthetic group of hemes (4 %). There are 4 heme groups. The heme represents protoporphyrin with an ion of iron (Fe2+) in the centre (Figure).

The key role in Hb activity is played by Fe^{++} ions.

Hemoglobin



Heme

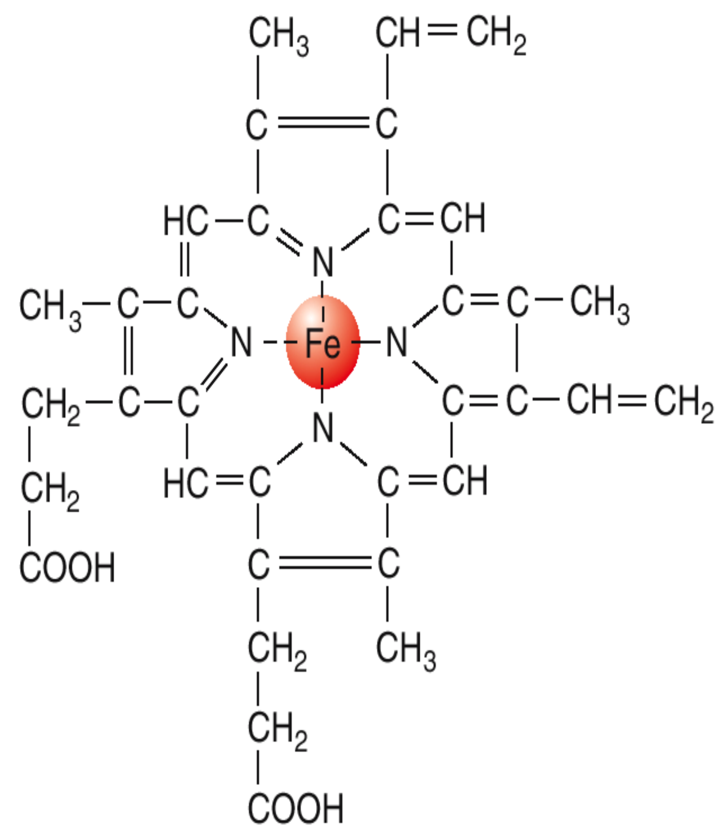


Figure — Structure of hemoglobin

The functions of hemoglobin:

- **Transport of O_2** — oxyhemoglobin ($HHbO_2$). One molecule of Hb attaches 4 oxygen molecules. 1 g of Hb binds 1.34 mL of O_2.
- **Transport of CO_2.**
- **Participation in the maintenance of acid-alkaline balance** (hemoglobin buffer).

Bonds of Hb:

1. Oxyhemoglobin ($HHbO_2$). Hemoglobin is bound to O_2. Arterial blood contains about 98 % $HHbO_2$, and venous — about 60 %. The form of Hb after oxygen is released in tissues is called *restored or reduced* hemoglobin. Hemoglobin has high affinity for oxygen.

2. Carbohemoglobin ($HHbCO_2$) is a stable formation of hemoglobin with carbon dioxide (CO_2).

3. Methhemoglobin (MetHb). It is formed under the influence of strong oxidants (permanganates of potassium, aniline, nitrites, pyrogallol, etc.). Thus, Fe^{2+} turns into Fe^{3+}). This bond is stable and can not be disconnected.

4. **Carboxyhemoglobin** **(HHbCO)** is a stable formation of hemoglobin with carbon monoxide (CO). This bond is 150–200 times stronger than that of $HHbO_2$. In 0.1 % CO concentration in the air, 80 % Hb turns into carboxyhemoglobin. The 1 % CO concentration causes death within a few minutes.

The physiological bonds of Hb are $HHbO_2$ and $HHbCO_2$.

Myoglobin is a respiratory pigment, or muscular hemoglobin contained in skeletal muscles and myocardium. It has higher affinity for oxygen in comparison with hemoglobin. It binds up to 14 % O_2 in the body. Its role is to supply muscles with oxygen during muscle contractions when capillaries are pressed and tissues do not receive blood. At this moment the main source of oxygen is myoglobin, which during the phase of muscle relaxation is filled with oxygen.

Types of Hb:

***HbP* — primitive** — is formed during 7–12 weeks of intra-uterine development.

***HbF* — fetus** — during the 9th week of intra-uterine development.

***HbA* — hemoglobin of adults** appears before birth.

HbF has high affinity for O_2 and binds 60 % O_2 at such partial pressure of O_2 (pO_2), whereas HbA is only 30 %. Due to the given property, HbF supplies tissues with oxygen in the conditions of low pO_2 in the arterial blood of a fetus. Within the first year of life, HbF is almost completely replaced by HbA.

Normal Hb ranges in the blood of **males** vary within **130–160 grams per liter**, **in females** — **120–140 grams per liter.**

A condition characterized by a low amount of Hb per unit of blood volume (more often in low red blood cell count) is called ***anemia***.

Anemia is observed when the Hb amount is less than 130 grams per liter in males, and less than 120 grams per liter in females (in pregnant females — less than 110 grams per liter).

The color index, taken as the ratio of the percentage of hemoglobin (compared to "normal") to the red blood cell count (compared to "normal") has been a useful clinical method to diagnose anemia. **Its normal ranges are 0.85–1.05.** Erythrocytes having such an index are called normochromal. If the parameter is above 1.5, erythrocytes are called hyperchromal and if under 0.85 — hypochromal.

6. Hemolysis and its varieties

Hemolysis refers to the destruction of the erythrocyte membrane accompanied by the release of Hb into blood plasma (laky blood, or pellucid blood).

Kinds of hemolysis:

1. *Mechanical* (in vivo excessive mechanical forces, in vitro in vial blood stirring).

2. *Thermal* (in vivo in burns, in vitro in blood freezing and de-freezing).

3. *Chemical* (in vivo under the influence of chemical substances, aspiration of volatiles (acetone, benzene, chloroform), destruction of the erythrocyte membrane, in vitro under the influence of acids, alkalis, heavy metals, etc.).

4. Osmotic. In hypotonic solutions hemolysis begins in 0.48 % sodium chloride (NaCl) solution, and in 0.32 % — full hemolysis of erythrocytes is observed.

The osmotic resistance of erythrocytes (ORE) is their susceptibility to hemolysis in hypotonic solutions.

***The minimal* ORE** is determined by the concentration of a NaCl solution **(0.48–0.46 %)** in which hemolysis begins.

***The maximal* ORE** is determined by the concentration of a NaCl solution **(0.34–0.32 %)**, in which all erythrocytes have been hemolysed.

The ORE depends on the degree of their maturity and form.

The young forms of erythrocytes which come from the bone marrow into the blood are more resistant to hypotonia.

5. *Immune hemolysis* occurs in transfusion of incompatible blood or if there are immune antibodies to erythrocytes.

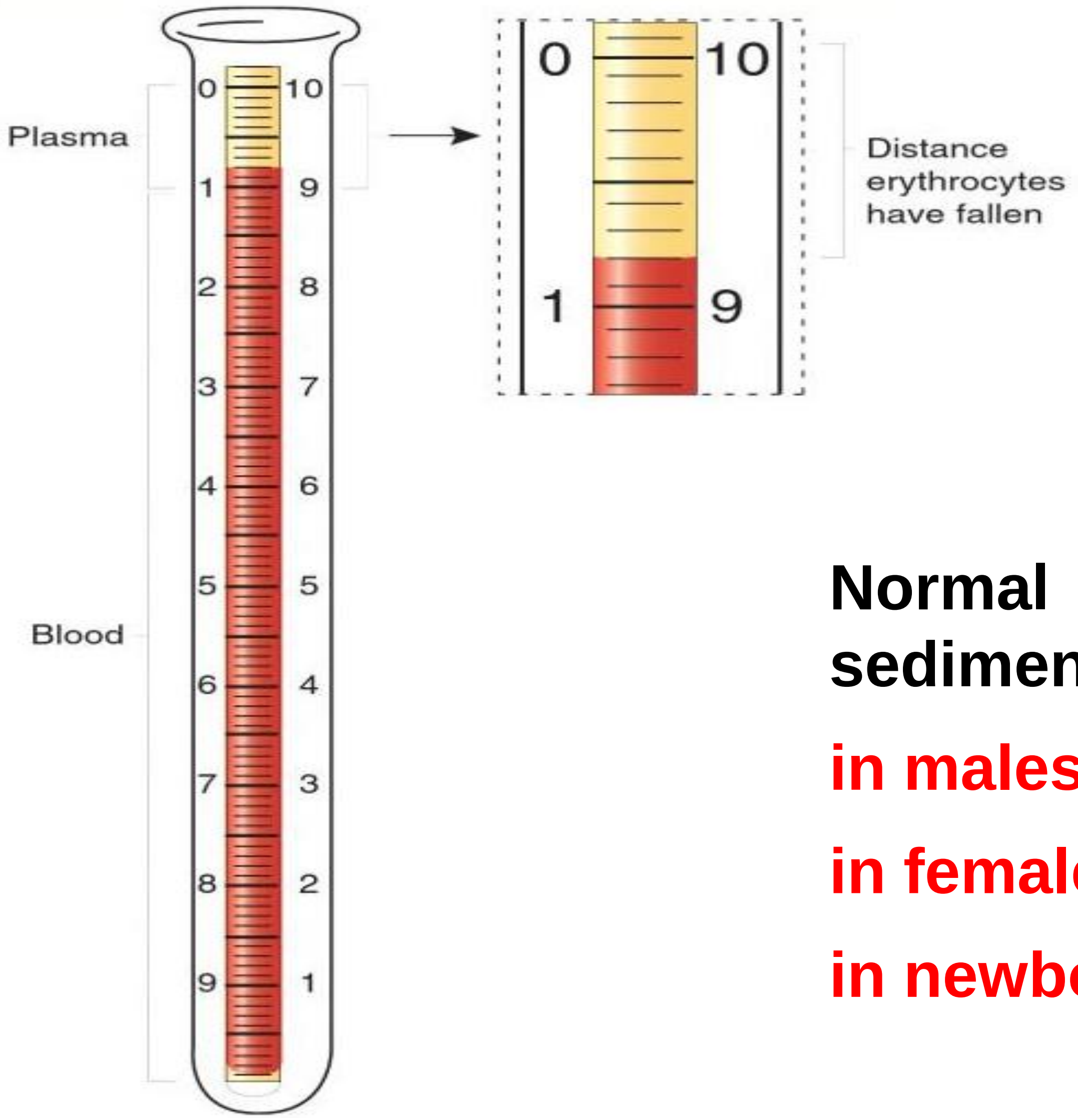
6. *Physiological hemolysis* is the hemolysis of erythrocytes at the end of their life cycle (in the liver, spleen, red bone marrow).

7. *Electrical* (in vivo due to damage caused by electric currents, in vitro during the transit of an electric current through the blood in the vial). On the «+» anode hemolysis is an acid, on the «–» cathode — alkaline.

8. *Biological.* Under the influence of biological factors (hemolysins, venoms of serpents, fungal poisons).

Erythrocyte sedimentation rate

The sedimentation of erythrocytes is observed when a blood sample with an anticoagulant (which prevents the blood from coagulation) is placed in a tall, thin, vertical tube. The erythrocyte sedimentation rate test is a hematological test which measures the rate of erythrocyte sedimentation, which is reported as the millimeters of plasma that are present at the top portion of the tube after one hour.



Normal erythrocyte sedimentation rates (ESR) are:

in males 1–10 mm / hour;

in females 2–15 mm / hour;

in newborns 1–2 mm / hour.

Figure — ESR measurement

The ESR depends on:

- The ESR accelerates due to an increased concentration of the molecules of large globulins and fibrinogen in particular. Their concentration rises due to inflammatory processes, pregnancy. They reduce the electrical charge of erythrocytes, promoting cohesion of erythrocytes and formation of monetary columns.
- The ESR decreases in an increased erythrocyte count (for example, the sedimentation of erythrocytes can stop completely owing to high blood viscosity). Anemia is responsible for accelerating ESR.
- The ESR goes down if the shape of erythrocytes changes (drepancytic anemia).
- The ESR slows down in a low pH value and, vice versa, accelerates in a high pH.
- The ESR increases in a high hemoglobin level.

8. Leukocytes, their classification, features, and functions

Leukocytes, or white blood cells, opposite to erythrocytes, have nuclei and other structural elements peculiar to cells. The size of leukocytes is 7.5–20 micrometres.

The functions of leukocytes:

- ***Protective*** (participation in the maintenance of nonspecific and cell immunity).
- ***Metabolic*** (release of nutrients into the digestive system, their seizure and transmission into the bloodstream. Especially, it has an essential value in the maintenance of immunity in newborns during their breast feeding).

- ***Dissolution of damaged tissues***;
- ***Morphogenetic*** — destruction of various malformations during the embryonic period.

Leukocytes also provide the ***regulatory function*** due to the production and secretion of cytokines, growth factors and other substances which regulate haemopoiesis and immune responses.

Leukocytes are capable to move towards the source of chemical substances formed in inflamed tissues. This processs is known as **chemotaxis**.

The classification and functions of leukocytes:

1. *Agranular:*

a) **Monocytes** — **2–11 %** of all leukocytes (macrophages). Monocytes turn into tissue macrophags in tissues. Monocytes are the largest blood cells. They have bactericidal activity, appear in the damaged area after neutrophils and perform phagocytosis of:

- Microorganisms.
- Dead leucocytes.
- Damaged tissue cells.
- Thus they clear the damaged area.
- Macrophages also perform the antigen-presenting function, they can present phagocyted antigen fragments to lymphocytes to initiate a specific immune reaction.

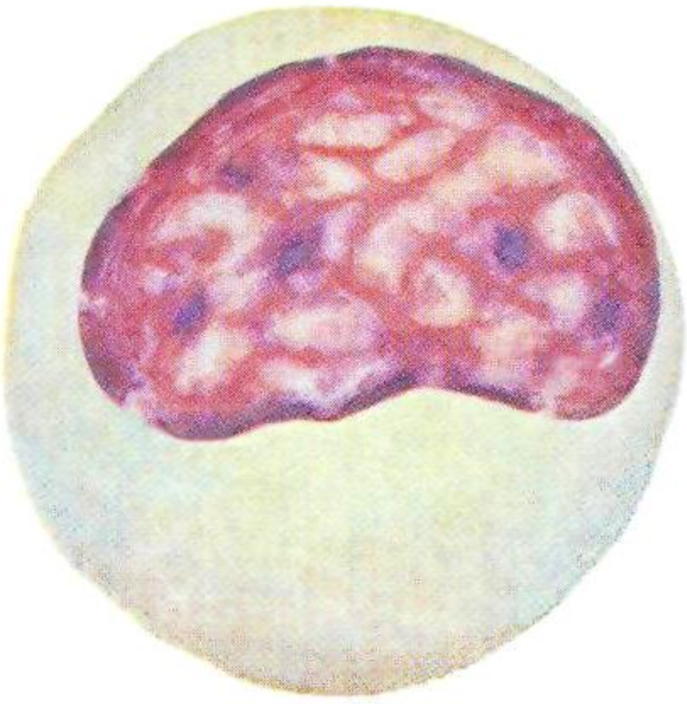


Figure — Monocyte

b) **Lymphocytes — 19–37 %** of all leucocytes.

Lymphocytes enter the circulatory system continually. After a few hours, they pass back into tissues through diapedesis, then re-enter the lymph and return to the blood again and again; thus, there is continual circulation of lymphocytes through tissues. The life span of lymphocytes is from several days, as in other leucocytes, to 20 and more years.

Lymphocytes are the central part of the immune system. They provide genetic constancy of the organism.

They perform the following functions:

- Antibody formation.
- Destruction of alien cells.
- Provide the reaction of transplant rejection.
- Keep immune memory.
- Destruction of the body`s own mutant cells.
- Sensitization.

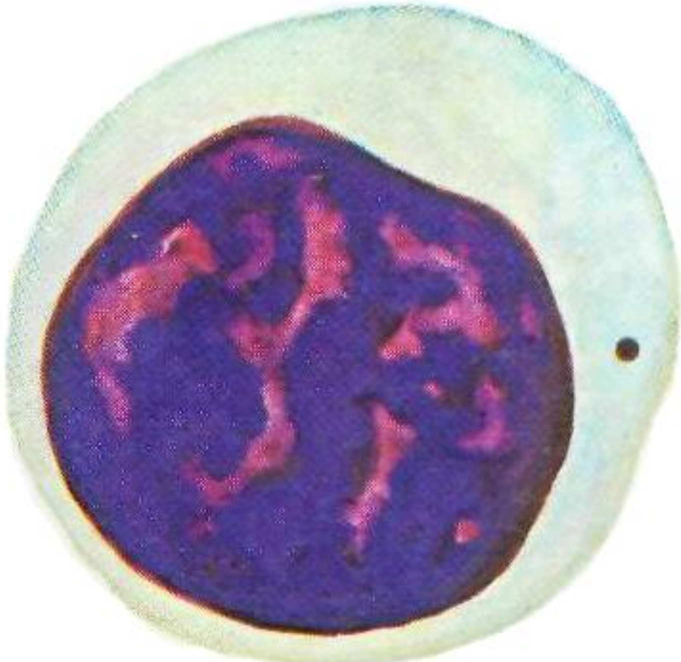


Figure — Lymphocyte

There are three main types known as T cells, B cells, and natural killer cells.

T-lymphocytes (provide cell-mediated immunity):

a) T-helpers (the major regulator of immune functions due to production of interleukins and other regulatory substances);

b) T-cytotoxic (or T-killers, these cells are capable of killing microorganisms);

c) T-cells of immune memory;

d) T-regulatory cells and others.

B-lymphocytes or bursacytes (provide humoral immunity). They differentiate into plasma cells which secret immunoglobulins (antibodies).

Lymphocytes are produced from common stem cells. The differentiation of T-lymphocytes occurs in the thymus gland, and bursacytes — in the red bone marrow, tonsils, lymph nodes, appendix.

Natural killer cells (NK-cells). They make **5–10 %** of circulating lymphocytes and play a major role in immune reactions against tumour cells and virally infected cells.

2. Granular:

a) **Neutrophils** are the most common of all leucocytes (comprise **50–70 %** of the total leucocyte count). They possess high bactericidal activity. They are carriers of receptors to IgG, to complement proteins. They are the first to appear in the damaged area and destroy harmful agents. One neutrophil is capable to destroy 20–30 bacteria.

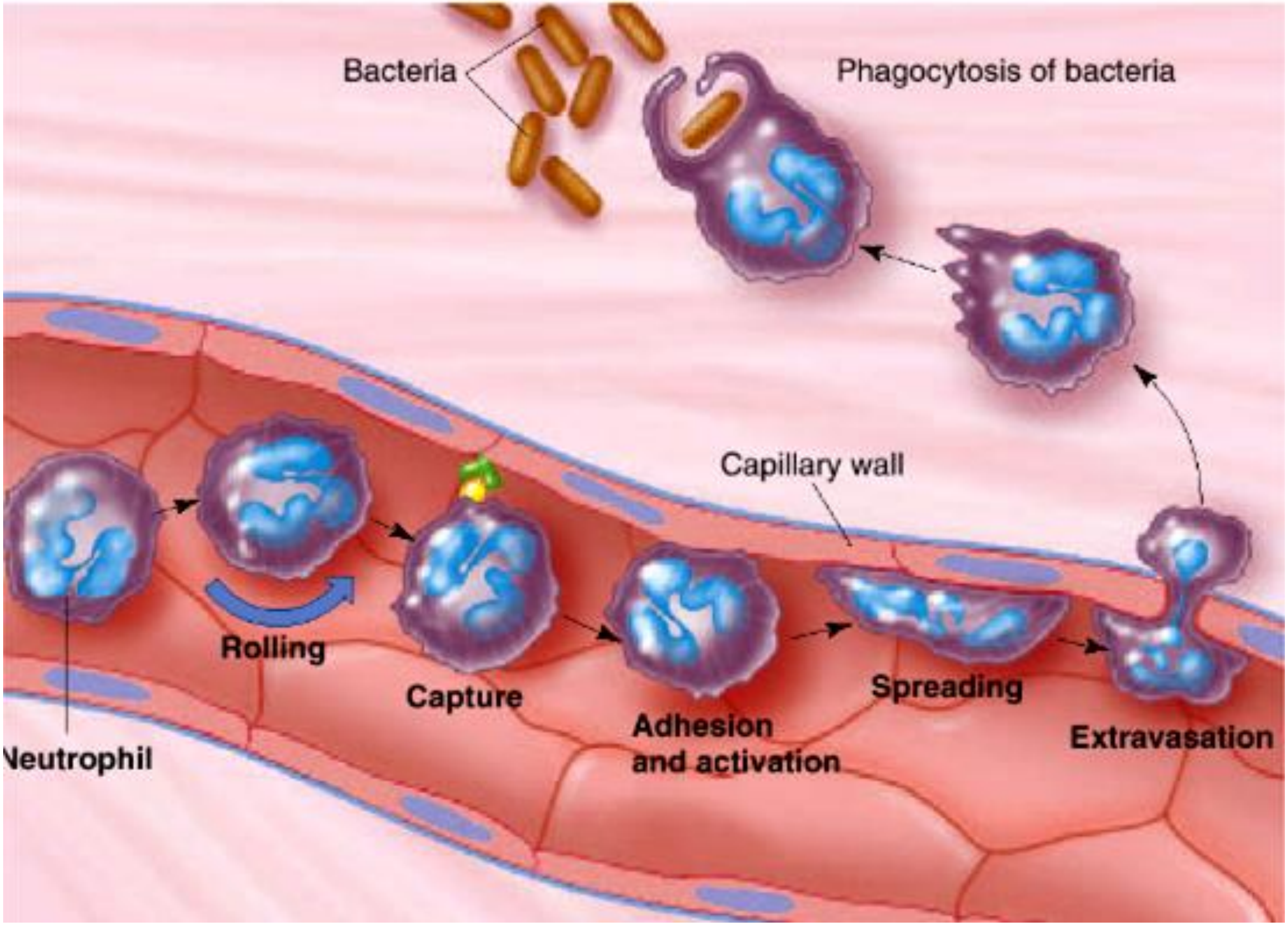


Figure — Functions of neutrophils: phagocytosis

<u>Neutrophils:</u>

- ***myelocytes***
- ***metamyelocytes***
- ***stab neutrophils***
- ***segmentonuclear***

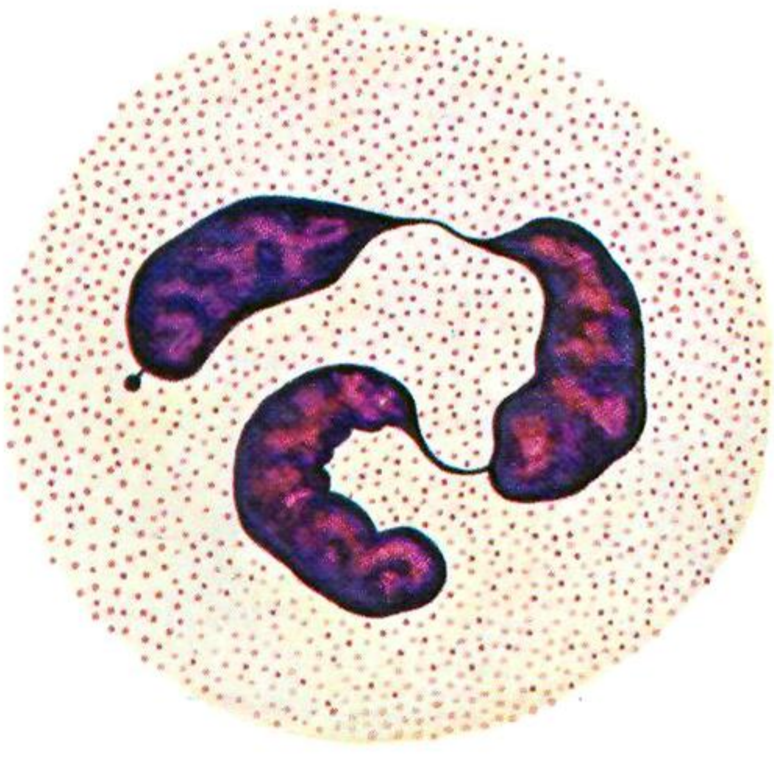


Figure — Segmentonuclear neutrophil

b) **Eosinophils** typically represent **0.5–5 %** of the total leucocyte count and are stained with eosin. They stay in the blood for some hours and then migrate into tissues where they are destructed.

The functions of eosinocytes:

- Phagocytosis.
- Neutralization of toxins of albuminous nature.
- Destruction of alien proteins and antigen-antibody complexes.
- Production of plasminogen, i.e. participation in fibrinolysis.
- Protection against parasitic infections.

High counts of eosinophils are typical of patients experiencing allergies and some autoimmune diseases. Eosinophils migrate toward the inflamed allergic tissue, detoxify some inflammation-inducing substances and also destroy allergen-antibody complexes, thus preventing the excess spread of a local inflammatory process. They are particularly effective against parasitic worms and their eggs.

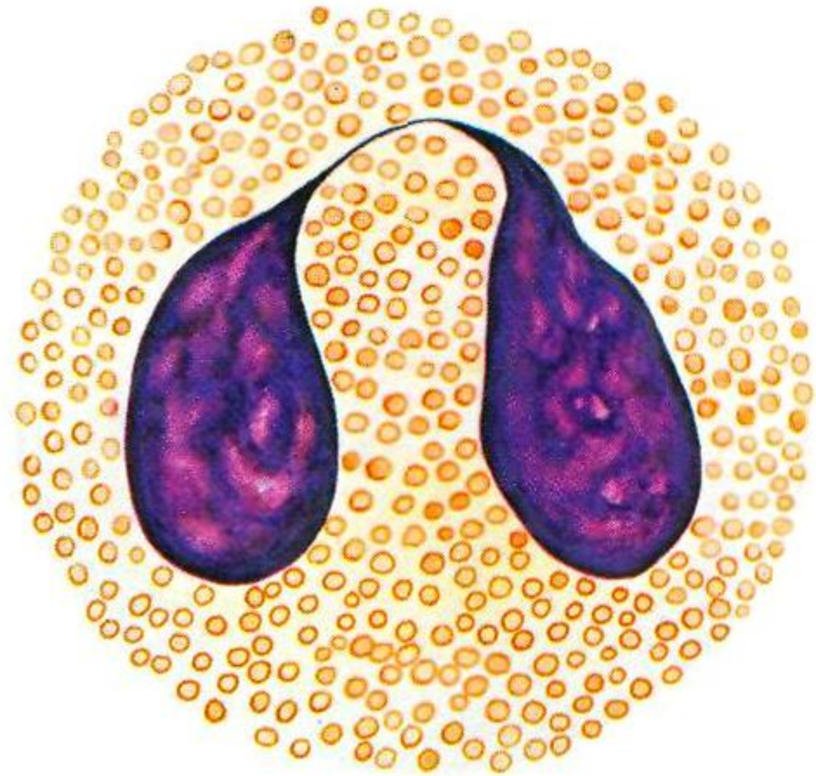


Figure — Eosinophil

c) Basophils are the least common leukocytes, typically comprising less than one percent of the total leukocyte count. They produce histamin and heparin (they are called heparinocytes). Heparin prevents blood coagulation, and histamin dilates capillaries, promotes resorption and wound healing.

The functions of basophils:

1. Regulation of the aggregate state of blood.
2. Regulation of the local blood flow (microcirculation) and permeability of capillaries.

Basophils and mast cells play an important role in some types of allergic reactions. Immunoglobulin E (IgE), which causes allergic reactions, has a special propensity to become attached to mast cells and basophils. Then, when specific antigens interreact with IgE, basophils release large quantities of histamine, heparin, and other substances which contribute to inflammation, cause local vascular and allergic reactions.

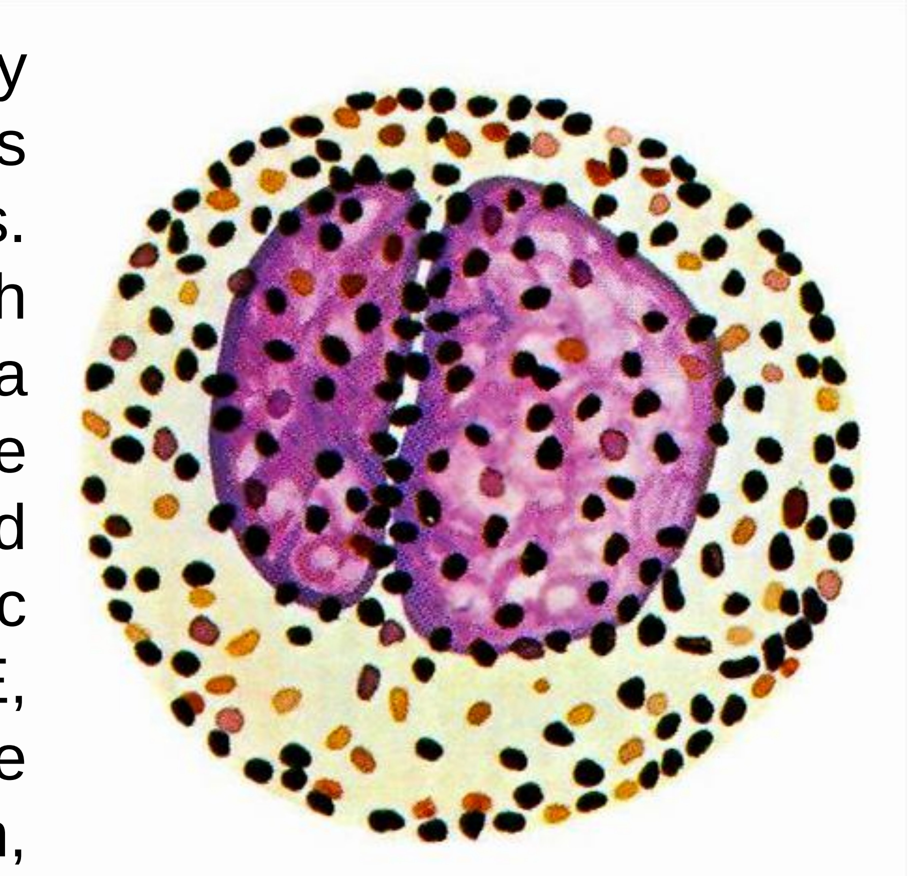


Figure — Basophil

The normal **count of leukocytes is 4–9 × 10^9 per liter.**

The leukocyte formula (the differencial white blood cells count) is the percentage of each type of leukocytes. A high number of immature leukocytes in peripherial blood is known as the left shift of the leukocyte formula. It is most often found in infectious and inflammatory processes.

A high leukocyte count is called leukocytosis. There are **physiological** and **pathological** causes of **leukocytosis**.

Physiological leukocytosis is caused by the redistribution of leukocytes among the blood vessels and organs.

The physiological causes of leukocytosis are:

- ***Nutrition***. After meals leukocytes leave the depot and enter the bloodstream. They accumulate in the sub-mucous layer of the intestines, where they carry out the protective function.
- ***Muscular.*** Under the influence of intensive muscle work the number of leukocytes increases by 3–5 times.
- ***Pregnancy.*** Leukocytes are accumulated in the sub-mucous layer of the uterus.
- ***Newborns (metabolic function).***
- ***Pain.***
- ***Emotional strain.***

The pathological causes of leukocytosis are **connected with:**

- **diseases,**
- **tissue damage,**
- **infections,**
- **purulent,**
- **inflammatory,**
- **septic,**
- **allergic processes.**

***Leukosis is* the excess production of leukocytes.** Leukocytes in these cases are poorly differentiated and do not carry out the physiological functions.

Leukocytopenia is an abnormally low number of leukocytes (**less than 4×10^9 per liter**).

The life span of various leukocytes differs (from 2–3 days till 2–3 weeks). Long-living lymphocytes (cells of immune memory) live for decades.

9. Thrombocytes, their structure, behavior, and functions

Thrombocytes (blood platelets) have an irregular round shape and are **1–4 μm long** and **0.5–0.75 μm deep** (Figure).

Their **amount in the blood is 150–450 × 10^9/L.** They are formed in the red bone marrow by means of separation from the part of the protoplasm of megakariocytes. One megalokariocyte forms 3–4 thousand thrombocytes. 2/3 thrombocytes circulate in the blood, the others are located in the spleen. Their life span in the blood is 5–11 days, then they are destroyed in the liver, red bone marrow, and spleen.

The plasma membrane of thrombocytes contains glycoproteins (receptors), which are required for adhesion and aggregation. Thrombocytes contain no nuclei. The range of the cytoplasm directly adjoining to the environment is not structured. The central part of the cytoplasm contains granules. **There are 3 types of granules:**

- **α-granules (alpha granules)** — contain proteins and glycoproteins which participate in blood coagulation (fibrinogen, fibronectin, Willebrand factor and others).
- **δ-granules (delta or dense granules)** — contain serotonin, calcium, ADP, ATP.
- **λ-granules (lambda granules, lysosomes)** – contain lysosome enzymes.

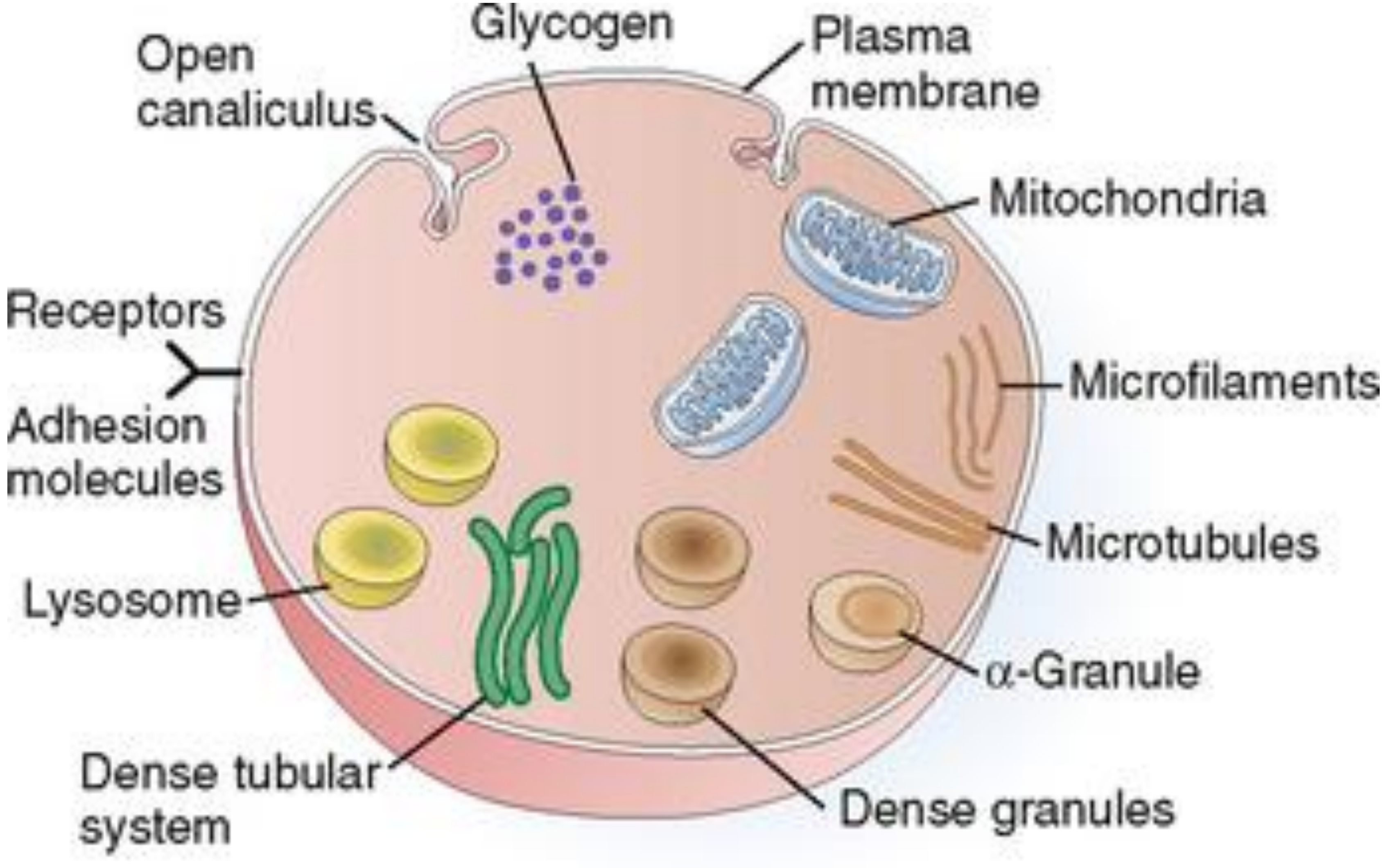


Figure — Strucure of thrombocytes

Thrombocytes are capable of englobing non-biological foreign bodies, viruses, cell-bound immune complexes, i. e. participate in the nonspecific protective system of the body.

The destruction of thrombocytes leads to the release of substances which:

— participate in blood coagulation;

— promote angiospasm (serotonin (F10), adrenalin, noradrenalin);

— produce adhesion and aggregation of thrombocytes.

There are daily fluctuations of the thrombocyte count: in the afternoon it increases, during night-time — it goes down. One of the basic functions of thrombocytes is their participation in blood coagulation.