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# Electrolytes and Blood Cells: The Possible Influence of the Former on Changes in the Amount of the Latter in the Blood

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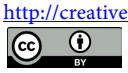



## Abstract

In this article we provide for your viewing a picture of the possible interaction of electrolytes in the body between themselves and with various acids produced in the cells of the body, as well as the possible effects of both the electrolytes themselves and their salts with acids on the hematopoietic sprouts of the bone marrow, leading to a change in the concentrations of various formed elements of the blood. The aim of this article is to better understand the role of various electrolytes in the body, their effect on cellular organelles, as well as on organelle membranes and cell membranes.

## Subject Areas

Clinical Medicine

## Keywords

Electrolytes, Blood Cells, Erythrocyte Sedimentation Rate

## 1. Introduction

Have you ever wondered why the "scissors symptom" is observed in myocardial infarction, *i.e.* why do leukocytes and ESR not increase simultaneously during myocardial infarction? Why during the same myocardial infarction is there a non-simultaneous release of enzymes, CPK, ALAT, LDH into the blood, despite the fact that damage, or even necrosis of the cell should affect its entire contents? Why do bacterial infections cause an increase in the level of leukocytes and ESR in the blood, while with viral infections there is mainly leucopenia (or a normal white blood cell count) and a normal ESR? Why do leukocytes and ESR increase simultaneously in some bacterial infections, while in others, leucocytosis pre-

cedes the increase in ESR?

In order to answer all these questions we have to consider several diseases, in particular, myocardial infarction, infectious diseases both bacterial and viral, as well as a number of endocrinologic diseases and to analyze in detail the movement of electrolytes and their salts both through the cell membrane and inside the cell in each of these diseases.

Let's try to figure it out. At first, let us remember how the "scissors symptom" is explained today in myocardial infarction, as well as how the erythrocyte sedimentation rate (ESR) is explained in general.

In case of myocardial infarction, we have resorption-necrotic syndrome: aseptic necrosis of the myocardium, *i.e.* a complex of signs that develop under the influence of resorption of the focus of necrosis in the myocardium, as well as aseptic inflammation of the myocardium during infarction, which is accompanied by leukocytosis and a febrile reaction [1]. In the very first hours after the occurrence of circulatory disorders in the myocardium, an increase in the number of leukocytes is detected, which after 1 - 3 days decreases to normal (according to other data, the number of leukocytes increases from the second hour and reaches a peak on days 2 - 4, decreasing by the end of the week) [2] [3]. By this time, *i.e.* 1 - 2 days after the appearance of leukocytosis, the ESR rises, the last increases during 1 - 3 weeks. When leukocytosis and ESR are graphically depicted, a characteristic "scissor" cross is obtained.

The erythrocyte sedimentation rate is explained by its dependence on the diameter and volume of erythrocytes, their number (an increase slows down, a decrease speeds up), the content of bile acids and pigments in the plasma, and blood viscosity. ESR is greatly influenced by changes in the ratio of various fractions of blood proteins, taking certain medications and therapeutic measures [4]. According to recent data, the aggregation of erythrocytes mainly depends on the value of their surface potential and the protein composition of the blood plasma. The degree of aggregation (and therefore ESR) increases with the increase in so-called plasma acute phase proteins, markers of the inflammatory process: first of all, fibrinogen and immunoglobulins, to a lesser extent, C-reactive protein, ceruloplasmin and others. Indeed, the content of fibrinogen in the blood increases with the occurrence of acute inflammatory diseases and tissue death. And it can affect the erythrocyte sedimentation rate. However, it is known that fibrinogen also increases during influenza, in which the ESR remains within normal limits. An increase in fibrinogen accompanies the use of estrogens and oral contraceptives. However, in practice, an increase in ESR when taking these medications is usually not observed. Although, according to some data, taking hormonal contraceptives leads to an increase in ESR, and steroids, which include estrogens, reduce this indicator. In addition, the level of fibrinogen decreases in diseases such as hepatitis, cirrhosis of the liver, toxicosis of pregnancy, which are often accompanied by an increase in ESR. Fibrinogen levels are reduced in cases of snake venom poisoning, in which the erythrocyte sedimentation rate may in-

crease [5]-[7]. Fibrinogen is reduced in chronic myeloid leukemia and polycythemia. Yes, indeed, for polycythemia vera (erythremia), in which a high level of hemoglobin and red blood cells is determined in the blood, a slowdown in ESR to 1 - 2 mm/h is very typical. However, is this caused due to low levels of fibrinogen or high levels of red blood cells or some other factor? As for chronic myeloid leukemia, with it the ESR rises to 30 - 40 mm/h [8].

In addition, we can remember that during physical activity, no inflammatory process or tissue death is observed and therefore fibrinogen should remain within normal limits, ESR, as a rule, increases.

As for immunoglobulins, they increase during viral infections, in which, generally, a normal ESR or a slight decrease is observed in it.

On the other hand, it is known that the process of erythrocyte gluing is observed during a "microcirculation crisis." When, as lactate accumulates in oxygen-starved tissues, it enters the bloodstream, its concentration in the blood increases from normal figures (12 - 15 mg per 100 ml of blood, or 12 - 15 mg %) to 75 - 80 mg % and increases deep disturbances of blood circulation in the capillaries. The walls of the capillaries begin to swell and, with high lactate levels, the membranes of red blood cells and other blood cells swell. Instead of floating in the plasma, they begin to stick together into columns of coins (aggregates, or sludges) and clog the capillaries [9].

It is also known that during physical activity, as mentioned above, healthy individuals experience an increase in ESR to certain values. And physical activity, *i.e.* the work of skeletal muscles is accompanied by the accumulation of lactic acid (lactate) in them.

Thus, under certain conditions, for example, during a "crisis of microcirculation", during intense physical activity, during myocardial infarction, inflammatory processes of bacterial etiology, during pregnancy, during malignant neoplasms, we have an increase in the erythrocyte sedimentation rate, ESR. At the same time, in all these cases there is a picture of hypoxia and accumulation of lactic acid, lactate. Summarizing all this, let us assume that it is lactate that promotes the clumping of red blood cells into coin columns and an increase in ESR? If this assumption is correct, then the question arises: does lactic acid itself directly contribute to this, or is the pH of the environment changed by its accumulation, or some salt of lactic acid?

The lactic acid formed in the cell must leave it. We know that $K^+$ and $Mg^{2+}$ ions predominate in cells. Most likely, in order to leave the cell, lactic acid will bind to one of these cations, forming a salt, and in the form of a salt will overcome the barrier of the cell membrane. The concentration of this salt in the blood plasma will increase, leading to red blood cells sticking together and increasing ESR. To find out which of the two cations, $K^+$ or $Mg^{2+}$, lactic acid will bind to, remember that during intense metabolism, intense physical activity, and hypoxia, carbonic acid, $H_2CO_3$, is formed in the cell first of all. Because since $K^+$ ions take part in the formation of the intracellular buffer system, potassium ions

are most likely spent on binding the carbonate anion, $HCO_3^-$ (carbonic acid). In addition, during hypoxia in the cell, ATP breaks down into ADP (AMP) and phosphoric acid. Since phosphoric acid takes part in the phosphate buffer system, potassium ions will be used to form not only carbonates, but also phosphates, removing acid residues from the cell [10]. Consequently, during hypoxia, potassium ions are occupied by other anions, and, apparently, their concentration in the cell will be insufficient to bind with lactic acid. In addition, let's remember two other diseases, Cushing's disease and Addison's disease. With Cushing's disease we have hypokalemia and normal ESR, and with Addison's disease we have hyperkalemia and a decrease in ESR. In the latter case, an increase in ESR may occur in the presence of an active tuberculosis process [11]. So, based on all this, it can be assumed that potassium ions do not take part in the formation of lactate, and, therefore, do not affect the erythrocyte sedimentation rate.

As for magnesium ions: $Mg^{2+}$ is mainly an intracellular divalent ion contained in the body in an amount of 15 mmol per 1 kg of body weight; the concentration of magnesium in plasma is 0.8 - 1.5 mmol/l, in erythrocytes, 2.4 - 2.8 mmol/l, in muscle tissue there is 10 times more magnesium than in blood plasma [10].

It is known that in case of toxemia of pregnant women, with cancer, chronic heart failure, acute and chronic pancreatitis, a pronounced decrease in magnesium in the blood serum is observed [12]. A decrease in magnesium occurs in the second and third trimesters of pregnancy. Doesn't this suggest that in these diseases (or conditions) magnesium ions may be associated with some anions and therefore their concentration in the blood plasma may be reduced?

In addition to all this, as mentioned above, the normal concentration of magnesium in plasma is 0.8 - 1.5 mmol/l, and the lactate content in the blood is normal 0.4 - 1.4 mmol/l [10] [13]. That is, the concentrations of magnesium and lactate ions in the blood are almost the same. Does this say anything?

Let's accept as true that it is magnesium ions that bind lactic acid and in the form of magnesium lactate, lactic acid is removed from the cell and develop this theory further.

## 2. Myocardial Infarction

In order to answer the questions we posed at the beginning of the article, let us, first of all, consider what happens in the myocardiocyte during myocardial infarction and try to explain the mechanism of the non-simultaneous release of enzymes, creatine phosphokinase (CPK), aspartate aminotransferase (ASAT) and lactate dehydrogenase (LDH), into the blood. Let us remember that from the first hours of myocardial infarction the concentration of myoglobin in the blood increases. Within 2 - 4 hours, the concentration of creatine phosphokinase (CPK) and its MB fractions increases in the blood, which persists for 2 - 3 days (according to other sources, 3 - 6 days). In acute myocardial infarction, the concentration of cardiac-specific troponin cTnI in the blood serum increases 3 - 6

hours after the onset of cardiac symptoms, reaching a peak after 12 - 16 hours. The concentration of aminotransferases (especially asparagine and, to a lesser extent, alanine) increases from the end of the first day, normalizing by days 3 - 5. According to some data, AST increases after 8 hours. The last to increase is LDH (in one or two days), in particular its first and second enzymes ($LDH_1$ and $LDH_2$) and lasts 10 - 14 days [1] [14] [15].

Apparently, this could be explained by their different molecular weights, the increase of which is associated with such a sequence of removal of these proteins and enzymes through the cell membrane, the damage to which also increases gradually. Indeed, the molecular weight of myoglobin, the concentration of which in the blood increases first, is 17.2 kDa. The molecular weight of cardiac-specific troponin is 22.5 - 23.9 kDa. The molecular weight of creatine phosphokinase CK-MB is 80 - 87 kDa, the molecular weight of aspartate aminotransferase is 100 kDa, and lactate dehydrogenase is 134 kDa. Yes, this is possible, especially with regard to proteins, myoglobin and troponin. However, some enzymes, in particular creatine phosphokinase, can outpace the protein troponin, despite the fact that the molecular weight of the former is greater than the latter.

And what if we try to explain the above sequence of increased enzymes in the blood during myocardial infarction a little differently?

So, first an ischemic zone is formed. In the ischemic area, the cells are in hypoxia. In a hypoxic state, the "creatine phosphate ↔ ATP" reaction does not simply shift to the right, but all creatine phosphate is consumed. As mentioned above, under hypoxic conditions, carbonic acid is formed, intensive breakdown of ATP occurs, which leads to the accumulation of large amounts of phosphoric acid. To remove such large quantities of carbonic and phosphoric acids, the intracellular buffer system is activated, *i.e.* their removal from the cell occurs with the help of potassium ions in the form of salts $KHCO_3$ and $KH_2PO_4$ ($K_2HPO_4$). This accumulation of acids in the cell leads to a decrease in the pH of the cell environment. It is known that in an acidic environment creatine phosphate is easily hydrolyzed with cleavage of the phosphamide bond N-P. Thus, creatine phosphate will be used to neutralize acids that are formed during hypoxia and increased cell function under hypoxic conditions. Therefore, there will not be enough phosphate groups to form ATP. The cell has energy hunger. Imagine what happens during ischemia, and then during myocardial infarction. As a result of hypoxia, a shift in the transphosphorylation reaction towards the formation of ATP occurs, the breakdown of creatine phosphate in an acidic environment, the cessation of the formation of ATP from creatine phosphate, the consumption of the entire ATP reserve, the accumulation of phosphoric acid residues in the cell both due to the breakdown of creatine phosphate and due to the breakdown of ATP, the combination of ions potassium with phosphoric acid residues, removal of phosphates from the cell in the form of salts $KH_2PO_4$ ($K_2HPO_4$), depletion of the cytoplasm in adenosine triphosphate. And creatinine phosphokinase leaves the cell as unnecessary within 2 - 4 hours after myocardial

damage (or myocardial infarction). The activity of creatine phosphokinase (CPK) in the blood increases.

Thus, creatine phosphokinase (CPK) is an enzyme whose concentration, before the other two enzymes (ACAT and LDH), increases in the blood during myocardial infarction, which is explained by cell hypoxia, the accumulation of phosphoric acid residues in the cell, a decrease in cell pH, the breakdown of creatine phosphate and, apparently, a decrease in the activity of creatine phosphokinase in the acidic environment of the cell with its removal from the latter into the extracellular environment.

As for aspartate aminotransferase (ASAT): with a lack of ATP (for example, during intense metabolism, during intense physical activity, during hypoxia), which is a donor of phosphate groups, the conversion of pyridoxal into the coenzyme (pyridoxal phosphate, pyridoxamine phosphate) is disrupted. Pyridoxal phosphate is a coenzyme of transaminases, which catalyze the transfer of an amino group from one substance to another [10]. Consequently, with a lack of phosphate groups, the synthesis of these cofactors is inhibited, the synthesis of transaminases is disrupted, and the transamination of amino acids is disrupted, including the conversion of aspartate into oxaloacetic and glutamic acids. Aspartic acid accumulates in the cell. Aspartate aminotransferase loses its function. This may be why during myocardial infarction ASAT begins to be removed from the cell after 3 - 5 hours (or 8 hours according to other sources), and its activity in the blood plasma increases sharply after this period of time. Aspartic acid accumulated in the cell exacerbates the already increased acidity of the cell. Potassium ions are occupied by carbonate and phosphate anions. But there are magnesium ions in the cytoplasm. After all, it is known that magnesium ions take part in the storage, utilization of energy, its transfer, in the synthesis of proteins, nucleic acids, in the hydrolysis of phosphates and in many other cellular reactions, many of which stop during hypoxia [10]. Thus, many unoccupied magnesium ions accumulate in the cell, which can freely contact aspartic acid and be removed from the cell in the form of magnesium aspartate salt.

Thus, the second most time-dependent increase in the blood concentration of the enzyme during myocardial infarction after CPK is aspartate aminotransferase (ASAT). Because during hypoxia in the cell, ATP first breaks down with the formation of phosphoric acid residues, their removal from the cell, and only after this, due to the lack of the latter, transamination reactions in the cell stop with the accumulation of aspartic acid in it, which apparently leads to a decrease in the activity of aspartate aminotransferase (ASAT) and its removal from the cell into the external environment.

And finally, about lactate dehydrogenase: however, before we move on to lactate dehydrogenase, let's look at what changes in the concentration of formed elements in the blood and electrolytes occur during bacterial and viral infections.

With bacterial infections, leukocytosis, lymphopenia and increased ESR are observed, and with viral infections, leukopenia, lymphocytosis and normal ESR

are observed. During viral infections, unlike bacterial infections, viruses penetrate into the cell, but do not destroy the host cells (at least at the beginning of the disease, immediately as they enter the cell, and subsequently, destruction of the affected cells may occur), because viruses need a nucleus and nucleic acids, DNA and RNA of the host cell for their replication. Bacteria do not need to maintain the integrity of the host's DNA in order to reproduce. A bacterium, infecting a host cell, immediately leads to its destruction. And the destruction of the host cell leads to the destruction of the nucleus and the breakdown of nucleic acids with the formation of uric acid. Consequently, during bacterial infections the concentration of uric acid in the form of salts increases, *i.e.* urates, which does not happen with viral infections. It is the destruction of host cell DNA and the accumulation of urates that distinguishes bacterial infections from viral ones. Can uric acid salts affect the amount of any blood cells and lead to some abnormalities in the blood picture?

In order to explain the possible influence of changes in the concentrations of various electrolytes in the blood on changes in the amount of formed elements in it, let's recall some endocrinological diseases, in particular, Cushing's disease, Addison's disease, diffuse toxic goiter, myxedema, hyper- and hypoparathyroidism and others.

With Cushing's disease, we have the following electrolyte changes in the blood: the release of $Ca^{2+}$ ions from the bones (according to some data, hypercalcemia, according to others hypocalcemia), hypernatremia, hypokalemia, hyperchloremia, as well as changes in the number of blood elements, an increase in the number of red blood cells, leukocytes, decreased lymphocytes, eosinophils and normal ESR [11]. With Addison's disease we have hyponatremia, hypochloremia, hyperkalemia, according to the latest data, hypercalcemia, and lymphocytosis, eosinophilia, neutropenia, and a decrease in ESR are noted in the blood [11]. If $K^+$ ions, as mentioned above, bind to carbonic and phosphoric acid residues, $Mg^{2+}$ ions (according to our assumption) bind to lactic acid and affect the erythrocyte sedimentation rate, *i.e.* potassium and magnesium ions are already occupied by other anions, then, given that in Cushing's disease we have hypernatremia and leukocytosis, and in Addison's disease we have hyponatremia and leukopenia, can we assume that sodium ions, $Na^+$ together with any anion have influence on changes in the number of leukocytes in the blood? Now, if we return to the bacterial and viral infections described above, where we indicated that with bacterial infections uric acid can accumulate and with them, unlike viral infections, there is a picture of leukocytosis in the blood, then can we assume that it is urates sodium influence (stimulate) the myelocytic clone of the bone marrow, leading to an increase in leukocytes in the blood. Moreover, an increase in the concentration of uric acid is also observed during bacterial infections.

In addition, it is known that with gout the concentration of sodium urate in the blood increases and during gout attacks a picture of leukocytosis is observed.

Now let's return to myocardial infarction and the enzyme lactate dehydro-

genase, and consider other changes in the concentration of electrolytes and their possible effect on the content of blood cells in endocrinological diseases later.

So, the third enzyme is lactate dehydrogenase.

It is known that in tissues with aerobic metabolism (tissue of the heart, kidneys, etc.) isoenzymes $LDH_1$ and $LDH_2$ predominate. These isoenzymes are inhibited by even small concentrations of pyruvate, which prevents the formation of lactic acid and promotes more complete oxidation of pyruvate (more precisely, acetyl CoA) in the tricarboxylic acid cycle. In human tissues that rely heavily on energy from glycolysis (e.g., skeletal muscle), the main isoenzymes are $LDH_5$ and $LDH_4$. $LDH_5$ activity is maximum at those pyruvate concentrations that inhibit $LDH_1$. The predominance of isoenzymes $LDH_4$ and $LDH_5$ causes intense anaerobic glycolysis with the rapid conversion of pyruvate to lactic acid [10].

So, in a normally functioning myocardial cell, even small concentrations of pyruvic acid inhibit the activity of $LDH_1$ and $LDH_2$. This is necessary so that lactic acid does not form in the cardiomyocyte and all pyruvic acid is used in the Krebs cycle for its more complete oxidation and the formation of ATP. The enzymes $LDH_1$ and $LDH_2$ are not removed from the cell in this mode; they are retained in the cytoplasm. Only some of their concentrations are found normally in blood plasma. Moreover, normally the activity of $LDH_2$ in the blood is higher than the activity of $LDH_1$. And during myocardial infarction, the activity of the latter increases sharply, while the activity of $LDH_2$ remains stable or increases slightly. This phenomenon is called LDH "isoenzyme crossover".

With myocardial infarction, as mentioned above, acceleration of ESR is observed on the second or third (2 - 3) day of the disease and follows an increase in the number of leukocytes [4]. Then, if our assumption about the connection between the accumulation of lactic acid in cells and an increase in the erythrocyte sedimentation rate is correct, then lactic acid should accumulate in myocardiocytes by this time. However, approximately at the same time (in the first 24 - 48 hours) during myocardial infarction, an increase in LDH in the blood is observed, more precisely $LDH_1$ and $LDH_2$. If the concentration of these two LDH isoenzymes in the blood increases, then it turns out that lactate dehydrogenase in myocardial cells does not work and pyruvic acid is not converted into lactic acid. This contradicts our assumption. How to explain this?

In an ischemic myocardial cell, hypoxia leads to the removal of carbonates, phosphates, potassium ions, aspartate, and magnesium ions from the cell. From the very first minutes of hypoxia, the cell turns on anaerobic glycolysis to produce energy. The Krebs cycle still continues to function, but its work is insufficient for a hypoxic cell. Glycolysis leads to the accumulation of large concentrations of pyruvic acid in it. The latter no longer enters the Krebs cycle, but also does not turn into lactic acid, because despite the fact that the activity of $LDH_5$ is maximum at those concentrations of pyruvate that inhibit $LDH_1$, apparently in the myocardiocytes of the two other fractions of LDH, $LDH_4$ and $LDH_5$ there is either a very small amount or they are not present at all in these cells. Due to the

lack of $K^+$ and $Mg^{2+}$ ions in the cytoplasm, $Na^+$ and $Ca^{2+}$ ions begin to enter the cell from the outside. Typically, sodium ions entering the cell are exchanged for calcium ions. In addition, $Ca^{2+}$ ions freely enter the cell cytoplasm and from the sarcoplasmic reticulum. These $Ca^{2+}$ ions combine with the pyruvic acid accumulated in the cell. The resulting salt, calcium pyruvate, can have a damaging effect on the internal organelles of the cell, in particular on the nuclear membrane, which will begin to collapse, leading to the breakdown of nucleic acids and the formation of uric acid. The latter will contact the $Na^+$ ions accumulated in the cytoplasm, forming urates, which, upon leaving the cell, enter the circulation, penetrate with the blood into the bone marrow and have a stimulating effect on myelopoiesis. In the blood of patients with myocardial infarction, a picture of leukocytosis will be noted from the very first hours. Consequently, cell damage, even more so their necrosis, leads to the breakdown of nucleic acids with the formation of uric acid which binds to sodium ions and these salts stimulate the bone marrow, increasing the number of leukocytes in the blood. Why from the very first hours? Because, during hypoxia, the cell quickly switches to anaerobic glycolysis, this leads to the accumulation of pyruvic acid, as mentioned above, potassium ions are removed from the cell, calcium ions enter the cytoplasm from the endoplasmic reticulum, they bind to pyruvic acid, leading to damage to the nuclear membranes and the accumulation of sodium urate salts in the cell.

And if small concentrations of pyruvic acid inhibit $LDH_1$, then a further increase in the concentration of pyruvate above $10^{-4}$ M completely reduces the activity of LDH, which, as unnecessary, begins to be removed from the cell and after 8 - 12 hours the concentration of $LDH_1$ in the blood increases. In order to understand why lactate dehydrogenase increases in the blood under hypoxic conditions, let us remember the following and try to explain this phenomenon.

It is known that the five LDH isoenzymes are formed from 4 subunits of approximately the same size, but of two different types, conventionally designated: H-type and M-type. H-protomers carry a more pronounced negative charge at pH 7.0 - 9.0 than M-protomers. So, the $LDH_1$ isoenzyme, which consists of 4 H-type subunits ($H_4$), during electrophoresis migrates in an electric field at the highest speed to the positive electrode (anode). Isoenzyme $M_4$ ($LDH_5$) moves at the lowest speed to the anode and the remaining isoenzymes occupy intermediate positions [10]. Thus, when pyruvic acid (and other acids as well) accumulates in the cell during hypoxia, the pH of the cell decreases and protons ($H^+$) begin to neutralize the inner layer of the cell membrane, which normally carries a negative charge. Apparently, during deep hypoxia, a decrease in cell pH leads to a sharp increase in protons in the cell and the internal membrane of the cell is recharged to positive. Then, negatively charged H-protomers ($LDH_1$) are directed to the positively charged inner membrane of the cell (like the anode) and, coming closer to the membrane, they are attracted to it and, being close to the membrane, are easily removed from the cell. As for other isoenzymes, they, like $LDH_1$, also carry a negative charge, but their charge is less than the first and

therefore they are less attracted by the inner cell membrane. Apparently, this can explain the phenomenon of "isoenzyme crossover," when during myocardial infarction in the blood the concentration of $LDH_1$ increases more than the $LDH_2$ isoenzyme.

If in myocardiocytes, in addition to the $LDH_1$ and $LDH_2$ isoenzymes, there are other isoenzymes, $LDH_4$ and $LDH_5$, then during myocardial infarction, when the first two isoenzymes are removed from the cell, pyruvic acid under the influence of the other two should turn into lactic acid. And if myocardiocytes normally contain only the isoenzymes $LDH_1$ and $LDH_2$, then after they are removed from the cell, pyruvic acid will not be able to turn into lactic acid and, combining with calcium ions, forms calcium pyruvate. That is, the formation of calcium lactate or calcium pyruvate depends on the presence of certain LDH isoenzymes in the cell. However, if we say that it is calcium pyruvate that damages the nuclear membrane of the cell, after which the breakdown of nucleic acids occurs with the formation of salts sodium urates, which, when released into the bloodstream, lead to stimulation of the bone marrow with a further increase in leukocytes in the blood, and leukocytosis during a heart attack myocardium precedes an increase in the erythrocyte sedimentation rate, it turns out that even if there were a sufficient amount of magnesium ions in the cytoplasm (apparently coming from the nucleus after damage to its membrane by calcium pyruvate), the presence of lactic acid in the cytoplasm would lead to the formation of magnesium lactate simultaneously with formation of sodium urates. And then we would have a picture of a simultaneous increase in leukocytes in the blood and erythrocyte sedimentation rate, which does not happen with myocardial infarction. This suggests that in myocardiocytes there are no other isoenzymes besides $LDH_1$ and $LDH_2$. And the increase in ESR occurs due to magnesium lactate, which is formed not in myocardiocytes, but in other cells. The question is raised in which cells?

To do this, consider the formed elements of blood. Let's start with red blood cells.

It is known that erythrocytes contain mainly two fractions of lactate dehydrogenase $LDH_1$ and $LDH_2$. It is also known that erythrocytes lack organelles such as the nucleus and mitochondria. If there are no mitochondria, then it turns out that aerobic oxidation of glucose to $CO_2$ and $H_2O$ does not occur in red blood cells. Only anaerobic glycolysis occurs until the formation of pyruvic acid. Since small concentrations of pyruvic acid inhibit the activity of $LDH_1$ and $LDH_2$, lactic acid is not formed in red blood cells. Here the question arises: if glucose is not broken down into $CO_2$ and $H_2O$ and if the accumulated pyruvic acid cannot be converted into lactic acid, then why is LDH present in erythrocytes at all? In addition, what is the further fate of pyruvic acid, which is constantly formed in the process of anaerobic glycolysis? It does not enter the Krebs cycle in red blood cells and does not turn into lactic acid. Then, it must leave the erythrocyte and enter the blood plasma. If we have $LDH_1$ and $LDH_2$ in erythrocytes, pyruvic acid

accumulates in them, and there are many magnesium ions in erythrocytes, then it turns out that the accumulated pyruvic acid, which does not enter the Krebs cycle (there are no mitochondria in erythrocytes), is not converted into lactic acid (in erythrocytes, there are mainly $LDH_1$ and $LDH_2$), then perhaps pyruvic acid binds to $Mg^{2+}$ ions and is removed from erythrocytes in the form of magnesium pyruvate salts. In addition to $Mg^{2+}$ ions, erythrocytes also contain a lot of $K^+$ ions. However, the latter are more occupied by the hemoglobin buffer system [16] [17]. Thus, it can be assumed that magnesium pyruvate prevents the adhesion of red blood cells, allowing them to move freely in the blood and perform their transport function, the transfer of $O_2$ and $CO_2$. If $LDH_4$ and $LDH_5$ predominated in erythrocytes instead of $LDH_1$ and $LDH_2$, then lactic acid would be formed from pyruvic acid, which, when bound with $Mg^{2+}$ ions, would form the salt magnesium lactate and, leaving the erythrocytes, would lead to their gluing. On the other hand, if there were not many magnesium ions in the red blood cells, then many $Ca^{2+}$ ions would accumulate in them from blood. From pyruvic acid and calcium ions a salt would be formed calcium pyruvate. It would lead to damage to the red blood cell membrane and destruction of the latter. Since red blood cells live for 120 days, it is possible that their destruction occurs in exactly this way, namely, the magnesium ions present in the red blood cells are gradually consumed by the pyruvic acid that is constantly formed in them and the formation of magnesium pyruvate salts with them, and the restoration of the reserves of magnesium ions in the red blood cells later this period no longer occurs. When $Mg^{2+}$ ions in red blood cells are completely used up, then $Ca^{2+}$ ions will begin to accumulate in these cells, which, when bound with the constantly formed pyruvic acid, form calcium pyruvate salt. The latter will damage the red blood cell membrane and ultimately lead to cell death. From this point of view, erythrocytes, to some extent, may be similar to myocarditis and, perhaps, brain cells. As long as $LDH_1$ and $LDH_2$ function normally in these cells, as long as they have a sufficient concentration of $Mg^{2+}$ ions, then these cells remain undamaged. When $LDH_1$ and $LDH_2$ are either removed from these cells, or $Mg^{2+}$ reserves are exhausted and the cell finds itself in an ischemic state, $Ca^{2+}$ pyruvate is formed, which leads to cell death (necrosis, infarction, destruction).

Thus, if pyruvic acid is constantly formed in erythrocytes and they have a large supply of magnesium ions, then magnesium pyruvate is constantly formed in these cells, which is removed from erythrocytes and not only prevents the adhesion of erythrocytes, but also inhibits the proliferation of the leukocyte clone in the bone marrow, *i.e.* to with hemolysis, in many cases there is an increase in ESR and a picture of leukocytosis in the blood. For example, in the acute form of autoimmune hemolytic anemia there is an increase in ESR and leukocytosis, in microspherocytic hemolytic anemia during hemolytic crises there is a slight leukocytosis with a shift to the left, in enzymopenic hemolytic anemia there is hyperleukocytosis with a shift to the left, in sickle cell anemia in the blood picture there is leukocytosis with a shift to myelocytes [18]. In addition, let's re-

member that in malaria hemolysis of red blood cells occurs. Hypochromic anemia develops, ESR is increased. According to some data, leukopenia, neutropenia, relative lymphocytosis and monocytosis are observed [19]. And according to other data, there is anemia (red blood cells, 2,000,000 - 1,500,000 in 1 μl of blood), thrombocytopenia is noted, during the first attacks moderate neutrophilic leukocytosis (9000 - 10,000) can be observed, and in malarial coma it can reach 20,000 [4]. During the interictal period, leukopenia, neutropenia, eosinopenia, and relative lymphocytosis may be observed. In prolonged cases, monocytosis occurs. ESR accelerated. All this can be explained as follows. With massive hemolysis, the formation of magnesium pyruvate in red blood cells stops; this salt no longer envelops the membrane of red blood cells and does not protect them from gluing. The absence of magnesium pyruvate leads to the fact that the inhibitory effect of magnesium pyruvate on the leukocyte clone ceases. Leukocytosis is observed, and in leukocytes located in hypoxic tissues during attacks of malaria, magnesium lactate is formed (why? we will explain this later), which, leaving the leukocytes, leads to the gluing of red blood cells and an increase in ESR. Thus, during attacks of malaria we have a picture of leukocytosis and an increase in ESR, and outside of attacks of malaria, hemolysis stops, magnesium pyruvate is formed in erythrocytes, which, leaving the erythrocytes, protects them from adhesiveness (ESR does not increase) and penetrating into the bone marrow, will lead to inhibition of leukocyte clone. Consequently, in the interictal period we have leukopenia and neutropenia.

As for leukocytes, on the contrary, $LDH_4$ and $LDH_5$ predominate in them. Therefore, if in leukocytes the pyruvic acid formed during the oxidation of glucose for some reason does not enter the Krebs cycle (after all, leukocytes, unlike erythrocytes, have mitochondria), then under the action of the enzymes $LDH_4$ and $LDH_5$ it is converted into lactic acid and magnesium lactate can form in leukocytes, which, with high leukocytosis, leaving the cells (leukocytes) will lead to the sticking of red blood cells and an increase in ESR. In order for pyruvic acid in leukocytes to be included in the Krebs cycle, that is, the process of oxidative phosphorylation to occur, oxygen must enter the leukocytes themselves. And in those tissues that, due to the inflammatory process, ischemia, infarction, etc. are in a hypoxic state, there is not enough oxygen not only for the cells of these tissues, but also for the formed elements of blood entering this focus of hypoxia, that is, for leukocytes, erythrocytes, platelets, lymphocytes, macrophages. So, in leukocytes (we will consider other blood cells later) under hypoxic conditions, pyruvic acid will undergo only anaerobic glycolysis with the formation of lactic acid, which, forming a salt with magnesium ions, magnesium lactate, will leave the leukocytes and lead to the gluing of red blood cells and increased ESR during inflammation, ischemia, and necrosis. It may also occur during myocardial infarction, when in the very first hours there is an increase in the concentration of leukocytes in the blood, a large amount of magnesium lactate accumulates in these cells and releases them into the blood, which leads to the adhesion of red

blood cells and an increase in ESR on the 2 - 3th day of myocardial infarction, that is, to the manifestation of the "scissors" picture. Consequently, the cause of an increase in ESR during myocardial infarction is not the myocardiocytes themselves, but leukocytosis with the release of magnesium lactate from leukocytes into the blood.

Summarizing all of the above about the three "infarction" enzymes (CPK, AST, LDH), let us note that CPK increases from the first hours of myocardial infarction and lasts for 2 - 3 days, AST increases from the end of the first day and normalizes by 3 - 5 days, and LDH rises after about 12 hours, or even two days, and lasts 10 - 14 days. At the same time, the number of leukocytes decreases to normal after 1 - 3 days, and the ESR increases after 1 - 2 days and increases over 1 - 3 weeks. Doesn't this suggest that there is a certain connection between LDH levels and an increase in ESR? They both last longer than other laboratory indicators.

These are $LDH_1$ and $LDH_2$. Now, as for $LDH_4$ and $LDH_5$, in addition to leukocytes, they are present in those tissues that depend on the energy generated during glycolysis, for example skeletal muscles, liver cells hepatocytes. Here, these enzymes are activated by small concentrations of pyruvic acid and, under hypoxic conditions, immediately convert pyruvic acid into lactic acid. Consequently, in skeletal muscles and in other tissues that depend on the energy of glycolysis, under normal conditions, during intense work there is a constant formation of lactic acid. Why? What is lactic acid for? After all, glycolysis is the process of oxidizing glucose to form pyruvic acid? However, apparently, it should turn into lactic acid, which is more easily removed from the cell than pyruvic acid and is more easily utilized by liver cells for gluconeogenesis than pyruvic acid. In addition, it is possible that pyruvic acid in high concentrations in blood plasma is more toxic to the body than lactic acid. After all, the normal ratio of lactate to pyruvate in the blood is 10:1. The level of pyruvate in the blood is 0.07 - 0.14 mmol/l, and the level of lactate in the blood is 0.4 - 1.4 mmol/l. Indeed, with B1-avitaminosis, the content of pyruvic acid in the blood of rats sharply increases, because the oxidative decarboxylation of pyruvic acid is disrupted due to a lack of TDP (thiamine diphosphate). And blocking the decarboxylation of keto acids with vitamin B1 deficiency affects, first of all, on the processes of nerve impulse conduction, the disruption of which causes neuromotor and mental disorders.

Lactic acid is removed, apparently, as mentioned above, in the form of magnesium salts. Their concentration in the blood is normally not so high. They, in such small quantities, lead to the gluing of only a small part of the red blood cells. Therefore, in a healthy person, the ESR always remains within certain limits approximately 10 mm/hour and the erythrocyte sedimentation rate never drops to zero. Consequently, a complete drop in ESR to zero, *i.e.* the absence of the process of gluing red blood cells would mean a complete cessation of the formation of lactic acid in the cells of the body.

In the cells of some tissues, for example, lungs, spleen, thyroid and pancreas, adrenal glands, lymphocytes, $LDH_3$ predominates. $LDH_4$ is found in all tissues with $LDH_3$. It is known that with some bacterial infections there is a gradual increase in ESR (for example, with pneumonia). Since $LDH_3$ is a specific enzyme in the lungs, pyruvic acid apparently has an intermediate effect on it (between $LDH_{1,2}$ and $LDH_{4,5}$) and therefore the increase in ESR occurs with some delay compared to leukocytosis [4]. And in tissues with a predominance of $LDH_4$ and $LDH_5$ (skeletal muscles, hepatocytes, granulocytes, etc.) under hypoxic conditions, lactic acid will immediately be formed from pyruvic acid and an increase in ESR will be noted from the very first hours of intensive work of these cells. Consequently, in some cells, in the first hours of hypoxia, more pyruvic acid is accumulated, while in others, more lactic acid is accumulated. This may be why myocardial and brain cells necrotize faster during ischemia (as a result of the formation of calcium pyruvate) than skeletal muscle cells and hepatocytes, in which pyruvic acid does not accumulate, but is immediately converted into lactic acid. The last of the skeletal muscle cells is easily removed and enters hepatocytes with its subsequent inclusion in gluconeogenesis, and in the hepatocytes themselves, the resulting lactic acid is used here for the formation of glycogen.

As to platelets: platelets contain large amounts of magnesium ions. It is known that the concentration of magnesium ions in the formed elements is composed as follows: in lymphocytes > granulocytes > platelets > erythrocytes [20]. In addition, platelets contain $\alpha$-granules and delta granules (or dense granules). Dense granules and the endoplasmic reticulum contain calcium ions [21]. These $Ca^{2+}$ ions in intact platelets flow through calcium ion pumps from the cell into the blood. This is facilitated by the activation of cAMP. The platelet membrane is composed of phospholipids. Negatively charged phospholipids, primarily phosphotidylserine, are concentrated in the inner layer of the membrane, and phosphotidylcholine in the outer layer binds coagulation factors much less well. Under normal conditions, the platelet membrane does not support the clotting reaction. When platelets are activated, the enzyme scramblase is activated, which transfers negatively charged phospholipids from one layer to another. As a result, phosphatidylserine in both layers is leveled. Now, according to our assumption, apparently, in an inactive platelet, $Mg^{2+}$ ions are concentrated near the inner layer of the membrane, which, due to the negatively charged phosphatidylserine, can attract positive $Mg^{2+}$ ions. During the platelet activation process, which occurs when the platelet comes into contact with damaged endothelium, a blood clot must form, *i.e.* platelet adhesion to the damaged endothelium must occur. Apparently, when a platelet is activated, if the negatively charged phosphatidylserines change their location, they will be followed by $Mg^{2+}$ ions and will freely leave the cell. Then $Ca^{2+}$ ions will begin to enter the cell from dense granules and the endoplasmic reticulum (as antagonists of $Mg^{2+}$ ions) and combine with pyruvic acid to form $Ca^{2+}$ pyruvate salts, which will damage the membrane of $\alpha$-granules and fibrinogen will begin to emerge from the latter, which, leaving

the cell, will lead to the formation thrombus. Normally, in platelets, pyruvic acid enters the Krebs cycle (platelet contains mitochondria) and pyruvic acid is not converted into lactic acid (in platelets from the LDH enzymes there are $LDH_1$ and $LDH_2$, which, as mentioned above, are inactivated by small concentrations of pyruvic acid). Pyruvic acid in platelets enters the Krebs cycle. Therefore, magnesium lactate is not formed in non-activated platelets. If there were no mitochondria in platelets, then in them, as in erythrocytes, pyruvic acid would accumulate and, combining with magnesium ions, would form the $Mg^{2+}$ pyruvate salt, which, having left the cell, as in the case of erythrocytes, would prevent their gluing. This is not beneficial to the body, since platelets, unlike red blood cells, must have a greater ability to stick together, *i.e.* aggregation, for further formation of a blood clot, which is necessary in case of damage to the vascular wall. Thus, the presence of mitochondria in platelets gives them the ability to more active aggregation. And $Mg^{2+}$ ions must be removed from platelets in order for them to perform their aggregation function.

Perhaps, by analogy with this mechanism occurring in platelets, it is possible to explain the process of destruction of the nuclear membrane by $Ca^{2+}$ pyruvate in myocardiocytes during myocardial infarction. That is, if under hypoxic conditions in platelets $Mg^{2+}$ ions are removed along with a change in the configuration of phosphatidylserine, then $Ca^{2+}$ pyruvate accumulates in platelets (since during hypoxia, pyruvic acid does not enter the mitochondria, and the removal of $Mg^{2+}$ ions from the cell leads to the release of $Ca^{2+}$ ions from endoplasmic reticulum, forming calcium pyruvate salt), which destroys $\alpha$-granules and dense granules in platelets without destroying the mitochondrial membrane. So, apparently, destruction of the nuclear membrane in myocardiocytes also occurs during myocardial infarction, without leading to destruction of the mitochondrial membrane in them. Thus, if in platelets, as anucleate cells, $Ca^{2+}$ pyruvate attacks $\alpha$-granules and dense granules, and in myocardiocytes, the nuclear membrane, then can we assume that the structure of the membranes of $\alpha$-granules and dense granules of platelets is somewhat similar to the structure of nuclear membranes myocardiocytes. Both become targets for calcium pyruvate, which accumulates in these cells during hypoxia.

In addition, if in erythrocytes, as mentioned above, $Mg^{2+}$ pyruvate is normally formed, which protects these cells from gluing, and in leukocytes, the salt $Mg^{2+}$ lactate formed during pathology (inflammation, hypoxia), leads to gluing of erythrocytes, then from sticking together red blood cells creates a barrier between damaged and normal tissues. This barrier of red blood cells prevents the spread of foreign agents or toxic substances from damaged tissue to healthy tissue. In this area limited by red blood cells, leukocytes must fulfill their phagocytic role. Lymphocytes and monocytes also participate in this role. Therefore, lymphocytes and monocytes should not be used to form the barrier line, like erythrocytes. $Mg^{2+}$ lactate, in theory, should not glue together leukocytes, lymphocytes, or monocytes. As for platelets, unlike erythrocytes, $Mg^{2+}$ pyruvate

should not accumulate in them, because platelets should not be protected for so long by $Mg^{2+}$ pyruvate from preventing them from sticking together, because, on the contrary, platelets, unlike erythrocytes, must be ready to stick together (aggregation and adhesion). This is achieved by the presence of mitochondria in platelets, the entry of pyruvic acid into the Krebs cycle under normal conditions (as opposed to erythrocytes), and the removal of $Mg^{2+}$ ions from the cells, the release of $Ca^{2+}$ ions into the cytoplasm with the formation of calcium pyruvate in activated platelets and the destruction of platelet granules to carry out their main function, aggregation and platelet adhesion.

Now, continuing our main idea, let's look at viral hepatitis. However, in order to better understand viral hepatitis, as well as other viral infections, let us return to endocrinological diseases and the possible relationship between electrolytes and blood cells.

## Endocrinological Diseases

As noted above, with Cushing's disease, lymphopenia and the release of calcium ions from the bones are observed with the development of osteoporosis, which is explained by the excessive production of glucocorticoids, leading to disruption of the formation of the protein framework of bone tissue with insufficient deposition of calcium salts in the bones. In Addison's disease, on the contrary, there is lymphocytosis and glucocorticoid deficiency, which, unlike Cushing's disease, should not lead to bone tissue resorption. Can calcium ions affect the lymphocyte clone and cause changes in their concentrations in the blood? In particular, is it possible to assume that calcium ions suppress the production of lymphocytes in the bone marrow, and also explain the increase in the number of lymphocytes in the blood by a decrease in the concentration of free calcium ions in the blood, or by their binding to some anions and thus washing them out of the body, or by binding calcium ions to fatty acids and depositing them in certain places in the body? Some sources note a decrease in the concentration of calcium ions in the blood in Cushing's disease. Why? If calcium ions are washed out of bones under the influence of glucocorticoids, then why does their concentration in the blood decrease? With Cushing's disease we have hypophosphatemia, hypoalbuminemia and fat deposition in the body. Perhaps calcium ions bind to phosphoric acid residues and are washed out of the body in the form of salts, being removed through the kidneys. In addition, if the level of albumin in the blood decreases, then calcium ions are excreted along with them in the urine. The deposition of fat in the body may also be associated with calcium ions, and it is in the form of calcium salts that fatty acids are deposited in the fat depots of the body. All three of these mechanisms can lead to decreased blood calcium levels in Cushing's disease, despite being washed out of the bones. And since the release of calcium ions occurs precisely in the bones, they can inhibit the lymphocytic clone here, leading to lymphopenia.

Absolute lymphocytosis in the blood can be observed in certain physiological

conditions, in early childhood and after ingestion of fats [4]. In early childhood, calcium is necessary for bone growth and skeletal strengthening. Apparently, this is why calcium is used for the formation of the skeletal system, and not washed out from the bones, which is observed in adults. Therefore, calcium used for bone growth in children is bound by some kind of anion and does not suppress the lymphocytic clone in the bone marrow, and lymphocytosis is observed in children in early childhood. As for lymphocytosis after eating fats, this can also be explained by the binding of calcium ions to fatty acids that enter the body with food and a decrease in the concentration of free calcium ions, leading to inhibition of their inhibitory effect on the bone marrow.

Now let's look at diffuse toxic goiter and myxedema.

In diffuse toxic goiter an excess of thyroid hormones leads to disruption of water-electrolyte metabolism, the release of water, sodium chloride, calcium, phosphorus and, to a lesser extent, potassium increases, and the content of bound magnesium in the blood serum increases [11]. According to laboratory data, with diffuse toxic goiter, "in some cases, especially with severe forms of the disease, leukopenia, relative or absolute neutropenia, relative and less often absolute lymphocytosis and monocytosis, a tendency to thrombocytopenia, and much less often eosinophilia can be observed" [11]. Thus, with diffuse toxic goiter we have hypocalcemia and lymphocytosis, *i.e.*, a decrease in the concentration of calcium in the blood leads to the proliferation of the lymphocytic clone in the bone marrow, because it is not suppressed by calcium ions. However, according to new sources, hypercalcemia is observed in hyperthyroidism. Then how to explain lymphocytosis in hyperthyroidism? With hyperthyroidism, due to intensive metabolism, there is an intensive consumption of ATP and the concentration of phosphates in the blood increases hyperphosphatemia, which will contribute to the leaching of calcium ions from the bones, which will lead to an increase in the concentration of calcium in the blood, but this calcium binds to phosphates. That is, there is an increase in the concentration of total calcium in the blood, but not ionized calcium. And the concentration of the latter may even decrease relative to the total calcium concentration. And since the lymphocytic clone is affected most likely by ionized calcium, so a decrease in the concentration of the latter leads to lymphocytosis. But the further fate of calcium phosphates will depend on the functional capacity of the kidneys. With their normal functioning, calcium phosphates can be washed out of the body in the urine and the concentration of calcium in the blood will either remain normal or decrease. And with insufficient kidney function, the concentration of calcium phosphates may be increased. The same picture will be observed in Cushing's disease, *i.e.* an increase or decrease in the concentration of calcium in the blood will depend on the functional state of the kidneys. Apparently, this can explain that, according to some sources, in these diseases the concentration of calcium in the blood is increased, and according to others, it is decreased.

Let's return to hyperthyroidism diffuse toxic goiter. Let's pay attention to an-

other fact: with hyperthyroidism we have hyponatremia and leukopenia, as with Addison's disease (sodium ions are removed from the body and leukopenia is observed in the blood). In diffuse toxic goiter, with a mild form of the disease, the electrocardiogram reveals high R, P and T waves and a shortening of the P-Q interval. With increasing severity of the disease the size of the waves decreases, the T wave becomes biphasic and negative. The S-T segment falls below the isoelectric line [11]. Let's explain it this way. In a mild form of the disease, apparently, the concentrations of $Na^+$ and $K^+$ ions are still high, high R and T waves. After all, we know that the R wave is the entry of sodium $Na^+$ ions into the cell. So there's enough sodium initially to create a tall R wave. As for the T wave, it is known that the most characteristic ECG changes that are detected with hyperkalemia are tall, narrow, pointed positive T waves, and a decrease in intracellular potassium content leads to characteristic changes in the final part of the ventricular complex, a horizontal displacement of the RS-T segment below the isoline, a decrease in the amplitude of the T wave or the formation of a biphasic (−+) or negative T wave [22]. If we continue our line of thought, it turns out that with diffuse toxic goiter, as the severity of the disease increases, the concentrations of $Na^+$ and $K^+$ ions in the plasma, and $K^+$ also inside the cell, decrease. Indeed, if an excess of thyroid hormones promotes the removal of calcium and phosphate ions, then magnesium ions can freely leave the cell (due to the absence of their antagonists, calcium, in the blood plasma). Also, at the beginning of the disease, $K^+$ ions could freely leave the cells (high T waves as a result of hyperkalemia). Gradually, with increasing severity of the disease, the concentration of $Na^+$ and $K^+$ ions in the blood plasma decreases. The R and T waves become smaller. $K^+$ ions begin to freely leave the cell (there is no antagonist, $Na^+$ ions). Due to a decrease in the concentration of intracellular $K^+$, $Ca^{2+}$ ions will freely enter the cytoplasm from the sarcoplasmic reticulum. On the ECG, the ST segment will drop below the isoelectric line. We have a similar mechanism of displacement of the RS-T segment with an overdose of cardiac glycosides. With an overdose of cardiac glycosides, there is a release of $K^+$ ions from the cell and, conversely, an increase in the content of intracellular calcium $Ca^{2+}$. This leads to a trough-shaped displacement of the RS-T segment below the isoline, a transition to a biphasic (−+) or negative asymmetric T wave [22]. Here we will dwell a little on cardiac glycosides. It is known that the cardiotonic effect of cardiac glycosides is associated with their inhibitory effect on $Na^+$, $K^+$, ATP-ase of muscle fiber membranes, which leads to an increase in the intracellular content of sodium ions and a decrease in potassium ions. An increase in the intracellular concentration of sodium ions leads to an increase in its exchange with extracellular calcium ions, the flow of which into the cell increases. In turn, the latter apparently contributes to the release of additional amounts of calcium ions from the sarcoplasmic reticulum. In general, the content of free calcium ions in the sarcoplasm increases. They interact with the troponin complex and eliminate its inhibitory effect on myocardial contractile proteins. Actin interacts with myosin, which is

manifested by rapid and strong contraction of the myocardium [23]. However, it is known that the $Na^+$-$K^+$ pump exhibits its activity only in the 4-th phase of the transmembrane action potential, in the repolarization phase. Under the action of this pump, or $Na^+$, $K^+$, ATP-ase, $Na^+$ and $Ca^{2+}$ ions are removed from the cell, and $K^+$ ions enter the cell. At this point, *i.e.* in the 4-th phase of TMPD, the contractile cells of the myocardium are already contracted and in this phase they should relax and not contract. The 4-th phase on the ECG is reflected by the T-P segment, and the electrical systole of the ventricles is the Q-T segment [22]. During this segment, $Na^+$, $K^+$, ATP-ase should not be activated and there is no need to inhibit its pumping function. After all, when electrical systole occurs, *i.e.* contraction of the ventricles (Q-T segment), $Na^+$ and $Ca^{2+}$ ions already enter the cell, and $K^+$ ions are removed from it [22]. It turns out that if the mechanism of action of cardiac glycosides is really associated with their inhibitory effect on $Na^+$, $K^+$, ATP-ase, then cardiac glycosides do not just cause the heart muscle to contract. No. They prolong the process of contraction of myofibrils, preventing them from relaxing in time. That is, they only lengthen the electrical systole due to the later onset of the process of their relaxation, *i.e.* resting potential. This leads to their enhanced inotropic effect.

Now let's look at what happens with myxedema, hypothyroidism, *i.e.* what changes in the concentration of electrolytes and formed elements are observed in this pathology. In hypothyroidism, a deficiency of thyroid hormones leads to disruption of all types of metabolism: protein (decreased synthesis and breakdown of protein), carbohydrate (increased tolerance to carbohydrates, tendency to hypoglycemia), lipid (increase in the blood of $\alpha$- and $\beta$-lipoproteins and, especially, cholesterol), water-salt (retention of water and sodium chloride in tissues). Retention of water and sodium chloride, accumulation of mucoproteins in the connective tissue, which have pronounced hydrophilic properties, lead to the development of mucous edema [11]. Consequently, if $Na^+$ in the form of sodium chloride is retained in tissues, then the concentration of $Na^+$ in the blood decreases, *i.e.* with hypothyroidism we have hyponatremia. According to laboratory data, with hypothyroidism, in some cases, leukopenia occurs with relative lymphocytosis [11]. It can be assumed that the occurrence of leukopenia in hypothyroidism is associated with hyponatremia similar to the above in other diseases (diffuse toxic goiter, Addison's disease). To explain lymphocytosis, let us turn to electrocardiographic changes in hypothyroidism. The ECG reveals sinus bradycardia, low wave voltage, weakly expressed T and P waves, a decrease in the S-T interval below the isoelectric line, and a prolongation of the P-Q interval [11]. If, as mentioned above, a decrease in the S-T interval below the isoelectric line is associated with hypokalemia, hypocalcemia, the release of $Ca^{2+}$ ions from the endoplasmic reticulum into the cytoplasm, then, apparently, with hypothyroidism we have hypocalcemia. $Ca^{2+}$ ions are consumed to bind fatty acids and deposit them in body tissues. With hypothyroidism, the content of $\alpha$- and $\beta$-lipoproteins in the blood is increased, hypercholesterolemia is noted, and se-

vere atherosclerosis often occurs with the development of coronary heart disease. Disorders of the cardiovascular system are associated with interstitial edema of the heart muscle and a decrease in potassium content, which plays an important role in the metabolic processes of the myocardium [11] [24]. Thus, with hypothyroidism we have hyponatremia and, therefore, due to the reduced concentration of $Na^+$ ions in the blood the process of stimulation of the granulocyte series in the bone marrow is suppressed, which leads to leukopenia. A decrease in the concentration of $K^+$ and $Ca^{2+}$ ions in the blood leads to a decrease in the S-T interval on the electrocardiogram, but the consumption of $Ca^{2+}$ ions for the formation of salts with fatty acids leads to disruption of the process of inhibition of the lymphocytic clone in the bone marrow by $Ca^{2+}$ ions, and consequently, their increased proliferation and lymphocytosis.

With hyperparathyroidism, excessive production of parathyroid hormone occurs, which acts directly on the bones, leading to an increase in the activity of osteoclasts with the release of citric acid. The resulting local acidosis leads to the mobilization of phosphate and calcium from the bones into the blood. In addition, parathyroid hormone acts directly on the kidneys, suppressing the reabsorption of phosphorus in the renal tubules, which leads to increased excretion in the urine and a decrease in concentration in the blood. This entails a compensatory release of inorganic phosphorus compounds from the bones into the blood. By delaying the release of calcium by the kidneys, parathyroid hormone leads to hypercalcemia. The latter reduces neuromuscular excitability with the development of muscle hypotension. Often the early complaints of patients are severe weakness [11]. Apparently this can be explained as follows. With hypercalcemia, it is difficult for $K^+$ and $Mg^{2+}$ ions to leave the cell. They are mainly retained in the cytoplasm. This makes it more difficult for $Na^+$ ions to penetrate into the cell. If $Na^+$ ions do not penetrate the cell, this will lead to a decrease in neuromuscular excitability. On the other hand, the accumulation of $K^+$ and $Mg^{2+}$ ions in the cell prevents the free release of $Ca^{2+}$ ions from the sarcoplasmic reticulum. And the lack of $Ca^{2+}$ ions inside the cell leads to the development of muscle hypotension. Confirmation of this, *i.e.* a decrease in the intracellular concentration of calcium ions is a shortening of the Q-T interval on the ECG in hyperparathyroidism. In addition, it is possible that hypercalcemia leads to a compensatory (or competitive) removal of $Na^+$ ions (and possibly Cl ions due to the release of phosphorus ions from the bones) from the body in different ways, one of which is an increase in the acidity of gastric juice, resulting in peptic ulcers of various locations in hyperparathyroidism are often observed: first of all, the duodenum, then the stomach, esophagus and intestines [11]. Similarly, in Cushing's disease, when there is a release of $Ca^{2+}$ ions from the bones into the blood, *i.e.* hypercalcemia, stomach ulcers often form. On the contrary, with hypoparathyroidism, which is caused by insufficient production of parathyroid hormone, attacks of tonic convulsions are observed. Parathyroid hormone deficiency leads to a decrease in calcium levels in the blood serum, and this, in turn, leads to a

sharp increase in neuromuscular excitability [11]. The appearance of muscle cramps, spasms of the muscles of the stomach wall and smooth muscles of the intestines, spasms of the muscles of the larynx, etc., apparently can be explained as follows: a decrease in the calcium content in the blood leads to the free movement of $K^+$ and $Mg^{2+}$ ions from the cell into the blood, and therefore, to more free penetration of $Na^+$ ions into the cell, which will lead to increased neuromuscular excitability. On the other hand, the release of $K^+$ and $Mg^{2+}$ ions from the cell into the extracellular space will lead to an easier release of $Ca^{2+}$ ions from the sarcoplasmic reticulum into the cytoplasm and to the contraction of muscle cells, *i.e.* to spasms and muscle cramps. This is confirmed by the prolongation of the QT interval on the ECG in hypoparathyroidism.

## 3. Bacterial and Viral Infections

Before we move on to viral hepatitis, we will consider three more diseases: meningococcal meningitis, tuberculous meningitis and serous (aseptic) meningitis. With meningococcal purulent meningitis, "pleocytosis, predominantly neutrophilic (only with a sluggish process, perhaps a predominance of lymphocytes) is observed in the cerebrospinal fluid; the sugar content in the cerebrospinal fluid is sharply reduced." With tuberculous meningitis in the cerebrospinal fluid there is an "increase in protein levels to 1 - 5 g/l or more, moderate lymphocytic pleocytosis, and a decrease in glucose content". In serous or aseptic meningitis, mainly of viral etiology, there is "lymphocytic pleocytosis in the cerebrospinal fluid, the amount of protein is slightly increased (0.6 - 1 g/l), but may be normal, the glucose content in the cerebrospinal fluid is normal" [13]. With meningococcal purulent meningitis, cytosis is up to $10 \times 10^9$/l due to neutrophils, protein content is increased, sugar, chlorides are reduced [19]. Based on these data, is it possible to assume that during bacterial infections (meningococcus, tuberculosis bacillus) microorganisms mainly use glucose for their reproduction, therefore the concentration of glucose in these cases in the cerebrospinal fluid is reduced, and cells affected by the virus do not consume glucose, the glucose concentration in them is normal. Further, with tuberculous and viral meningitis there is lymphocytic pleocytosis. The concentration of lymphocytes increases in the blood with hypocalcemia and decreases with hypercalcemia. According to our assumption, calcium ions inhibit the proliferation of the lymphocytic clone in the bone marrow. Then, with tuberculous and viral meningitis, an increase in lymphocytes in the cerebrospinal fluid can be explained by a decrease in calcium concentration, apparently, both in the blood and in the cerebrospinal fluid. Then where does the calcium go? Apparently, if some microorganisms (meningococci) use mainly glucose as an energy source, others (tuberculosis bacillus, viral cells) use fatty acids as an energy source. And fatty acids can enter the cell in the form of calcium salts. It turns out that calcium is spent on binding with fatty acids used by microorganisms, the calcium concentration decreases and, consequently, the number of lymphocytes increases. In addition, the entry of glucose and

fatty acids into cells occurs with the participation of $K^+$ ions, *i.e.* their penetration into the cell [25]. Apparently, the penetration of $K^+$ ions into the cell facilitates the utilization of glucose and fatty acids by cells (the latter in the form of $Ca^{2+}$ salts). There is a decrease in the concentration of $K^+$ in plasma and extracellular fluid. But a decrease in the concentration of $K^+$ in the extracellular fluid and in the blood leads to inhibition of the formation of eosinophils in the bone marrow. Since it is known that in Cushing's disease we have hypokalemia and eosinopenia, and in Addison's disease we have hyperkalemia and eosinophilia, then, based on the latter, we can assume that in all infectious diseases (both bacterial and viral) at the onset of the disease there is a decrease in the concentration of $K^+$ in the blood, because potassium is used for intensive absorption of glucose and fatty acids by microorganisms. Therefore, with all infections (with the exception of infectious-allergic diseases), eosinopenia is observed at the onset of the disease and only upon recovery, when as a result of treatment microorganisms are killed, glucose and fatty acids are not consumed by them, $K^+$ remains in the blood and the number of eosinophils in blood begins to rise. Indeed, as the patient recovers, we have a picture of eosinophilia in the blood [26]. If we summarize the above, it turns out that meningococci mainly use glucose as an energy source for their growth and reproduction. Tuberculosis bacilli use glucose and fatty acids for these purposes. And cells affected by the virus use mainly fatty acids.

Another phenomenon, procalcitonin: procalcitonin is a precursor to the thyroid hormone calcitonin. An increase in procalcitonin levels occurs during bacterial infections. But it does not increase during viral infections. Procalcitonin (calcitonin) reacts to the concentration of $Ca^{2+}$ ions in the blood. When calcium in the blood increases, calcitonin (its precursor, procalcitonin) is synthesized. However, if during viral infections, unlike bacterial ones, the level of procalcitonin does not increase (or increases only slightly), then can it be assumed that during viral infections there is hypocalcemia. A decrease in the level of calcium in the blood leads to a disruption of the inhibitory effect of calcium on the lymphocyte clone in the bone marrow and, consequently, their proliferation. Indeed, lymphocytosis is often observed with viral infections. On the other hand, if we ask ourself: why does the concentration of calcium in the blood decrease during viral infections? Is it spent on binding with fatty acids and forming salts with them? Then this fact can further confirm our assumption that cells affected by the virus use (mainly) fatty acids as an energy source, which enter these cells in the form of their calcium salts.

In viral hepatitis in hepatocytes, as in all inflammatory processes, a picture of hypoxia is observed. They accumulate pyruvic acid, which does not enter the Krebs cycle. Since, during viral hepatitis, the enzymes $LDH_4$ and $LDH_5$, which were supposed to convert pyruvic acid into lactic acid, are removed from the cells, pyruvic acid accumulates in them, which is removed from the cell in the form of magnesium pyruvate salts. Consequently, if magnesium lactate is not formed in hepatocytes, then red blood cell adhesion will not occur. And, indeed,

with viral hepatitis, as with other viral infections, ESR remains within normal limits. In addition, during viral infections, the flow of leukocytes to the site of inflammation is inhibited. Let's try to explain why in viral hepatitis, and possibly in other viral infections, the enzymes $LDH_4$ and $LDH_5$ are removed from cells, and why in viral infections the flow of leukocytes to the site of inflammation is inhibited?

To do this, we can remember the following. During glycolysis in the third reaction, the resulting fructose-6-phosphate is again phosphorylated due to the second ATP molecule. The reaction is catalyzed by the enzyme phosphofructokinase. This reaction, like the hexokinase reaction (the first reaction of glycolysis), occurs in the presence of magnesium ions and is the slowest reaction of glycolysis. Phosphofructokinase is inhibited by ATP and stimulated by ADP and AMP. Phosphofructokinase activity is also inhibited by citrate. It has been shown that in diabetes, fasting and some other conditions, when fats are intensively used as a source of energy, the citrate content in tissue cells can increase several times. Under these conditions, a sharp inhibition of phosphofructokinase activity by citrate occurs [10]. This means that if citrates are formed during the destruction of fats, then during fasting, when a person already receives a reduced amount of carbohydrates, inhibition of the phosphofructokinase enzyme by citrate will lead to less use of carbohydrates, *i.e.* glucose, which already enters the body in small quantities and the body thus retains this small amount of glucose, preventing it from being completely used up. And in diabetes mellitus, when glucose accumulates in the body in large quantities, because it cannot be utilized by cells, inhibition of the phosphofructokinase enzyme by citrate leads to the accumulation of even more glucose in the cells, which, after leaving the cells, further increases its concentration in the blood. So, if we inhibit citrate, perhaps it will be possible to help the body turn on glycolysis and thereby, to some extent, reduce the level of hyperglycemia in the blood? Perhaps this can explain the effect of meldonium? Indeed, perhaps the disruption of citrate formation during inhibition of the breakdown of fatty acids can explain the effect of meldonium in diabetes mellitus and myocardial infarction? It is known that in the human body carnitine is synthesized from $\gamma$-butyrobetaine. Meldonium is a structural analogue of $\gamma$-butyrobetaine and therefore can inhibit the enzyme $\gamma$-butyrobetaine hydroxylase (gamma-butyrobetainedioxidase), responsible for the synthesis of carnitine. Meldonium also reduces the absorption of exogenous carnitine in the small intestine (from food, drinks, etc.) due to its competitive effect on a specific protein, the OCTN2 transporter (organic carnitine cation transporter 2). As a result, the concentration of carnitine in the body decreases and the process of transfer of fatty acids through the mitochondrial membranes of heart cells slows down (carnitine acts as a carrier of fatty acids in this process). Simultaneously with the slowdown in fatty acid metabolism, the rate of carbohydrate metabolism (glycolysis) increases. In addition, as explained, meldonium itself promotes the activation of glycolysis, enhancing the expression of hexokinase, which catalyzes the conversion of glucose into glucose-6-phosphate [27]. However, in our

opinion, perhaps, citrate really is not formed and, as a result, the enzyme phosphofructokinase is not inhibited and therefore glycolysis proceeds normally?

Thus, if during the breakdown of fats citrates are formed, which inhibit phosphofructokinase, inhibition of glycolysis occurs, then during viral infections, if our assumption is that viruses mainly use fatty acids as an energy source, there will indeed be a decrease in the activity of glycolysis (and, possibly, complete inhibition of the glycolysis process) and in cells affected by viruses, pyruvic acid, and, consequently, lactic acid will not be formed. Then, during viral infections, due to inhibition of the glycolysis process, LDH enzymes will be unnecessary for the cell and these enzymes, possibly as a result of changes in the pH of the cytoplasm in the absence of pyruvic and lactic acids will be removed from the cell. Indeed, with viral hepatitis, there is an increase in $LDH_4$ and $LDH_5$ in the blood. It is these isoenzymes that are contained in hepatocytes and normally glycolysis occurs intensively in them, which is sharply inhibited when these cells are damaged by viruses. Then, what happens in red blood cells during viral infections? There are no mitochondria in erythrocytes and, therefore, in them, both normally and in any pathology, the breakdown of fatty acids does not occur at all, *i.e.* in erythrocytes, citrate is not formed at all. Anaerobic glycolysis occurs intensively in erythrocytes. Thus, during viral infections, especially those that contain neuraminidase, and with the help of which, probably, fatty acids enter the cell (which we will talk about a little later), the breakdown of the latter in these cells will not occur. In red blood cells, citrates are not formed and the phosphofructokinase enzyme will not be inactivated. Consequently, even when viruses are adsorbed onto erythrocytes, glycolysis will proceed in the usual way in the latter and pyruvic acid will accumulate in them, which, in the form of magnesium pyruvate salt, having left the cell, will prevent their adhesion (ESR is not increased in viral infections), as well as inhibit leukocyte clone in the bone marrow (leukopenia due to viral infections). Preventing the adhesion of red blood cells during viral infections will be facilitated not only by magnesium pyruvate from the red blood cells themselves, but also by the absence of the formation of magnesium lactate in other cells affected by the virus (as mentioned above, in such cells glycolysis is sharply inhibited). This is how we can explain leukopenia or the normal concentration of leukocytes in the blood and normal ESR during viral infections.

As to leukocytes in viral infections, in leukocytes, if we take into accounts that $LDH_4$ and $LDH_5$ predominate among the isoenzymes, we can assume that glycolysis mainly occurs, both aerobic and anaerobic. After all, leukocytes are cells that must quickly respond to any changes in the body and, apparently, glycolysis in them must proceed more intensely than the breakdown of fatty acids. So, during viral infections, when a virus collides with a leukocyte, the virus, having penetrated the leukocyte, can lead to the breakdown of fatty acids, even if they are present in them in small quantities. When fatty acids break down in leukocytes, citrate is formed, which inhibits phosphofructokinase and glycolysis in the leukocyte stops completely. In addition, it is possible that the mitochondria of

leukocytes, like nerve cells, contain fewer enzymes involved in the oxidation of fatty acids and amino acids [10]. Then, when leukocytes are damaged by viruses, even if a minor process of fatty acid oxidation takes place and citrate is formed, which inhibits glycolysis and, in addition, the mitochondria of leukocytes do not have sufficient enzymes for the oxidation of fatty acids (and amino acids), then the leukocyte will simply die. Perhaps this is also the reason for the decrease in the number of leukocytes in the blood during viral infections.

Let's continue the topic of viruses and talk a little about hemagglutinin and neuraminidase enzymes that some viruses contain. For example, the influenza virus contains both hemagglutinin and neuraminidase, while the measles virus causes both hemagglutination and hemolysis of red blood cells. Rhinoviruses do not contain hemagglutinin and do not cause hemagglutination or hemolysis of red blood cells. Neither hemagglutinins nor hemolysins have been identified in Marburg (Ebola) viruses [19]. In addition, it is known that red blood cell agglutination is not stable. That is, if during viral infections, regardless of the presence or absence of hemagglutinins and neuraminidase, there is no increase in ESR, then despite the fact that hemagglutinin causes agglutination of erythrocytes these enzymes do not affect the erythrocyte sedimentation rate. It is known that neuraminidase helps viral particles penetrate through mucosal secretions rich in sialic acid to reach target cells by virions and also facilitates the release of newly formed viral particles from the surface of infected cells. However, in our opinion, these enzymes may also play another role. It is known that hemagglutinin attaches to polysaccharide chains on the surface of red blood cells containing sialic acid residues. And neuraminidase specifically cleaves off the sialic (N-acetylneuraminic) acid residue from the polysaccharides of the erythrocyte membrane, thereby destroying the receptors for the virus on the cells of the host body. But it is also known that N-acetylneuraminic acid binds calcium macromolecules to tissue cells [28]. In this case, if the latter promotes the binding of calcium macromolecules to tissue cells, perhaps the neuraminidase of viruses, having contacted N-acetylneuraminic acid of the cell, when the virus penetrates into the latter, will facilitate the entry of fatty acid salts with calcium ions into this cell for the use of fatty acids by this cell as a source of energy. Neuraminidase is part of the envelopes of some viruses, and it is also found in the culture of the causative agent of gas gangrene, Clostridium perfringens and in Vibrio cholerae. Vibrio cholerae contains neuraminidase. If neuraminidase promotes the entry of calcium ions with macromolecules, then we must remember that in cholera, vibrio forms a choleragen-specific receptor complex that activates adenylate cyclase, and the latter, in turn, catalyzes the production of cAMP, which, through an ion pump, increases the secretion of water and electrolytes from cells into the intestinal lumen. This secretion contains the following electrolytes, $Na^+$, $K^+$, $Cl^-$ and bicarbonates [19]. However, $Ca^{2+}$ is not secreted from cells into the intestinal lumen. Apparently, $Ca^{2+}$ actually enters cells with the help of neuraminidase, and together with macromolecules. Apparently, calcium ions bound by macromolecules are not capable of exerting a spastic effect on cells and therefore

there is no pain or tenesmus with cholera, despite the loss of other electrolytes, in particular $K^+$ ions. This is for a mild form of cholera. In the moderate form, isolated cramps appear, and in severe forms, patients are bothered by muscle cramps in the extremities (calf muscles, fingers, abdominal muscles). These latter phenomena can be explained by the release of calcium ions from the endoplasmic reticulum as a result of the loss of large quantities of potassium ions by the cell. Neuraminidase has not been found in plants. Regarding hemagglutinin, plants contain phytohemagglutinin (PHA). This is a plant-derived lectin protein, or legumin. PHA includes two proteins: leukoagglutinin L-PHA (PHA-L), which agglutinates leukocytes, and R-PHA (PHA-E), which agglutinates erythrocytes. PHA (Lectin) induces mitosis and affects the cell membrane, increasing protein transport and membrane permeability to proteins. It agglutinates most mammalian red blood cells regardless of their blood type [29]. Is it possible to assume that viral hemagglutinin also promotes enhanced penetration of proteins into cells affected by the virus? After all, proteins are necessary for the replication of viruses and the creation of a viral shell. By the way, rhinoviruses do not contain hemagglutinin and they lack a lipoprotein envelope [19].

With most viral infections we have a normal ESR and leukopenia (or normal white blood cell count). However, with some viral infections, such as rhinovirus, leukocytosis is observed. How to explain this? Let's try to explain it this way. With influenza, for example, the release of mature viral particles is often accompanied by cell death. In these cases, the nucleic acids of the affected host cell seem to be destroyed, which, in our opinion, should lead to the formation of sodium urates. But in influenza, unlike rhinovirus infection, when the virus replicates, the influenza virus appears to completely use the nucleic acids of the host cells for its replication, without leading to the destruction of nucleic acids. Therefore, with influenza there is no leukocytosis, and with rhinovirus infection, apparently, replication of rhinoviruses occurs with incomplete use of host nucleic acids and destruction of nucleic acids is observed as a result of the death of host cells with the formation and accumulation of sodium urates in the blood, leading to stimulation of the leukocyte clone of the bone marrow and, consequently, leukocytosis. That is, although red blood cells produce magnesium pyruvate, which should suppress the leukocyte clone of the bone marrow and lead to leukopenia, due to the breakdown of nucleic acids of host cells affected by the virus and the formation of sodium urates, the latter stimulates the leukocyte clone, which leads to leukocytosis.

Thus, if the idea about the connection between the concentration of calcium ions in the blood and the number of lymphocytes in the blood is correct, and also if, in fact, during viral infections, as mentioned above, there is an intensive breakdown of fatty acids and inhibition of glycolysis, and meldonium prevents the oxidation of fatty acids due to inhibition of the synthesis of carnitine, which was supposed to transfer fatty acids to mitochondria, then is it possible to assume that meldonium, by inhibiting the breakdown of fatty acids and inducing glycolysis, may lead to certain changes in the cell affected by the virus and the

elimination of viral particles from it?

And finally, let's consider the intracellular interaction of $K^+$, $Ca^{2+}$ ions and phosphoric acid residues. What exactly promotes the release of $Ca^{2+}$ ions from the endoplasmic reticulum? To do this, let's look at how inositol triphosphate acts on the removal of $Ca^{2+}$ ions from the endoplasmic reticulum. It is known that phospholipase C, like phospholipase D, belongs to phosphodiesterases. Phospholipase C hydrolyzes the phosphodiester bond between the glycerol moiety of the phospholipid (from the cell membrane) and the polar phosphate group. Phospholipase C hydrolyzes phosphatidylinositol into two secondary mediators, inositol triphosphate and diacylglycerol. These two mediators take part in signal transmission in the cell. Inositol triphosphate interacts with the $Ca^{2+}$ channels of the endoplasmic reticulum membrane, resulting in the release of $Ca^{2+}$ ions from the endoplasmic reticulum. Inositol is a hexabasic cyclic alcohol. Three of the five hydroxyl free groups on the inositol ring at positions 3, 4, and 5 can be phosphorylated by kinases. The substrate for these signaling molecules is phosphatidylinositol. And positions 2 and 6 are obviously inaccessible to these enzymes due to steric hindrance. So, phosphorylated inositol leads to the release of $Ca^{2+}$ ions from the endoplasmic reticulum. But let us pay attention to the fact that signaling kinases phosphorylate inositol, *i.e.* phosphate residues are not free in the cytoplasm. On the other hand, it is known that nitric oxide, originating from the vascular endothelium, stimulates guanylate cyclase, which catalyzes the conversion of guanosine triphosphate into cyclic guanosine monophosphate (cGMP), and cGMP initiates phosphorylation of protein kinases, resulting in a decrease in the content of calcium ions in the cytosol and relaxation of vascular smooth muscle cells of arteries and venules [30]. If in the latter case, phosphorylation of protein kinases inhibits the release of $Ca^{2+}$ ions into the cytosol, then why does phosphorylation of inositol lead to the release of $Ca^{2+}$ from the endoplasmic reticulum into the cytoplasm? After all, in both cases, phosphoric acid residues are associated with secondary signal transmitters (mediators, or kinases) and there are no free phosphoric acids or their active residues in the cytoplasm? In addition, it is known that sympathomimetics activate bronchial $\beta_2$-adrenergic receptors and the associated adenylate cyclase, which leads to an increase in the intracellular content of cAMP (in turn, this reduces the concentration of calcium ions inside the cells) and a decrease in the tone of bronchial smooth muscles. Substances that block the cholinergic innervation of the bronchi, especially m-anticholinergic blockers, also have bronchodilator properties. In this case, the bronchodilator effect is associated with a decrease in cGMP content [23]. Consequently, in the case of m-anticholinergic blockers, phosphorylation of secondary signal messengers (kinases) does not occur and phosphoric acid residues either do not accumulate in the cytoplasm at all, or they are associated with some other cations. Acetylcholine inhibits guanylate cyclase by binding to $M_2$ or $M_4$ muscarinic receptors [31], thereby leading, on the one hand, to the dilation of blood vessels, and on the other hand, to an increase in the tone and contractile activity of the muscles of the bronchi, digestive tract,

etc. [23]. If acetylcholine, similar to m-anticholinergic blockers, inhibits guanylate cyclase, then phosphorylation of the kinases does not occur. However, when acetylcholine acts on blood vessels, calcium ions apparently do not enter the cytosol, which leads to their expansion, while when acetylcholine acts on the muscles of the bronchi and digestive tract, calcium ions enter the cytosol, leading to their contraction. How can we explain all this? If we remember the above about the connection and formation of potassium phosphate salts (or rather, the intracellular phosphate buffer system), it may be possible to assume that phosphate groups, combining with protein kinases, inositol triphosphate or any other secondary messengers, lead to the accumulation of potassium ions in the cytoplasm. An increase in the concentration of potassium ions in the cytoplasm, as mentioned above, can lead to inhibition of the release of calcium ions from the endoplasmic reticulum, as, for example, in the case of NO or $\beta_2$-adrenergic receptors. When guanylate cyclase is inhibited, for example, when the latter is exposed to m-anticholinergic blockers or acetycholine on blood vessels, apparently, phosphoric acid residues do not accumulate in the cytoplasm at all, the concentration of $K^+$ ions in the cytoplasm does not decrease, which leads to inhibition of calcium channels in the membrane of the endoplasmic reticulum. But in cases with inositol triphosphate, when phosphate residues are associated with the latter, potassium ions accumulated in the cytoplasm begin to be removed from the cell, which leads to the free release of calcium ions from the endoplasmic reticulum. A similar picture should be observed when acetycholine acts on the muscles of the bronchi and the muscles of the digestive tract.

## 4. Conclusions

Summarizing the above, according to our ideas, the effect of electrolytes and their salts on the amount of formed elements in the blood can be briefly presented in the following form:

1) $Na^+$ ions in the form of sodium salt of uric acid affect the myelocytic clone of the bone marrow and lead to stimulation of the production of leukocytes and an increase in their concentration in the blood, leukocytosis. Conversely, a decrease in the concentration of $Na^+$ ions in the blood leads to leukopenia.

2) $Ca^{2+}$ ions suppress the lymphocyte clone of the bone marrow and lead to a decrease in the number of lymphocytes in the blood, lymphopenia. A decrease in the concentration of $Ca^{2+}$ ions in the blood removes the inhibitory effect of the latter on the lymphocytic clone, leading to lymphocytosis.

3) $K^+$ ions stimulate the eosinophilic clone, leading to an increase in the number of eosinophils in the blood, eosinophilia. Conversely, a decrease in the concentration of $K^+$ ions in the blood leads to eosinopenia.

4) An increase in the concentration of $Mg^{2+}$ lactate in the blood leads to the gluing of red blood cells and an increase in ESR.

5) $Mg^{2+}$ pyruvate protects red blood cells from gluing, inhibits the increase in ESR, giving red blood cells the opportunity to freely transport gases. In addition,

$Mg^{2+}$ pyruvate can suppress the myelocytic clone in the bone marrow, leading to leukopenia.

6) The accumulation of pyruvate $Ca^{2+}$ in the cytoplasm of cells leads to the destruction of the membranes of the cell nucleus, as well as the membranes of $\alpha$-granules and dense granules in platelets.

Thus, summarizing everything stated in the article, according to our assumptions, electrolytes and their salts should play a greater role in various functions of the body than is currently known.

We hope that our assumptions will be correct and will help clinicians in making or confirming the diagnosis of various diseases in the future. We ourselves have relied on them more than once and, quite successfully.

## Conflicts of Interest

The authors declare no conflicts of interest.

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