Efferent therapy

Therapeutic plasmapheresis

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Reviewer:
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The book provides pathogenetic substantiation of efferent therapy and indications to it in various types of acute and chronic diseases. There are shown advantages of membrane plasmapheresis.

The book is intended for both, specialists in efferent therapy and doctors of other specialties.
Professor V.A. Voinov is an old friend of ours and a partner in implementing the project of “KONKOR Group” - introduction of progressive medical technology of membrane plasmapheresis in Russia. Medicine of XXI century implies using methods activating the strength of the organism itself with minimal external interference. In this respect efferent therapy has no alternative, and you will find a lot of proofs to it in the book of V.A. Voinov.

“TRACKPORE TECHNOLOGY Corporation”, the company-member of “KONKOR Group”, started implementation of our common great project in 1998 having begun with the construction of the plant producing plasmafilters on the basis of track membranes. Currently the scientific and production complex “ALFA” in Dubna, Moscow region, operates at full capacity – up to million plasmafilters a year and more than 1000 devices for performing plasmapheresis procedures.

We have started the second part of the project – creation of the net of efferent therapy centers in Moscow region and all over Russia, which will contribute to the health of millions of Russian people. I have no doubt that “ROSA” and “HEMOFENIX” will become national brands symbolizing health.

Our company is an active participant of the national Project in the sphere of healthcare. Within 10 years of the company’s experience in the market, our products gained popularity not only in our country, but also far beyond it – in Ukraine, Moldova, Kazakhstan and Tadzikistan, Armenia and Azerbaijan. In Uzbekistan, towns Navoiy and Zaravshan, apart from our partner, Navoiy Mining and Metallurgical Plant, there have been created and now are operating 5 centers of efferent therapy. The work is also being done in India and China.

In the process of developing plasmafilter “ROSA” and device “HEMOFENIX” took part hundreds of scientists from Joint Institute of Nuclear Research in Dubna, Scientific research institute of electrophysical equipment in Saint-Petersburg, Scientific research institute of pulmanology of St. Petersburg State I.P. Pavlov Medical University and other leading scientific and medical organizations. Thus “TRACKPORE TECHNOLOGY Corporation”, having combined all the achievements of native scientific idea, high tech potential and private Russian funds, has started socially-oriented business. The business which not only brings profit to its shareholders, but also improves people’s health. We have made a long way of transferring plasmapheresis from expensive, seldom dedicated procedure to mass and affordable method of health improvement and organism rejuvenation.

Therapeutic plasmapheresis is known to successfully supplement traditional methods, in many cases substituting pharmaceutical treatment, and in some cases being the only possible option for life saving, which was successfully confirmed by experience of our doctors in Ministry of emergency situations after an earthquake in Pakistan, China.

Donor plasmapheresis is a possibility to receive large amount of blood plasma quickly and cheaply, and to process it, which will contribute to revival of the Blood Service in Russia that was almost destroyed during the last decade. Blood is a strategic recourse, guaranty of saving many people’s lives in emergency situations.

We are looking to cooperate with representatives of medical organizations ready to introduce high tech achievements to their medical practice. Each medical institution, having a room for plasmapheresis,
receives an opportunity to make quantum leap in the treatment of patients and provide effective paid services to the population. Investments to the efferent therapy centers delivered by “TRACKPORE TECHNOLOGY Corporation” ready-to-operate and supported with all consumable materials, according to the experience, pay their way within a year.

Nation’s health is a colossal energy, the power capable of transforming Russia to the great country. None of natural recourses can solve the problem themselves. That is why maintenance and strengthening of health is both the matter of human himself and a problem of state. And at the same time is the sphere of business interests.

V.M. Kononov
Chairman of the Board of Directors,
“KONKOR Group”
Valery A. Voinov – Doctor of Medicine, Professor, Head of Efferent Therapy Department, Scientific research institute of pulmonology of St. Petersburg State I.P. Pavlov Medical University. He is the author of more than 300 scientific papers, 22 inventions and patents. Sphere of his scientific interests includes studying of the problems of endotoxicosis and efferent therapy, including pathogenesis and principles of treatment of respiratory distress syndrome and multiple organ failure, pathogenesis of fetal development disorders and methods of newborns rehabilitation at preeclampsia, hidden genital infections, Rhesus-conflicts and autoimmune diseases of pregnant women, pathogenesis and treatment of different types of allergies and autoimmune diseases, pathogenesis and prevention of premature aging. Valery Voinov participated in creating the first domestic plasma filters PFM-800 as well as plasma filter of new generation PFM-TT “ROSA” and development of devices and methods of membrane plasmapheresis and their introduction in medical institutions of Russia. Now he is focusing his efforts on development of new membrane plasma filters, devices and methods of cascade plasmapheresis.
PREFACE

The reason for writing this book became an increasing conviction that in a variety of acute diseases with the development of multiple organ failure, the main causes of severe conditions and failures is endotoxicosis - the accumulation of various toxic products, without the removal of which neither a body, nor a surgery, nor the most effective medication and intensive care measures can lead to a cure.

On the other hand, in case of a huge number of chronic human diseases, their chronicity and severity of organ lesions are also based on the accumulation of toxic metabolites, mainly autoantibodies. Applied immunosuppression methods (steroids, cytotoxic agents, etc.) themselves cause severe side effects that require additional treatment measures.

And for many years in all these diseases, different in many respects, there are applied methods of efferent therapy based on removal from the body of what the organism cannot remove itself (kidneys cannot remove such large molecules, liver cannot destroy).

However, unfortunately, far not all experts share this opinion and the author's main objective was to justify the need in this efferent therapy for various diseases and their complications.
LEGEND

BAS – biologically active substances.
VILF – volume of intravascular lung fluid.
DIC - disseminated intravascular coagulation.
AR – artificial respiration.
CPV - circulating plasma volume.
MPC - maximum permissible concentration.
RDS - respiratory distress syndrome.
TMP – transmembrane pressure.
UBI - ultraviolet blood irradiation.
CIC – circulating immune complexes.
ECMO – extracorporeal membrane oxygenation.

FiO₂ – concentration of oxygen in inspired mixture.
Ht – hematocrite (blood cells volume).
Ig - immunoglobulins.
IL - interleukins.
PaO₂ - arterial oxygen tension.
TNF-α - tumor necrosis factor - α.
INTRODUCTION

Plasmapheresis is one of the forms of efferent therapy intended to eliminate from the organism various pathological products (the Latin *efferens* - elimination). These methods existed in ancient times already – use of diuretics, emetics, purgatives, choleretics, diaphoretics.

In the past, rather popular was such a form of efferent therapy as **bloodletting** which apart from eliminating excessive circulating blood volume (CBV) released the organism from toxic elements. Even barbers were allowed to perform it. However, even in hands of experienced doctors this method was not deprived of hazards, so much the more the history knows the cases of failures of such procedure.

More safe method of efferent therapy is the removal of not the whole blood, but of its liquid part – plasma, components of which are the main carriers of pathological products in the organism, what’s more, it is restored much quicker than blood formed elements. This particular method is called **plasmapheresis** (from the Greek πλάσμα - plasma, **liquid part of blood**, and ἀφαίρεσις - aphairesis, taking away). In this context "*aphairesis*" is from the Greek “removal”.

Hippocrates himself wrote that “*medicine is addition and withdrawal. Withdrawal of everything that is superfluous; addition of the missing. And the one, who does this best, is the best doctor*”.

Nevertheless, the most popular methods of contemporary medicine are intended mainly to introduce into the organism of various drug preparations that are far from being harmless, but the number of which is continuously growing. Development of efferent therapy methods was hindered by lack of simple, cheap and accessible devices, and only during the last decade successes of membrane technology allowed to draw them nearer to the wide medical practice. What contributed most to it in Russia was creation of plasmaphilter “ROSA” and device for membrane plasmapheresis “HEMOFENIX” developed by the Russian company “TRACKPORE TECHNOLOGY Corporation” and produced in Dubna, Moscow region.

The work aims to give more complete substantiation of efferent therapy indications in various acute and chronic diseases.
INTERNAL ENVIRONMENT OF THE HUMAN AND MECHANISMS OF ITS REGULATIONS

Human, like any biological entity, is in constant contact and interaction with the environment. Life is a constant process of metabolism both within the body, and with environment, absorption of oxygen and release of carbon dioxide, water and food intake and excretion of end products of metabolism. The very existence of the organism depends on the ability of constancy maintaining within certain limits of its internal environment.

During thousands of years of evolution there were perfected mechanisms of autoregulation of internal environment - homeostasis and protection against aggressive influences both from outside, and from poisonous and toxic substances, and microbial-viral contamination. But during the process of own metabolism as well, there are formed relatively toxic intermediate and final products of metabolism, which are subject to slow inactivation or removal. Therefore, formed a complex and multi-stage system of protection and correction of the internal environment. It consists of three main components:

1. Microsomal monooxygenase system of liver detoxification.
2. Immune system
3. Excretory system.

Hundreds of thousands of foreign compounds - xenobiotics - always get to the body from outside. The main liposoluble toxic substances undergo biotransformation during the process of digestion in intestine, from which by portal vein they can not bypass liver, where due to oxidation and enzymatic processes they finally convert into non-toxic water-soluble compounds, which are further metabolized in all organs and tissues.

Liver is a barrier not only for exogenous, but also for endogenous toxic compounds, constantly arising during the process of metabolism - synthesis of some and decay of other substances: lactate and pyruvate, urea and creatinine, ammonia and fatty acids, aromatic amino acids, alcohols and aldehydes, phenols and ketones, products of proteolysis and hydrolysis, activity of automicroflora and viruses, etc.

Immune system, in its turn, consists of three components: the central organs (thymus and bone marrow), lymphoid structures scattered over the body (spleen, lymph nodes), and immunocompetent cells.

There are the following parts of the immune system: recognition of foreign substances - antigens, phagocytosis, a cooperative function of T-lymphocytes and antibody production, interaction of antibodies with antigen and of complement with immunoglobulins and target cells. There are physical and chemical processes occuring: reception, immune adhesion and adsorption.
Interaction of antibodies with antigen is an adsorption process of forming the **immune complex** "antigen + antibody + complement". It is retained in the lymphoid tissue, phagocytized and degraded by lysosomal enzymes. Natural serum factors - opsonins - promote adherence of microorganisms, dead cells and their fragments ("detritus") to the plasma membrane of phagocytes (monocytes, neutrophils), increase the velocity of phagocytosis. It should be borne in mind that in case of depletion or absence of opsonins of complement, even normal phagocyte is not capable of capturing the bacteria, so defects in humoral immunity entails failure and cell-phagocytic defense mechanism.

But humoral immunity depends on the cell immunity as well, since T-cells are required for both, start of antibody forming by B-lymphocytes, and regulation of this process. In particular, T-helper cells (CD4) stimulate production of antibodies, and T-suppressor (CD8) inhibit this process, and, depending on the relations between the two subclasses (CD4/CD8), there are possible hyperimmune reactions and immunosuppression.

The task of the immune system also includes a struggle not only with food of foreign origin, but also with those arising within the body, including ever-emerging abnormal cells, which include tumor ones. Here also works a mechanism of a "friend or foe" reaction, and own cell with anomalous properties is destroyed along with the foreign ones by natural killer cells (T-killers) and other macrophages.

All final products of own metabolism and degradation of foreign substances, require removal from the body. The structure of **excretory system** consists of four components: kidneys, gastrointestinal tract, lungs, sweat and sebaceous glands of skin.

**Kidneys** remove water (1.5-2 liters a day) and dissolved urea, creatinine, potassium, sodium, chloride, calcium, magnesium, sulfates, phosphates. In addition, kidneys eliminate water-soluble products of biotransformation xenobiotics, products of proteolysis of immune complexes, remains of bacteria, viruses, protozoa, fungi digested by phagocytes, and substances spontaneously transformed into foreign substances.

**Gastrointestinal tract** eliminates lipids, cholesterol, bile acids, steroids, bilirubin, water, food debris, nonviable microbial body unabsorbed xenobiotics.

Through **lungs** there are removed carbon dioxide, water, volatile xenobiotics (ethanol, ether, etc.).

Sweat and sebaceous glands of **skin** derive water (400-600 ml), sodium, potassium, calcium, magnesium, phosphorus, chloride. Also urea, creatinine in case of uremia; in diabetes - glucose; in hepatic failure - ammonia, bile acids; in poisonings - mercury, arsenic, iron, iodine, bromine, quinine, benzoic acid, succinic and hippuricacid, salicylates, salol, antipyrine, methylene blue, etc.
Ecology and homeostasis

That is not to say that earlier it was "well". Even in Garden of Eden environment was not probably really clean. However, civilization in all its benefits and achievements has brought in a lot of anthropogenic pollutions growing from year to year. Every year millions of tons of nickel, arsenic, cadmium, silicon, cobalt and zinc are emitted to the atmosphere. It is polluted with oxides of carbon and nitrogen, sulfuric anhydride and sulfuric acid, sulfates, etc.

Tens of thousands of toxic or at least unnecessary substances are constantly penetrating to the human body through food, water, air. These are products of "household" chemicals, chemicalization of agriculture (pesticides, insecticides, defoliants, chemical fertilizers), products of tobacco smoke, transport and industries fumes, alcohol, drugs, even medicines, including antibiotics and hormones fed to domestic animals and contained in their meat.

To an even greater extent this is applied to large industrial centers. Usually the maximum permissible concentrations (MPC) of toxic compounds are established for a workplace, considering that within the rest of a plant, not to mention sites outside it, there should not be any of these products at all, but in our practice multiple excess of MPC is usual not only inside plants themselves, but also outside.

It should be noted that about 30% in the structure of atmospheric pollution of residential areas make toxic exhaust fumes of motor vehicles, which is not uncommon even for the suburbs and recreation areas.

Water purification system, though with difficulty, but is capable of maintaining satisfactory titers of microorganisms, but purification from harmful chemical substances, including oxides and salts of heavy metals, is far from being perfect. Food does not always comply with environmental regulations.

There is another aspect of human relationship with the environment, and this problem arose back in ancient times, when people began to build houses, depriving themselves of the opportunity to breathe the outer air. The latter, in addition to the oxygen necessary for life, contains so-called atmospheric electricity in the form of negatively charged ions resulting from thunderstorm electrical discharges in the atmosphere and other natural phenomena. The whole evolution of living beings proceeded in such ionized air, and all internal metabolic processes also formed on the basis of electrical phenomena - transfer of nerve impulses, muscle contraction, and metabolism - transfer of molecules across biological membranes. Everywhere the leading role played the potential difference, which causes some substances to move into the cell, others - out.

When breathing, negative air ions charge the walls of airways with negative potential and, proceeding from them, quickly reach the alveoli. All body fluids are electrostatic colloids and carry a negative charge. Blood, enriched with air ions, washes
all tissues and cells, providing them with a negative charge and sol condition of their cytoplasm, which is essential for optimal metabolism. Reduction of electric negative potential of cell membranes leads to their "electrical discharge" with sol-gel transition of colloidal state of the cytoplasm, which contributes to their coagulation with sharp violation of metabolism.

Membranes themselves also have a certain electrical charge. Moreover, the blood is a rather dense mass of cells that should not stick together, create cell aggregates or conglomerates that would immediately plug the small vessels, and life within the body would stand still. This does not happen only because each such a cell also carries a negative electrostatic charge, which contributes to their mutual repulsion. Therefore, not only oxygen, but also electricity are needed for life provision in inhaled air. In the same way as breathing in oxygen, people exhale carbon dioxide, and breathing in negative ions, people exhale positive ions.

Negative ions are formed as a result of capturing free electrons by the molecule of oxygen, the peripheral shell of which contains 6 electrons, and seeks to acquire stability by capturing two more electrons, which transforms a neutral molecule to the negatively charged ion. Positive ion is formed mainly from carbon dioxide, when its molecule loses one of the valence electrons [V.P. Skipetrov et al, 1995].

Inside houses the number of these negative ions is much smaller, especially in crowded places. But outer air is not always rich enough with negative air ions. In village, mountain and sea air there are about 1,000 negative ions per 1 cc of air. In many sanitaria their number reaches 10,000, and near waterfalls – 100,000. In city air the number of ions does not exceed 500, indoors - 50-100, and in smoky and overcrowded places negative ions may disappear entirely, which will have the most negative impact on the metabolic processes and the health of people there.

Sometimes with adequate site ventilation, but with air passing through a fine filter and even air conditioners, as well as internal "air purifiers" and heating devices, negative ions are almost entirely lingering. They are also destroyed by air passing through a layer of glowing tobacco when smoking. The presence of the same concentration of oxygen, as outside (21%), in these conditions does not ensure proper quality of indoor air.

The famous Russian physiologist A.L. Chizhevsky (1959) back in the 20s proved the effect of negatively charged ions on the health and life of humans and animals. In particular, he showed that animals in a room devoid of any negative ions by filtering the outer air, after 8-10 days become lethargic, lose appetite, become weak and within 13-18 days inevitably die. In case of timely free access to the outside air, the animals again recover their strength and health. Exactly the same processes can occur in people under similar circumstances.

Developed during millennia, system of protection and correction of the internal environment is not able to deal with ever-increasing flow of a wide variety of
substances, both of organic and inorganic origin. A number of compounds can not be metabolized at all. As a result of spontaneous reactions of xenobiotics or their intermediate reaction compounds with proteins, cell membranes or nucleic acids there are formed autoallergens, membranotoxins or carcinogens.

Contact with the body of any foreign substance, even in a minimal amount, does not disappear unnoticed. In some cases, there comes the selective damage of central nervous system (acrylamides, azides, barbiturates, cyanide, glutamate), liver (carbon tetrachloride, chloroform, trichlorethylene, Bromobenzyl, ethanol), lungs (carbon monoxide, dust and fumes containing quartz, graphite, kaolin, talc, asbestos), kidneys (chlorpromazine, trifluoperazine), gonads (isoprene, tetraethyl lead), embryo during fetal development (extraction solene, ethanol, aniline, ethylene glycol).

Numerous studies have shown the impact of such adverse conditions on health indicators. What became the confirmation of this concept were results of comparative studies of health status of two cities in Volgograd region with roughly similar climatic conditions - Volzhsky and Kamyshin. Their only one difference is a greater concentration of industrial enterprises in the first one (due to closeness of Volga hydroelectric station). At the same time in the air of the city Volzhsky almost always were about 10 toxic chemicals at the MPC (N₂O, SO₂, CO, asbestos, graphite, mercaptan). The most significant results are shown during not examination of employees of these enterprises, but the mass screening of children. Particular attention was drawn to disease incidence in children of the first years of life in pre-schools of these cities. There was revealed almost complete absence of healthy children under the age of two with a significant prevalence of frequent and long diseases in Volzhsky.

The same trend is observed when examining children of older age groups in kindergartens in these cities. Thus, the number of children ailing often and long, is reducing in Volzhsky (from 62.1% in the first year and 41.5% in the second year to 23.0% in older age), but always remains significantly (2-3 times) higher than in Kamyshin. Thus, among the causes of disease of the children in these age groups the leading role play respiratory diseases, allergies and chronic rhinitis. In particular, there is shown a twofold prevalence of respiratory diseases, and almost threefold - of allergic diseases.

Especially noteworthy is absence of children that never fell ill during the first year of life in Volzhsky, and it may indirectly evidence of more adverse conditions of intrauterine development of children in this city. This is confirmed by higher level of adverse pregnancy in Volzhsky. There is indicated a significant (threelfold) increase of frequency of late toxicosis of pregnant (preecclampsia) in Volzhsky, which undoubtedly caused higher perinatal mortality and morbidity among newborns. It is to be supposed, that in this city a fetus is under double oppression - of endotoxins, typical for an ordinary pregnancy toxemia, and exotoxins, which penetrate to the mother's body with air, water and food.
Thus, presence of active oxidants (nitrogen oxides, sulfur dioxide, etc.) in the atmosphere of residential areas of Volzhsky leads to the depletion of antioxidant protective system of the body with accumulation of toxic final products of lipid peroxidation, which, in turn, activate the processes of proteolysis and other types of metabolic disorders with the subsequent suppression of immune defense mechanisms. All this, obviously, leads to a significant weakening of children's health, which will undoubtedly leave its mark on the rest of their life. Additional immunoassay of random cohorts of children and adults in the city confirmed the status of moderate immunodeficiency expressed in reduction of immunoglobulins A, M, G, and phagocytic activity.

Similar data have been published by M. Mikulska (1998) on the basis of observations in environmentally unfriendly district of Upper Silesia. Thus, in 1985-1995 there was observed an increase in perinatal mortality from 11.9 to 24.0%. The number of infants with extremely low birth weight (from 3.1 to 10.4%) increased as well. The most common cause of neonatal mortality was the increasing frequency of abnormal development (38.3%).

Thus, the presented results of medical and environmental studies strongly support the connection between adverse external conditions of human habitation with disorders of its internal environment and, consequently, the general weakening of health.

**Mechanisms of homeostasis disorders**

In addition to the direct toxic effects of a number of xenobiotics, perversions of metabolic processes occur in the body. For example, penetration of oxidants stimulates lipid peroxidation with depletion, and then depression of antioxidant defense system. Final products of peroxidation, as malondialdehyde, diene conjugates, Schiff bases are accumulated. Increase of concentration of these natural metabolites leads to disorders and other metabolic processes, in particular, to excitation of proteolysis.

Another big disorder of homeostasis occurs in certain diseases. Thus, in acute inflammatory processes an important role play mediators of inflammatory with increase of kininogenase-kinin cascade products in blood - biogenic amines (serotonin, histamine, kallikrein) contributing to worsening of shock-producing reactions.

Upcoming biochemical disorders of internal environment can not affect the protection system - organs of detoxification, immunity, excretion. Developing "toxic press" causes a cascade of subsequent disorders with the emergence of a number of vicious circles that the body itself is no longer able to break, even with the help of various drug therapies, which leads to formation of many chronic and even terminal illnesses.
Various biochemical disorders of homeostasis contribute to various shifts of immune system that can be subdivided into three main groups - stress, depression and immunity distortion.

Immunity effort contributes to autoimmune pathology appearing. There are possible increased formation of autoantibodies and immune complexes, and violation of the processes of their degradation and excretion, or combination of these mechanisms. In any case, this is accompanied by an increased concentration of circulating immune complexes (CIC), and their delay in various structures of interstitium leading to the development of fibrosis, granulomatosis, etc. Thus formed different manifestations of connective tissue, glomerulonephritis, rheumatic fever.

Immunity depression reduces the resistance of microbe-virus infection with increasing frequency of respiratory viral infections and formation of chronic bronchitis, various chronioinfections (for example - urinogenital). Weakened recognition of alien structures in immunodeficiency promotes tumor processes.

Distortion of the immune response generates different types of allergies.

For all the variety of chronic diseases, they have many common features in pathogenetic mechanisms of their development, severity of symptoms, torpid flow, and to some extent incurability. These common features are disorders of internal environment - homeostasis - due to either increased revenues or xenobiotics, including toxic and outside, or violations of various levels of protection - detoxification, immunity, removal of pathological products of the organism, and in some cases, a combination of these factors.

Traditional approaches to treatment in most cases have symptomatic nature, such as the use of bronchodilators in asthma and antibiotics for infections. At the best case there are considered immune system disorders, which are used for the correction of immune modulators, but most frequently, steroid hormones, giving, in turn, a lot of side effects. If kidneys are not able to eliminate some products, then diuretics are not able to restore this function.

Without liquidating the reasons of depression or distortion of immune responses it is difficult to rely on a persistent immune correction. Without sanation of internal environment, excretion of pathological products, restoration of the normal course of metabolic processes, including lipid peroxidation and proteolysis, i.e., without liquidation of the "toxic press" on immunity, it is difficult to count on its recovery with only medical stimulation, without which it is impossible to achieve a breakthrough in the disease course. Excretion of abnormal substances and sanation of the internal environment are the aims of a variety of efferent therapy methods.

It should be noted that the concept of "pathological products" presupposes not so much toxic substances of exogenous or endogenous origin, as autoantibodies, immune complexes and other practical natural metabolites whose concentration exceeds physiological limits, which has pathological effects on organs and body systems.
Methods of efferent therapy

There are two groups of such methods. One of them is based on the possibility of applying sorption methods of fixation of various substances circulating in blood, and their subsequent removal. Another group includes methods of removing harmful substances together with a part of the blood – plasma.

**Hemodialysis** is also one of efferent therapy types. Clinical indications to it are limited mainly to acute and chronic nephropathy and some kinds of poisoning [Gotloib L., 1996]. These issues were rather fully described in a special literature and thus not included in the aims of this work.

In the intensive therapy practice more popular are methods of **hemofiltration** – **hemodiafiltration and ultrafiltration**. They are based on removal of liquid part of blood except for **proteins**, what makes them close to hemodialysis, but water exudation mechanism is based on filtration through microporous membranes. In this mode, can operate both conventional dialyzers and special hemofilters that allow to perform relatively long sessions for up to 180 hours with removal of up to 20-40 liters of liquid a day. Such intensive removal of the liquid needs special polyionic and buffer substitute solutions under the control of acid-base balance and ionogram.

In our practice we have used conventional dialyzers in a softer mode with removal of up to 2-3 liters of liquid that with the simultaneous sorption detoxication also provided positive results. Removing the “toxic press” from kidneys contributed to the restoration of their functional abilities without additional hemodialysis. If necessary, these sessions were repeated every 1-2 days.

**Sorption** methods are based on such peculiarity of many harmful products, as presence of the charge in these molecules or free radicals in their structure that in contact with the sorbent, consisting of activated carbon or other surface structures (sometimes coated with enzymes or ion exchange resins), are able to be adsorbed to the latter. Transmission of blood through the columns with sorbents is called **hemosorption** (hemocarboperfusion).

It should be noted that many natural metabolites – protein molecules, lipids, mucopolysaccharides – have “closed” molecular structures electrically and, therefore, biologically inert. That is why “normal” metabolites can contact with active sorbents - they easily pass them by and remain in circulation, thus minimizing the possible harmful effects of the procedure. Despite the common alienation of specialists, such nonspecific hemosorption still finds its application in the treatment of patients with sepsis, allergic and autoimmune diseases.

It is possible to apply sorption method without removal of pathological products and without elimination from the organism of any internal environment elements. This is an
**enterosorption.** There is used a process of physiological filtration and reabsorption of liquid from the bloodstream into the intestine glimpse by its villi. The products that were removed with the liquid part of blood contact with enterosorbtent taken beforehand, fix on it and together with it are removed from the body. Considering that the intestinal villi are able to pass all of the ingredients, the molecular weight of which is lower than the mass of albumin, and toxic substances at their core are of medium-molecular mass, the effectiveness of enterosorption in eliminating endotoxicosis becomes clear. The advantage of this method is the possibility of its use in ambulatory (home) conditions, although its efficiency yields to a direct adsorption of these substances directly from the blood flowing through the column during hemosorption [V.G. Nikolaev et al, 2005].

However far not all substances, subject to elimination from the organism, can be captured and fixed on sorbents. Electro-chemically inert molecules are incapable of adhesion and remain in circulation, which makes hemosorption procedure inadequate. In such cases the elimination effect of such substances can be obtained during **plasmapheresis**, when some part of plasma is **completely** removed together with **all** the pathological products that were there.

Removed volume of plasma is completed with plasma-substituting solutions, albumin and donor plasma. In the latter case, especially when the removed plasma is completely substituted with donor plasma, the operation is called **plasma exchange**. Unlike hemosorption, plasmapheresis has more or less **universal** character, when all the pathological elements are removed irrespective of presence and amount of electrostatic charge of their molecules.

There are two main methods of plasmapheresis – **gravitational** and **filtrational**. The first one is performed by centrifugation of blood with constant or intermittent flow in special devices produced by Gambro, Fresenius, Cobe, Dideco, Terumo or in bags in ordinary centrifuges.

The second method is based on blood filtration in special plasma filters. As a rule, there are produced filters, where filtration if performed through hollow porous fibers. In Russia there has been organised production of plasma filters PFM-800 containing **flat** hollow “track” porous membranes (“PLASMOFILTER”, Saint-Petersburg). In 2011 appeared a filter of new generation PFM-TT “Rosa”, developed by “TRACKPORE TECHNOLOGY Corporation” and produced in Dubna, Moscow region. Description of peculiarities of the latter as well as different techniques of its application will be detailed below in the conclusion of the work.

In any of these methods after plasma removal, concentrated cell mass of blood (“erythromass”) is diluted with sodium chloride isotonic solution or other plasma substitute and returned to a patient. During one session it is possible to remove from 1/3 to ½ of circulating plasma volume (CPV). In case of donor **plasma** or albumine substitution, up to 1 or 2 CPV can be removed.
CPV of an adult person with an average weight is 2.0 – 2.5 l. It is easy enough to calculate knowing the circulating blood volume (CBV), which makes about 7% from body weight and hematocrit index (Ht). Then there is elementary calculation:

\[ CPV = CBV - \frac{\text{Ht} \times CBV}{100}, \]

where hematocrit index is percentage, and circulating blood and plasma volume – in milliliters.

If hematocrit was not measured directly, then it can be roughly calculated from the number of erythrocytes, which multiplied by 10 approximately corresponds to hematocrit (3,6 \times 10^{12}/l erythrocytes correspond to hematocrit 36%), or from hemoglobin content divided into three (hemoglobin 120 g/l - approximately 40% hematocrit).

In donor practice of U.S.A, the usual dose for the one who donates plasma for the first time is 500-600 ml, and for repeatedly and regularly donating every two weeks - up to 900 ml, after which these donors go home. When taking plasma from relatives it is even allowed to take 1200 ml. To some extent it is permissible to be guided by such doses in clinical practice. Therefore, taking 700-900 ml of plasma for therapeutic purposes is safe enough, even with only crystalloid solution substitution.

After plasmapheresis session a significant decrease in the concentration of pathological products can be observed, but after a few hours their content in the blood is close to the original level. This suggests that substances, which before had been in the interstitium, or even in the cells, penetrated to the bloodstream. Subsequent sessions of plasmapheresis promote removal of these substances, which leads to a more complete sanitation of the whole internal environment, given that most of the harmful products are in extravascular space. It should be borne in mind that there is a "moving equilibrium" of concentrations of various substances in intracellular, extracellular (interstitial) and intravascular spaces of the organism. Change of their content in one of these spaces (in this case - intravascular) leads to redistribution in the others.

Thus can be removed xenobiotics, having been in organism for a long time and received from the environment, and natural pathological metabolites.

Such a “mild” technique of plasmapheresis that does not require substitution of removed plasma with albumine preparations or donor plasma, is the most preferable. For the patients prone to allergic reactions, introduction of any protein product possesses a threat of anaphylaxis, up to a heavy terminal shock. In autoimmune diseases in more than half of these cases we have also observed some or other allergic or vegetative reactions.

At the same time it should be admitted that in America and European countries there are generally used operations with more massive plasma removal - up to two
CPV, which, of course, is impossible without use of donor plasma. In addition to much higher cost of such operations in these countries (from 1000 and more U.S. dollars), substitution with donor plasma decreases the reflex of immediate restoration of plasma and CBV on the whole by drainage of fluid from tissues, when the latter is purified from pathological substances. In this case there should occur conditions for removal even of earlier “fixed” pathological products in tissue structures, including radionuclides. In case protein preparations were used for substitution, no changes in oncotic pressure or in CBP on the whole could not happen. That is why in these cases alignment of concentrations of various ingredients in vascular and extravascular spaces occurs more slowly – during not hours, but days. Creation of artificial hypovolemia triggers the most ancient and powerful reflex of priority restoration of circulating volume and the “spurt” of tissue fluid contributes to equalization of the concentrations in these spaces during the next few hours.

This enables further sessions on the second day already, which reduces the treatment period to two weeks maximum. Therefore, the recommended technique is more affordable and functional from both economic and organisation sides.

A complete sanation of the internal environment usually requires 4 sessions of plasmapheresis, during which altogether there is removed 1-1.5 CPV. The intervals between treatments are 1-2 days. In this mode, even in case of plasma substitution with only isotonic sodium chloride solution, there appear no significant changes in core components of the internal environment (protein, fat, carbohydrates, electrolytes, hormones, etc.). The newly formed cellular and humoral elements of homeostasis in "refreshed" internal environment devoid of "toxic press" of removed pathological products retain their natural functions and properties much longer.

Table 1 shows the dynamics of circulating immune complexes’ levels during the plasmapheresis course performed by us.

<table>
<thead>
<tr>
<th>Sessions</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>In a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before plasmapheresis</td>
<td>252.3</td>
<td>278.4</td>
<td>175.5</td>
<td>131.6</td>
<td>140.2</td>
</tr>
<tr>
<td>±12.2</td>
<td>±15.4</td>
<td>±9.5</td>
<td>±8.4</td>
<td>±9.3</td>
<td></td>
</tr>
<tr>
<td>After plasmapheresis</td>
<td>139.7</td>
<td>132.4</td>
<td>111.3</td>
<td>85.1</td>
<td></td>
</tr>
<tr>
<td>±8.5</td>
<td>±8.8</td>
<td>±7.4</td>
<td>±6.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table shows that hazard of "rebound effect" or immediate resumption and even enhance of antibody production in response to their removal by plasmapheresis is quite groundless. After the initial surge of CIC level, further rises of their contents gradually fade after a week, and their level remains quite acceptable. That is to say, the highest possible clinical effect is achieved with minimal adverse effects.
The process of abnormal ingredients accumulation is more gradual, it takes weeks and months. Therefore, if etiological factors of diseases are not eliminated, then, by the example of autoimmune (or so-called immunocomplex) diseases, performing repeated courses of plasmapheresis twice a year keeps patients on fairly manageable level of remission while maintaining an acceptable "quality of life" and even the ability to work timely warning crises exacerbations, which is clearly illustrated in Table 2.

Table 2. Amount of circulating immune complexes in consistent courses of plasmapheresis (n=28)

<table>
<thead>
<tr>
<th>Plasmapheresis courses</th>
<th>The 1st course</th>
<th>In 6 months</th>
<th>In a year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before course</td>
<td>252.3±12.2</td>
<td>221.2±12.5</td>
<td>198.8±10.3</td>
</tr>
<tr>
<td>After course</td>
<td>140.2±9.3</td>
<td>131.4±8.3</td>
<td>126.1±7.8</td>
</tr>
</tbody>
</table>

Table 2 shows that after 6 months, the content of CIC certainly rises, but it does not reach the previous level. The same trend continues in the next 6 months. This all can significantly increase the lifetime of these patients, even at a lower (up to 40%) level of medical support.

More selective methods of plasmapheresis are also used, when received plasma is subjected to cooling, which promotes the precipitation of some proteins and immune complexes, lipoproteins and triglycerides, fibrinogen, and other "acute phase" proteins, which in the future (after thawing) can be removed again by centrifugation or by sorption, and the remaining components of the plasma can be returned to the patient.

This method is called "cryoprecipitation", "cryosorption" or "cryosorption modification of autoplasma" [K.J. Gurevich, A.L. Kostyuchenko, 1991]. Cold precipitation is enhanced in the presence of heparin, therefore one of such methods is known as heparin-induced extracorporeal precipitation of cholesterol (Heparin-induced extracorporeal LDL precipitation - HELP-apheresis). Even more selective binding of lipoproteins is possible, including lipoprotein(a) (Lp(a)) with special immunosorption columns POKARD of S.N. Pokrovsky [Konovalov, GA, 2004]. However, in the Technical Manual of the American Association of Blood Banks (2000) it is emphasized that by means of adsorption or cryopheresis it is possible to remove only a part of the pathological component, so the expected efficiency of these methods is lower than of those for which plasma is removed entirely.

Another method of selective plasmapheresis is cascade plasmafiltration when plasma obtained with one of the methods re-passes through a special microporous filter that passes only low molecular weight proteins (albumins) and holds those with high
molecular weight, including immunoglobulins and atherogenic lipoproteins [Bruni R. et al., 1999; Valbonesi M. et al., 2001; G.A. Konovalov, 2004; E.V. Petukhov, G.A. Konovalov, 2004; Matsuda Y et al., 2004; Stegmayr BG, 2005; Hanafusa N. et al., 2006]. For the first time cascade plasmafiltration was performed by T. Agishi et al. in 1980 [Agishi T. et al., 2000]. As a secondary cascade plasmafilters there are used Albusave (Dideco, Italy), EVA-Flux EVAL 2-5A (Kawasumi, Japan), EC-20W (Asahi, Japan), Kuraray Evaflux 4 (Kuraray, Japan), etc.

Nevertheless, despite its importance, efferent therapy intended to remove pathological products of the internal environment, is only the first step in correcting its violations. The second one is elimination of secondary effects of these disorders - restoration of natural protective systems, mainly immunity.

In this book we use somewhat expansive notion of efferent therapy, including in it not only the removal of harmful substances from the body, but other methods of correcting defects of internal environment by physico-chemical influence on its individual components (blood, plasma, lymph) outside the body (extracorporeally), or even inside it.

The basis of extracorporeal methods of immune correction is quantum therapy (blood photomodification) - blood irradiation with ultraviolet or laser beams. There are many reports of favorable effects of such therapy: in patients with immunosuppression effect of immune stimulation is revealed, and with various allergies - immune correction, that is, reducing pathological allergic reactions. In patients with inflammatory diseases of lungs after ultraviolet irradiation of blood electron microscopy indicates restoration of specific intracellular organelles in neutrophil leukocytes, suggesting an increase of their phagocytic ability. Also increases the number of immunoglobulins, T- and B-lymphocytes, reduces leukocytic index of intoxication [I.P. Nazarov, Y.S. Vinnik, 2002].

Among methods of laser irradiation of blood the most common is a helium-neon (He-Ne) laser as a light source of red light (\( \lambda = 0.633 \mu m \)). In case of coincidence of the enzymes absorption spectrum in a cell or in its membrane with energy spectrum of laser radiation, they are activated. In particular, catalase is activated, which has the same spectrum (0.633 \( \mu m \)), as He-Ne laser. Copper-containing redox enzymes - cytochrome oxidase and ceruloplasmin - may be acceptors. Activation of these enzymes is enhanced in the presence of singlet oxygen, which emphasizes the combination of this method with addition of substances containing free oxygen. It is possible a selective absorption of red quanta by oxygen with its transition to the singlet state. In such cases, it is justified to add substances containing singlet oxygen, for example - sodium hypochlorite.

Enzymes, such as superoxide dismutase, lactate dehydrogenase, phosphatase, can be acceptors of such radiation. The red light of He-Ne laser influences hemoglobin molecules with decrease of its affinity for oxygen, which increases its impact on
tissues in hypoxia. This radiation has a favorable effect on the lipid composition of erythrocyte membranes, normalizing their aggregation properties, deformability, which improves rheological properties and oxygen-transport function of blood [R.Z. Losev, O. Tsarev, 1998].

The most common in Russia are various devices of helium-neon radiation ("Shuttle", ALOK-1) or with a mercury-quartz lamp (OVK-3). Irradiation can be conducted by light guides intravascularly or extracorporeally. It should be noted that in the first case it is not always possible to ensure constant and reproducible conditions for blood passing through the vein, part of gleam in which is occupied by light guide, and after removal of the binder, vessels of arm subside again and even spasm in response to injury. When combined with efferent therapy, it is always possible to use extracorporeal circuit of perfusion and to perform more dosing irradiation. Eases the situation a good permeability for laser beams of the walls of PVC blood lines. A particular area of such tube can be placed inside a mirror sphere in which the tangential beam creates the effect of "inner radiance" and radiation of blood passing from all directions in the device "SHUTTLE" (JSC "Medlaz", St. Petersburg), which makes it possible to dispense irradiation with regard to the speed of blood flow and body weight. Combined application of laser irradiation of blood with hemosorption and plasmapheresis significantly potentiates their immuno- and rheologic impact, significantly increases efficacy of coronary heart disease, hypertension, chronic infections.

External irradiation of separate parts of the skin with He-Ne laser is also possible, but penetration of these rays is limited to only a few millimeters, which allows to irradiate superficial wounds or trophic ulcers. More deeply (up to 8 cm) penetrates radiation of infrared lasers with emission spectrum of 0.89 µm, which allows to use them in irradiation of both superficial large blood vessels and some of internal organs (liver, kidneys, heart, joints).

But in any case, plasmapheresis is associated with a temporary, renewable, but still lost of certain part of immunoglobulins, complement, opsonins, which, undoubtedly, at some time weakens immune protection capability of a patient. Thus, almost every operation of plasmapheresis (as well as hemosorption) must be accompanied by a quantum immunocorrection.

On the other hand, in almost all cases when quantum therapy is performed for immunocorrection, it is meaningless without parallel efferent therapy. This also can be said about different types of drug immunomodulation - without efferent therapy its effect will not be stable and long enough.

But after plasmapheresis it is possible, and in some cases necessary, to perform various types of medical support as well as non-drug therapies - acupuncture, physiotherapy and balneotherapy, etc.
Efferent therapy can also be combined with methods of "oxidative detoxification" – low-flow membrane oxygenation and indirect electrochemical oxidation and ozonation of blood.

In case of absence of a special small-sized membrane oxygenator, blood oxygenation can be performed even with the help of dialyzer.

For the electrochemical oxidation it is used effect of electrolytic decomposition of usual isotonic sodium chloride solution with the device EDC-4 with formation of the above sodium hypochlorite (NaClO). Active radical ("singlet oxygen") of the latter in addition to bactericidal activity has the ability to rapidly oxidize hydrophobic toxic substances, such as bilirubin, creatinine, urea, fatty acids and other substances in the blood, which potentiates the detoxication process. Pre-treatment of hemosorbents with sodium hypochlorite increases their sorption capacity.

Ozonation of blood can be performed by passing it through a special membrane oxygenators, through gas chambers of which passes oxygen with ozone. Most commonly ozonation of solutions is used with subsequent intravenous infusion. In such ozonation of blood there are reached effects of immunomodulatory, anti-inflammatory, anti-allergic. Decrease of concentrations of LDL, triglycerides, and glucose is also possible. Effect on the immune system manifests itself by activation of lymphocytes and macrophages with increased production of cytokines (interleukin-2), γ-interferon, β2-microglobulin [A.A. Sokolov, A.N. Belsky, 2003]. Apart from that, in introduction of ozonated solutions there is observed an effect of microcirculation improvement.

Cannot be ignored aeroionotherapy by means of electroeffluvial chandeliers designed by A.L. Chizhevskiy, allowing to obtain a sufficient number of negatively charged ions - up to 10,000 in 1 cm³ of air, which corresponds to the terms of the best ski resorts. Effluvio means to flow, and in Chizhevsky chandelier a special generator provides such a flow from multiple needles of electron flow, which combining with oxygen molecules provides their transformation into the negatively charged air ions of oxygen.

Experiments on animals have shown a significant increase in their motor and sexual activity, resistance to infections and increase of life time for 40% in case of providing ventilation of their premises with air enriched with negative air ions. Positive results were obtained when using aeroionotherapy in clinical practice of treatment of many human diseases.

Positive effect of inhaling air with negatively charged air ions can be sensed by anyone staying outdoors immediately after storm. If within a few hours before, one felt sultriness and lack of air due to the almost complete disappearance of negative ions in the atmosphere, after the storm one breathes freely and remarkably easily, though the oxygen content remains at the same level, but concentration of negative ions reaches 100,000 in 1 cm³ of air.
In particular, there is noted a connection between ozone level in the atmosphere with the frequency and severity of asthma attacks. Biologically ozone is formed as a result of a photochemical reaction of nitrogen oxides and oxygen catalyzed by sunlight. There was described the negative impact of ozone on bronchial epithelium with the fall of expiratory flow rate for 1 sec, vital and total lung capacity, increased airway resistance at a concentration of O₃ in the range of 0.24 - 0.8 parts per million. Even the 0.08 ppm is enough to cause inflammation in the airways [Krishna M.T., 1995]. In exposure of cell culture of the nasal mucosa of patients with allergic rhinitis in the atmosphere containing ozone, within 24 hours there is recorded an increase of histamine release and development of inflammatory response [Schierhorn K. et al., 1999].

Ozone content in ambient air is not constant and is normally 40 to 100 µg/m³. In some days, this concentration increases to 200 µg/m³. In 1985 in Los Angeles it reached 400-700 µg/m³. Strange as it may seem, concentration of ozone in city outskirts and in countrysides is higher than in city centers due to inactivation with nitric oxide (NO), although it is emitted with exhaust gases of vehicles. And inside houses ozone is also rapidly inactivated by contact with a pieces of furniture. World Health Organisation recommends not to exceed the maximum ozone concentrations above 150-200 µg/m³ (0.076-0.1 ppm) in contact during 1 hour, and at 8-hour exposure - not more than 100-120 µg/m³ (0.05-0.06 ppm).

It should be noted that 10% of the population are "sensitive" to ozone and can react to smaller doses. At the same time increased sensitivity to ozone is more frequent in asthmatics and children, than in healthy adults [K.E. Müh lendahl, 1997]. Special studies have shown that excess of ozone levels above 0.22 ppm during 4 hours resulted in sixfold increase of polymorphonuclear leukocytes number in the airways, and of such cytokines, as IL-6 and IL-8, 10 times, and in later period the number of lymphocytes, eosinophils, and mast cells increased. This all is accompanied by development of bronchoconstriction [Krishna M.T. et al., 1997; Torres A. et al., 1997].

Therefore we would like to warn against using air ionizers allowing ozone admixture, while chandelier produced on the bases of A.L. Chizhevsky, is absolutely free from such admixture.
PARTICULAR ISSUES OF EFFERENT THERAPY

EXIGENT CONDITIONS

Respiratory distress syndrome

Acute respiratory damages of lung parenchyma are frequent and serious complications in a number of diseases. First of all of it is referred to viral and bacterial pneumonia, which sometimes has a cacoethic course and is accompanied by massive, sometimes total, ambilateral damages of lung parenchyma with severe, hard correctable respiratory failure, which for several days, sometimes hours, can lead to death. Secondary to this there can develop destructive processes and even gangrene of the lungs.

The next group consists of acute lung damage, combined by the term "shock lung", developing in patients with severe trauma, who underwent surgery, including cardiopulmonary bypass on open heart (postperfusion pulmonary syndrome), hemorrhagic, septic or anaphylactic shock, massive blood transfusions (syndrome of "homologous blood").

Apart from that, lungs are affected in various exogenous intoxications and poisonings. In obstetric practice lung damages develop in eclampsia, amniotic fluid embolism, disseminated intravascular coagulation (DIC) syndrome. Many types of endogenous intoxications, especially such as those developing in acute pancreatitis, are also accompanied by lung damage.

All these types of acute damages of respiratory lung parenchyma are usually combined by one term - respiratory distress syndrome (RDS).

In Western literature it was commonly referred to as "adult respiratory distress syndrome", or ARDS, where the first letter corresponds to the word adult (adult), which far not everyone was satisfied with, since a similar complication is characteristic for both adults and children. Therefore in 1994 the Conciliation Commission (Consensus) of scientists of European and American countries dealing with the problem had reviewed the terminology and, leaving the same initials ARDS, introduced a new term more close to the reality - acute respiratory distress syndrome, and the first letter in the abbreviation of the word has become acute (sharp) [G.R. Bernard et al., 1994].

This book uses more simple term "respiratory distress syndrome" - RDS, because this syndrome can not be other than acute.

Considering such a large group of diseases associated with RDS, there are practically no compound statistical information about its frequency, although in 1980, in the U.S.A. there were cited the following data - about 150,000 patients with RDS a year. It is interesting that the materials of mentioned Conciliation Commission exactly the same figures are quoted for the United States for 1994. M.A.Matthay and R.L.Zemans
(2011) describe approximately 200,000 critically ill patients with ARDS causes 40% mortality annually in the United States. Given the difficulties in treatment of this complication, accompanied by high mortality (10 to 90% depending on the severity of damage), this problem is extremely urgent.

Since in the solutions of Conciliation Commission, despite recognizing the essential role of endotoxemia in the genesis of this complication, was not mentioned the possibility of efferent therapy and detoxication in RDS, we have to give more detailed justification of such approach to its treatment and prevention.

Pathogenesis of respiratory distress syndrome

From the above list of diseases and pathological conditions accompanied by RDS, it is possible to make conclusion about polyetiology of this complication, however pathogenetic mechanisms are common for all types of RDS. They lie in the development of toxic interstitial and then alveolar pulmonary edema due to the cell membranes’ permeability failure on the basis of endotoxaemia.

To prove this, in the Research Institute of Pulmonology, USSR Ministry of Health, there were conducted toxicity studies of blood in patients with acute pneumonia using the test of "protozoa survival time" [Kostyanets E.Yu., 1992]. As the protozoa there were used tetrahymena. In the blood of healthy people (and animals) the survival time is about 20 minutes and, depending on the severity of condition of patients with acute pneumonia, this time was reduced to 10, 5 and even 2 minutes. However, this increase in toxicity of blood might have been only one of the consequences of acute pneumonia and have no independent significance in the further development of lung damage, which could have occured simply from the progression of the basic pathological process in the same organ.

In clinical conditions the local pathological process and the accompanying intoxication can not be separated from each other, so it is impossible to identify those changes in the lungs, which are the direct consequence of the local pathological process, and those that arise from the impact of circulating toxic products. In one case, the process should be going in the direction of "alveolar epithelium - interstitium - vascular endothelium", in another - in the opposite direction, that is, from the blood. Only studies in the experiment could shed light on this question.

Our first experiments on rabbits with intratracheal administration of pathogenic (isolated from real patients) pneumococci culture gave quite amazing results - after only 5-10 minutes this pathogen was sown from blood and internal organs (liver, kidney, spleen), and the toxicity of blood increased to the same extent as in patients with acute pneumonia [Kostyanets E.Yu., 1992]. In all probability, the same bacteremia occurs in patients, and only the early start of antibiotic therapy does not allow to identify this phenomenon in more than 30% of them.
In histologic lung study of these animals there is revealed a picture of interstitial and alveolar edema against inflammation - expansion of interalveolar septa with infiltration of interstitium with lymphoid cells; in alveoli there was alveolar fluid rich with protein. Weight of the lungs increased by 32%.

When reproducing a similar level of endotoxemia with intravenous insertion of living or killed cultures of pneumococci there were also observed manifestations of pulmonary edema, such as those described above, but somewhat of smaller scale. Weight of the lungs increased by 25%.

It is interesting that both in intratracheal and intravenous insertion of the causative agent there was also observed a pattern of edema and extravascular fluid volume increase in liver, kidney, spleen [V.A.Voinov, L.A. Vishnyakova et al 1991].

In experiments on dogs there were carried out thoracotomy and intravital contact lung biomicroscopy. Within 15 min after intravenous injection of both living and killed pneumococci cultures, on the surface of lungs there was noted an increase of interalveolar septa with accumulation of frothy fluid in the lumen of alveoli. By the 30th minute, changes in the lung had been increasing, and had reached their maximum by the 180th minute.

For another series of experiments on dogs preliminarily there was received blood ultrafiltrate in its hemodiafiltration under pressure through the dialysis membrane in patients with severe lung damages and concomitant renal insufficiency. The liquid received was rich with medium molecular products. The powder resulting after lyophilization was redissolved for intravenous injection to dogs in such a way that the concentration of medium molecules in the blood of dogs corresponded to that of patients from which the ultrafiltrate had been obtained.

After intravenous injection of this solution in contact biomicroscopy there also may be noted the rapid development of interstitial and alveolar pulmonary edema on the surface of the dogs’ lungs. Electron microscopy revealed a picture of destructive processes in the alveolar-capillary membrane, starting from the capillary endothelium. Similar results were obtained in a model of isolated perfused dogs’ lungs [Levanovich V.V. et al 1989]. A similar pattern of acute pulmonary damages on the basis of impaired vascular endothelial permeability was detected after adding endotoxins (LPS) of Gram-negative bacteria and Escherichia coli exotoxin [Schütte H. et al., 1997]. Moreover, it is exactly the lipopolysaccharide of Gram-negative enterobacteria and cytokines emitted by them (TNF-α) that play a key role in the development of septic shock, accompanied by refractory hypotension with violation of tissue perfusion and subsequent multiple organ failure [Zhang H. et al., 1997].

Experiments showed that in the development of respiratory lung parenchyma lesions arising against acute pneumonia, the leading role plays not so much the spread of the primary pathological process in the respiratory pathways, as endotoxemia due to release into the circulation of both living microbes and inflammation products leading to
the permeability disorder in endothelial cell membranes with the release into the interstitium not only of liquid but also of protein. This was proved by a significant hypoproteinemia with the development of endotoxemia - a common protein in experimental animals reduced within an hour from 67.0 to 51.9 g/l, mainly due to albumin (albumin-globulin ratio decreased from 1.3 to 0.7). These observations confirm that the observed hypoproteinemia, reaching a protein level of 40 g/l, is also a consequence of proteins moving to interstitium through more porous membranes of capillary endothelium. This correlates with the increase of protein concentration in lymph also approaching the level of 40 g/l, instead of usual 20 g/l.

Thus, in patients with acute pneumonia, develops a dual type of lung disease - primary, depending on spread of pathogens in airways, and secondary, arising due to penetration of bacteria and inflammatory products from the primary site into the blood with the development of toxemia. Risk of lung parenchyma was no longer threatened by epithelium of respiratory tract, but by blood through from vascular endothelium [V.A. Voinov, 1992].

Toxemia character is also multicomponent. Apart from actual bacterial toxins (for pneumococc it is hyaluronidase, neuraminidase), both living and dead microbial bodies, in the blood penetrate tissue decay products, inflammatory mediators, the whole complex of biologically active substances (BAS) - products of kallikrein-kinin cascade, histamine, serotonin, products of lipid and proteolysis peroxidation and metabolism of tissues (medium molecular oligopeptides), leucocyte decay (lysosomal enzymes).

With electron-microscopic studies in lung microvessels it was possible to detect evidence of previously described marginal leukocyte position syndrome, when leukocyte was observed in decay stage, adhered to endothelium, with lysosomal corpuscles fixed to the endothelium and outside leukocyte with significant perifocal zone of the vascular wall destruction.

All types of these toxic substances disturb the permeability of cell membranes, not only of lungs, but virtually of all other internal organs and tissue structure with their functional status failure and development of multiple organ failure syndrome. Although this condition is often characterized as RDS by the most manifesting signs of respiratory failure and radiographically detectable changes, while disturbances of other organs are apparently not so striking, yet it is difficult to imagine an isolated RDS during normal operation of other organs. In septic shock with acute endotoxemia there may develop hemodynamic disorder manifested in a blood pressure fall, total peripheral vascular resistance reduction, decrease of cerebral blood flow and intensity of oxygen consumption of brain tissue [Pollard V. et al., 1997].

Moreover, there appears a series of vicious circles, when the toxic pulmonary edema and hypoxemia stimulate hypoxic disturbances in membrane permeability; renal irritation contributes to the additional retention of fluid (edema is stimulated) and slag (toxemia increases); liver damage with the suppression of its detoxication function also
enhances toxemia; toxic **myocardopathy** aggravates organ microcirculatory disorders, and toxic **encephalopathy** leads to brain disorders, while released neuropeptides stimulate *neurogenic* pulmonary edema. Exactly this "summation" of damages in multiple organ failure determines extremely high mortality rate - up to 80% [Gotloib L., 1996]. The syndrome of multiple organ failure reflects a biological disaster, type of biological suicide that occurs in a wide range of clinical situations.

Pulmonary capillary endothelium damages, in addition to the development of interstitial edema, also lead to the failure of microcirculation and mikrothrombosis, which leads to appearance of ischemic lung parenchyma foci and subsequent *destructions*. Alveolar edema prevents the oxygen access to the interstitium, which in the presence of local ischemia and anaerobic microflora leads to the lung **gangrene**.

Interstitial and alveolar toxic pulmonary edema blocks gas exchange at the alveoli level due to the expansion of aerohematic barrier (alveolar-capillary membrane). This leads to severe and hard correctable **parenchymatous respiratory failure**, a leading factor of **thanatogenesis**.

Approximately the same mechanism of RDS development is in septic and burn shock, other types of endotoxemia [I.A. Eryuhin, B.V. Shashkov, 1995]. In traumatic shock a fat embolism significantly contributes to the general background of endotoxemia. However, there meant not so much the fact of penetrating to the circulation of free fat from tissue destruction areas (which, of course, takes place), as the failure of the lipid suspension state and formation of fatty globules in the vascular bed already. This activating *lipase*, and as a result of *lipolysis* there is sharp increase of free fatty acids and *lysophosphatides* concentration with pronounced membrane activity.

In severe injuries and, mainly, **crushing syndrome**, prolonged tissue ischemisation and autolysis development there are formed highly toxic products of tissue decay, myoglobin and free hemoglobin (due to hemolysis), which have the most damaging effects on their excretion ways - on parenchyma and kidney function, which often results in hemodialysis need.

Toxic products circulating in the blood have a damaging effect not only on the endothelium of blood vessels, but on the blood ingredients, mainly on the cells. Permeability disorder, mechanical and electrostatic properties of erythrocyte membranes contribute to their aggregation (*sludge*) and even greater disorder of blood rheology and microcirculation. Excitation of leukocyte membranes contributes to the increase of their adhesive properties and retention in microvessels (**marginal leukocyte position syndrome**). Platelet activation also enhances their adhesiveness, appearance of micro-aggregates that become like *nuclei* for subsequent formation of DIC cascade stimulating microthrombosis and bleeding.

Thus, RDS is a **secondary toxic damage of respiratory parenchyma**, occurring not only in lung diseases but also in a number of other pathological conditions that
share common pathogenetic mechanisms. The main among them is toxic cell membrane permeability disorder.

Special studies conducted in the 70's showed the activity disorder of surfactant in the development of shock lung [Wichert P., Kohl F.V., 1977]. Surfactant reducing the surface tension in alveoli and thus ensuring their stability on the exhale, also reduces the hydrostatic pressure in pulmonary capillaries, preventing the extravasation of fluid from them [Pattle R.E., 1965]. Thus, lack of surfactant leads to atelectasis as well as to pulmonary edema. The main active agent of surfactant is a phospholipid dipalmititl-phosphatidyl choline, but there are protein components, it means that surfactant is a lipoprotein, synthesis of which occurs in alveolocytes type II.

There are several attempts to explain the decrease of surfactant activity. In particular, it is assumed that the fluid and protein entering alveoli in edema disrupt surfactant layer and wash it away. However, direct inhibition surfactant is also possible under the influence of some toxic substances, among which are the free fatty acids [Yanev E. et al., 1990; Günter A. et al., 2001; Zasadzinski J.A. et al., 2010; Lu K.W. et al., 2011]. Histochemical studies have shown that as early as 2 hours after the start of hemorrhagic shock changes occur surfactant film alveoli, its fragmentation. In experiments in animals have also been shown inhibition of the activity of the surfactant after administration of bacterial endotoxin [Davidson KG et al., 2002].

Status of lung surfactant system and reasons of its damages have been studied by us (with E.N. Danilov and A.F. Ovchinin) using the procedure J.A.Clements (1957). For this purpose, 3 g of lung tissue minced with scissors and surfactant extracted in 50 ml of isotonic sodium chloride solution. After 30 minutes of exposure to constant agitation extract was placed in a special cell with fortified movable barrier. The area of the cell smoothly or tiers could be reduced from 100 to 20%, making it possible to record the hysteresis loop of the surface tension, which was measured by a quartz plate retracting force on the balance of Wilhelmy -Longmyur. Most informative was the surface tension while reducing the area of the cell up to 20% (corresponding to the expiration of light), which reflected the greatest possible activity of the surfactant in the extract or "minimal surface tension." In the description below of research results, the term "surface tension" it is meant "the minimum surface tension", expressed in dyne / cm (mN / m), (normal - 2-6 dyn/cm).

The norm of surfactant activity taking surface tension similar pieces lung tissue of 20 healthy dogs that under intratracheal anesthesia, thoracotomy was performed and the subsequent experiments, unrelated to the current tasks, with the further breeding of their experience.

Surfactant activity was determined by measuring the surface tension of lung extracts obtained from 12 patients who died with symptoms of RDS on the basis of
acute pneumonia and infectious lung destructions. There was showed a significant increase in the surface tension of extracts taken from the most altered parts of the lungs on the stage of their “hepatization” (23.37 ± 1.48 dyn/cm to a maximum of 32 dyn/cm), while in areas with the aerial, suppression of surfactant was less pronounced (14.41 ± 1.29 dyn/cm). This difference of surfactant activity in different parts of lungs of the same patient might have depended on its additional inhibition in the places, where in toxic pulmonary edema the maximum yield of the toxic components of blood plasma in the alveoli took pace.

Possibility of direct inhibition of surfactant by some substances circulating in blood at first glance may seem unlikely, since the surfactant lining the alveoli inside is protected from exposure to these substances alveolo-capillary membrane. However, in RDS development, permeability of the membrane is disturbed, what allows to penetrate into the alveoli with edema fluid and these toxic substances. In such case, the direct contact with their surfactant is possible.

To elucidate the causes of the activity of the surfactant that was possible influence of the whole organism, were special experiments in vitro, when to the lungs of dogs extracts were added to 10 ml of blood from healthy dogs (5), healthy donors (5) and 10 patients suffering from RDS, pneumonia, abscess or gangrene of the lungs.

Surface tension extracts lungs of healthy dogs had an average of 5.2 ± 0.7 dynes/cm, whereas patients it was 20.29 ± 1.6 dynes/cm. However, at more detailed examination reveals that the surface tension in the extracts of the changed portions of their lungs with "hepatization" (often from the back-bottom of their divisions) reached 27.37 ± 3.2 dyne/cm.

At the same time, in the areas of tissue with symptoms of edema, but the preservation of lightness (in the upper-front of the lungs), the surface tension was only 14.41 ± 1.29 dyne/cm. Even more clearly this difference is seen in Fig. 1, which shows the hysteresis loop of the surface activity of the extracts of lung tissue from the lower and the upper lobe of the right lung of the patient K., 33 years old. In in vitro experiments were initially found to lack any inhibitory effect on the activity of the surfactant blood of healthy humans and animals (blood donors). At the same time, the addition of the blood of patients are significantly inhibited the activity of a surfactant (Table. One).

Table 1.

<table>
<thead>
<tr>
<th>№</th>
<th>Object of research</th>
<th>Initial level</th>
<th>After blood addition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Healthy dogs</td>
<td>5.2±0.5</td>
<td>5.7±1.1</td>
</tr>
<tr>
<td>---</td>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>2</td>
<td>Healthy volunteers</td>
<td>4.9±0.7</td>
<td>5.4±0.9</td>
</tr>
<tr>
<td>3</td>
<td>Patients</td>
<td>5.2±0.7</td>
<td>25.08±3.76*</td>
</tr>
</tbody>
</table>

Note: marked with * reliability of differences from baseline (P<0.05).

The observed difference in activity of surfactant in different parts of the lung may depend on more of its inhibition in the place where the maximum yield in the alveoli of toxic components from the plasma at a toxic edema of the lungs. The possibility of direct inhibition of surfactant some substances circulating in the blood, at first glance it may seem unlikely, since the surfactant lining the alveoli inside, protected from the effects of these substances alveolar-capillary membrane. However, during the development of RDS permeability of the membrane is broken, and that allows it to penetrate into the alveoli with edematous fluid and such toxic substances. In this case the chance of direct contact with the surfactant. More clearly it is presented in Fig. 2, which shows the effect of adding to the extract lung dog blood of the same patient K.

Thus, these studies have convinced us that in pathogenesis of acute pulmonary damages surfactant system disturbances play a secondary role, being not so much the cause as a consequence of these damages.

**Clinic and diagnostics of respiratory distress syndrome**

One of the most characteristic and early manifestation of RDS are dyspnea, cyanosis, and tachycardia. Auscultatorily are early marked hard, and then bronchial, breath due to increased sound conductivity of pulmonary stroma with interstitial edema. On later stages, breathing may be impaired or not even be present at all ("mute" or "silent lung"), especially in lowback parts. Rales are not abundant, mostly dry, although a crackling sound can be heard. Sputum is poor or may be absent unlike hemodynamic ("heart") pulmonary edema, which is characterized by copious amounts of foamy sputum.

In blood gase analysis the first sign is hypocapnia, then appears and increases hypoxemia and only in the terminal phase hypercapnia increases. It is characteristic of metabolic alkalosis.

X-ray pattern reflects the main stages in RDS development. Initial stage is characterized by signs of interstitial pulmonary edema: general strengthening of the pulmonary pattern over all parts by means of perivascular and peribronchial fluid accumulation. Unlike other organs, lungs are normally characterized by two ways of
lymph outflow - to the center and to the periphery (in the direction of pleural cavity). Therefore, increase of lymph outflow toward the center leads to the increase of shade and loss of lung structural roots. Direction of lymph outflow to the periphery of lungs contributes to appearance of moderate excess fluid in pleural cavity and stressed interlobular boundaries.

In RDS progression and development of alveolar edema phase, first there appear small (a "blizzard" symptom), and then larger focal and confluent shadowing, mainly in lowback of lungs.

Approaching to the terminal phase is characterized by intense homogenous shading of lung tissue in the lower and middle sections, merging with shadows of heart and diaphragm (liver). Airiness retain only on the top of lungs.

Radiographically detectable signs of RDS can be completely balanced or dominate in any part, especially in cases of prior pneumonic foci, around which perifocal changes in lung tissue are more pronounced.

As noted above, RDS is accompanied by severe hypoproteinemia, which leads to decrease in oncotic pressure and hypovolemia with blood clotting (thickening), which contributes to microcirculatory disorders and labilizes central hemodynamics. Disorders of the latter and direct influence of toxic substances to kidneys are accompanied by decreased urine output and positive water balance in general, hepatic dysfunctions reflect the moderate increase in concentration of bilirubin and transaminases.

Mild leukocytosis is possible, but often the total number of leukocytes is not excessive, with a slight shift to the left and relative decrease in the number of lymphocytes. Also falls the phagocytic activity of leukocytes. There is marked the toxic granulation of neutrophils.

One of the few methods of objectifying and quantifying the intoxication level is to determine the concentration of medium molecular oligopeptides of blood (level medium molecules). The most simple and affordable rapid test is in fact a method proposed by N.I. Gabrielian, giving an integral characteristic of this indicator. The normal level of medium molecules is retained within 220-250 units. In moderate intoxication, this index rises to 350-400 units, in severe - to 500-600 units, with maximum increase to 900-1200 units, which reflects almost incurable state. More fully the nature of endotoxemia is identified with the method of determining medium molecules, proposed by M. Ya. Malakhova (1995). In recent years, to diagnose the severity of septic complications there has been determed the level of procalcitonin (normal – 0.1-0.5 ng/ml, 0.5-2.0 ng/ml – moderately excessive, 3.0-30.0 ng/ml – high, 100.0-1000.0 ng/ml – very high) [O.P. Shestenko et al, 2005].

One of the most precise criteria for RDS diagnostics are various methods for determining the volume of extravascular lung fluid (ELF). In vivo, in dynamics as well, there can be used various colorful, radionuclide techniques and thermodilution. Noteworthy are the results of such research, testifying that even after mild surgical
procedures outside the chest cavity, there are signs of ELF increasing. It is also noted that even a twofold increase of ELF volume still could not be accompanied by changes determined clinically, radiologically, or laboratory (blood gases). When the first signs of RDS are observed, it means there is already the far gone disease process.

Taking into account these data, the true frequency of this complication can be questioned. It can be assumed that RDS phenomenon is almost constant companion of many pathological conditions and diseases. There should be referred not so much the frequency, y of RDS, as the frequency of the particular RDS severity. Probably this is the extreme view, but it is closer to the essence of the problem, than actually its complete negation in a wide range of diseases, because, admitting the fact of RDS, we can duly put the question of pathogenetic therapy.

Treatment of respiratory distress syndrome

Unfortunately, at present, RDS is not always diagnosed. In case of complications against viral and bacterial pneumonia, only the dynamics of the process spread in the lungs is recorded without proper pathogenesis evaluation of the observed changes in respiratory parenchyma. When RDS arises against severe injury and operative interventions, pancreatitis, septic and burn shock, there are often made such unconvincing diagnoses as "hypoventilation" and "hypostatic pneumonia".

Traditional approaches to the treatment are largely determined by the above diagnoses and therefore inadequate evaluation of the causes of this complication. Where the cause is only the inflammatory component of pathogenesis, the effort is aimed at providing antibacterial therapy, search for new, more powerful antibiotics of "super wide" action. It is believed that the process progression is associated only with low sensitivity of causative agents to antibiotics.

Of course, it would be unwise to reject the use of antibiotics in those cases where microbial flora is a major etiologic factor. Even with the development of RDS against injuries and major operations, microbial inflammation can be easily added to those changes in lungs, which occurred due to permeability failure in cell membranes and toxic pulmonary edema. Therefore, antibiotics should remain in complex treatment and prevention.

Similarly, it is necessary to use remedies to improve the resistance of organism (vitamins, immune-boosting drugs), cardiotonics, stabilizers of membranes, antioxidants, disaggregants.

However, any, even the most effective antibiotics, killing bacteria, are not able to eliminate their toxins, and microbial bodies themselves require a special system of elimination, but with reduced phagocytic activity they linger in the body and continue their harmful effects. The very fact of microbial infection activation suggests the
weakening of the organism's defense system, its inability to cope with the pathological condition. One of the major reasons for the suppression of immune defense is the fact of initially transferred influenza or other respiratory viral infections, immunosuppression in patients weakened by previous chronic illnesses, intoxication. Among the latter, significant are not only alcoholism and drug addiction traditionally considered in such cases, but consequences of a number of environmental, industrial, food factors, etc.

Many doubts are caused by the cases of using drugs and transfusion means improving the rheology of blood. Justification of this treatment appear quite convincing, as above mentioned hypoproteinemia reduces the oncotic blood pressure, that prevents necessary amount of liquid from keeping in the bloodstream, a natural consequence of which is hypovolemia, only partially compensated by increase in cardiac output during tachycardia. A logical tendency is to use transfusion therapy to restore oncotic pressure and CBV by colloid plasma substitutes and even albumin [Shoemaker W.C., Wo C.C., 1998].

When these solutions are retained by endothelium and remain in circulation for a long time, everything would go well in the norm, but in terms of increased porosity of the vessel wall, they "fall" to the interstitial space, increasing the oncotic pressure there, even more stimulating the passage of fluid from the bloodstream to tissues [Nazarov I.P., Vinnik Yu.S., 2002]. And it wasn't once, when transfusion tactics done with the best intentions and being quite justified, in just a day resulted in almost total lung hepatization, severe respiratory failure.

Even in absence of frank endotoxemia in patients undergone major surgery, with excessive positive water balance of more than 67 ml/kg of body weight within a day, there may develop severe pulmonary edema with a fatal outcome [Arieff A.I., 1999]. Extrapolating own clinical data to the nationwide (USA), the author believes that there can occur from 8,000 to 74,000 fatal cases a year from postoperative pulmonary edema.

In no doubt is oxygen therapy, i.e., by some means adding oxygen to the inspired air, since extension of the alveolar-capillary membrane in edema sharply reduces diffusion of oxygen through it, although carbon dioxide as a more soluble, still retains the ability of adequate elimination. However, hopes for recovery of gas exchange function in lungs by means of artificial lung ventilation (ALV) seem rather illusory, since the ventilation is really capable of correcting the ventilative respiratory insufficiency, but diffusion failures at the level of alveoli make its use in parenchymatous respiratory failure unsuccessful. Though resuscitators of Europe and America are still hoping to select some special ALV parameters, in particular by increasing pressure in the airways at the end of exhalation.

One must admit that maintaining pressure of 5-10 cm H\_2O at some point can improve gas exchange by hyperinflation with not yet completely filled alveoli exudate. However, special physiological studies have shown that not only isn't VELF reduced,
but even increased because of higher porosity of hyperinflated alveolo-capillary membrane, increased filtration area and obstacles in lymph outflow from lung parenchyma with increase of intrathoracic pressure [Caldini P. et al., 1975; Demling R.H. et al., 1975]. It is known that long-term artificial ventilation even in ventilative disorders stimulates fluid retention in lungs, inhibits diuresis, contributes to lung barotrauma [Kolesnichenko A.P., Gritsan A.I., 2000].

Apart from that, almost natural complication of prolonged ALV is pneumonia that develops not only as a result of microbial insemination of respiratory tract, but also in the development of systemic inflammatory response syndrome (septic shock) with the release of cytokines such as interleukins 6 and 8 (IL-6, IL-8) and tumor necrosis factor alpha (TNF-α). At the same time it is noted that increase in their level occurs even 3-4 days prior to pneumonia development [Bouten M.J. et al., 1997; Ranieri V.M. et al., 1999]. Joining pneumonia against RDS is difficult to diagnose, because its symptoms such as leukocytosis, fever, and radiographically determined changes (infiltration of lungs), are already available in RDS without infection. On the other hand, endobronchial and pathomorphological studies suggest the presence of respiratory infection on 2-6 days, and pneumonia signs on 5-12 days of RDS development [Delclaux C. et al., 1997]. In addition, ALV leads to damage of tissues and other organs, in particular to apoptosis of epithelial cells of kidneys and small intestine, which enhances the manifestation of multiple organ failure even more [Imai Y. et al., 2003].

Because of development of methods on producing synthetic or semi-synthetic surfactants, in recent years has increased interest in the possibility of their use in RDS treatment. S.V. Baudouin (1997) used a synthetic surfactant drug (dipalmitoyl-phosphatidylcholine 13.5 mg/l) in 364 patients with RDS. Comparison group consisted of 360 patients similar in age, APACHE III severity level (70.5% of these patients were in both groups). However, no effect on the survival rate, ALV duration and stay in the intensive care department or a state of physiological lung function was observed. The same conclusion was reached by A. Anzueto et al. (1996) when analyzing the results of large randomized study of surfactant therapy effectiveness in 700 patients. Surfactant use could reduce ALV duration and length of staying in the intensive care department, but there was no significant reduction in mortality rate (causes of deaths were sepsis and multi organ failure). Surfactant use in infants provided a more rapid decline of FiO₂ up to 40% and reduction of ALV length, but survival increase by 7 and 28 days wasn't achieved as well [Shalamov V.Y. et al, 1999].

This is understandable, since our above studies have shown that surfactant is destroyed as a result of circulating toxic products penetrating into alveoli. Therefore, no matter how much surfactant is added to the lungs, but if toxic substances are not removed from blood, re-injected surfactant will be destroyed, just as the own one.
In connection with the development of methods for the preparation of synthetic or semi-synthetic surfactants in recent years has been increasing interest in the possibility of their use in the treatment of RDS [Yakovlev V.N. et al. 2011]. However A. Anzueto et al. (1996) when analyzing the results of a large randomized trial of surfactant therapy in 700 patients revealed no any effect on the rate of survival, duration of mechanical ventilation and stay in the ICU, or the state of the physiological functions of the lungs. Many later studies have also noted a short-term effect of administration of exogenous surfactant [Briel M. et al., 2010; Matthay M.A., Zemans R.L., 2011].

Use of surfactant can reduce the duration of mechanical ventilation and length of stay in the ICU, but a significant decrease in mortality did not occur [Vlasenko A.V. et al. 2006; Cerkova M., Matthay M.A., 2006]. Surfactant administration in infants provided more rapid decline in FiO2 to 40% and reduction in the duration of mechanical ventilation, but to increase the survival rate of 7 and 28 days also has not been achieved [Shalamov V.Y. et al. 1999].

This is understandable, since our studies described above have shown that the surfactant is destroyed as a result of penetration into the alveolus of circulating toxic products. Therefore, no matter how much of surfactant added to the light, but if you do not remove toxic substances from the blood, re-entered the surfactant will be just as well to break down, as well as your own.

Thus it is not entirely satisfactory use of surfactant, on the one hand, and achieving much better results in the application of methods of detoxification for the RDS, on the other hand, suggests that the true cause of the fall of surfactant activity is its inhibition of toxic substances that penetrate into the alveolus in toxic violation of vascular permeability. Thus introduced exogenous surfactant, as well as natural and falls under the effect of these toxic substances and stops its activity.

Using detoxification, promotes the elimination of porosity vascular pathogenesis is more than justified by the treatment of RDS, because after the cessation of receipt in the alveolus of toxic substances in the coming hours restored reproduction of natural surfactant, which eliminates the need for its introduction of exogenous drugs.

This also applies to cases of RDS in premature infants, in whom there is indeed a shortage of surfactant, but most often develops in the RDS "adult" type – as toxic pulmonary edema as a result of entering to the bloodstream of the fetus endotoxin mother in violation of the pregnancy, which caused the premature birth. Therefore, such a newborn is more justified use of detoxification – a specially developed method syringe membrane plasmapheresis [Voinov V.A. et al. 1996], after which there is no need in the additional introduction of exogenous surfactant.

Thus, the results of the studies, confirming the toxic nature of the violations of surfactant activity in acute lesions of the lungs, give reason to assume that the termination of admission to the alveolus of toxic substances from the bloodstream by
the methods of detoxification is more justified than the additional administration of exogenous surfactant.

In the seventies of the XX century these facts made some scientists refer to using extracorporeal gas exchange with the help of membrane oxygenators, which by then had been produced to improve the results of open heart surgery. In animal experiments it was possible and safe to maintain gas exchange for up to three weeks with the membrane oxygenator. This provided a basis for their use as supporting extracorporeal membrane oxygenation (ECMO) in acute parenchymatous respiratory failure.

The first results of RDS treatment with ECMO were quite encouraging. Indeed, immediately after connection of membrane oxygenators gas exchange was restored, patients’ condition stabilized. However, the inverse dynamics of considerable pathological changes in lungs were not noted. After the procedure, inflammatory and destructive processes progressed again. Favourable outcome could be reached only in 20-30%, mostly among children. In recent years, ECMO effectiveness has increased to 47-60% [Bartlett R.H. et al., 1996; Kolla S. et al., 1997; Zabrocki L.A. et al., 2011].

GJ Peek et al. (1997) summed up the seven year experience in ECMO applying in 50 patients with RDS and the overall survivability of 66%. With the help of percutaneous cannulation it was possible to reach speeds of veno-venous perfusion of up to 120 \( \text{ml/kg} \cdot \text{min} \) and provide extracorporeal gas exchange for an average of 207 hours. During this period the patient needed the transfer of up to 19 doses of blood, significant values of donor plasma, platelet concentrates, provision of parenteral nutrition, day and night surveillance and maintenance of highly skilled specialists, which required considerable financial expenses far exceeding $100,000. Use of ECMO for the treatment of neonatal respiratory distress also required not less than $50,000 [Roberts T.E., 1998]. Given such difficulties and complexity of ECMO operations, they are not widely known. However, extracorporeal membrane oxygenation has taken a definite place in treatment of RDS, recommended by mentioned Conciliation Commission.

In some cases there is used a method of extracorporeal CO\(_2\) removal through membrane oxygenators, but own lungs are maintained in a state of functional rest, ensuring constant and almost oscillating flow of oxygen to maintain an adequate level of oxygenation [Morris A. et al., 1994; Falke K.J., 1997].

In recent years there have been describes attempts to use the full or partial liquid ventilation with perfluorocarbon with maintaining the normal mode of gas ventilation or ECMO, which have shown quite promising results in treating RDS, in both adults and neonates [Cox P.N. et al., 1997; Kolla S. et al., 1997; Yoxall C.W. et al., 1997]. Using high ventilatory support against partial liquid ventilation has showed no advantages over the conventional volumetric ALV [Smith K.M. et al., 1997].

Nevertheless, conventional methods of intensive therapy are still most commonly used with different variants of lung ventilation. S. Vasilyev et al. (1995) summed up the
experience of 25 centers in the USA and Europe, where there were 1426 patients with RDS. Everyone was performed artificial ventilation. If in the beginning of ALV with FiO$_2$ of 0.5 and more, there was no hypoxemia or hypercapnia, but survivability was 63.6%, if there was a significant hypoxemia and hypercapnia, survived 33.3% of patients. If there was only insufficient acute respiratory distress, 40% of patients survived, with multiple organ dysfunction there were not more than 10% survivors.

It is possible to find information about financial expenses for conservative RDS treatment [Angus D.C. et al., 1996]. Average cost was $79.355 (for survivors - $83.437, for the dead - $ 71.073), which is not much less than in using ECMO. Given that annually in the U.S.A. RDS occurs in 126,000-159,000 patients (mortality - 30-60%), the total cost of treatment ranged from 9.6 to 12.7 billion dollars. In this case, therapy, which had reduced treatment cost for at least 1%, would have resulted in total saving of up to $100 million a year.

The presented analysis shows the complexity of RDS treatment issues, but also the almost complete absence of pathogenic approach to its therapy, which consists in ignoring the fact of endotoxic nature of lungs' and other organs' damage and, as a result, not using methods of detoxification, apart from a number of cases of hemofiltration against ECMO.

Our own initial attempts of extracorporeal membrane oxygenation in RDS did not yield the expected results because of inability to halt the progression of pathological processes in lungs and multiple organ failure, despite the correction of impaired gas exchange during surgery.

On the one hand, these failures and, on the other hand, results of experimental studies that showed the toxic nature of lungs' and other organs' damages, have convinced us of the need to use methods of detoxification. In these conditions only methods of direct blood detoxification can halt progression of the process, breaking various vicious circles.

**Detoxication methods in respiratory distress syndrome**

In 1980-1990 Russia's most accessible and safe method of detoxification in RDS was **hemosorption** (hemocarboperfusion) using activated carbon of SKN, SUGS, VNIITU marks, etc. When passing up to 3-4 CBV through a column, many pathological products were completely eliminated, and even live bacteria were retained and fixed, which, for example, in infections caused by *Pseudomonas aeruginosa* is the only truly effective method of treatment, because antimicrobial therapy is inadequate. The level of medium molecules reduced as well as toxicity of blood in general (according to the survival time of protozoa), the general condition improved, changes in lungs underwent involution seen in X-ray study [Voinov V.A. et al, 1985, 1989, 1992].
Hemosorption was effective in destructive processes, and even in pulmonary gangrene. It is natural that areas of lungs subject to ichorization could not restore the structure, but perifocal changes and intoxication reduced, which allowed to prepare patients quickly for the inevitable surgery that was easier tolerated. Despite the remaining areas of gangrene, disappearance of quite intolerable smell of breath was surprising. This indicated that the smell of breath is formed not only in the respiratory tract, but mainly by penetration of pathological products from blood through aerohematic barrier. It means, this was the smell of the blood itself, reflecting the accumulation a large number of pathological decay products in it.

However, in advanced stages of RDS against frank parenchymatous respiratory failure that required artificial ventilation, hemosorption was no longer capable of changing the course of the pathological process. Instead of the expected decline, the level of medium molecules increased above the initial, apparently due to their leaching from depot and damaged tissues, improval of microcirculation and blood rheology. The clinical picture also showed increasing severity of multiple organ failure. In these conditions only extracorporeal membrane oxygenation (ECMO) at a speed of 25-30% of blood flow cardiac output and up to two days made it possible to gain time, i.e., to maintain gas exchange at the lowest appropriate level and during this time to provide more active detoxication. Only this combination of a massive detoxication (up to three hemosorption sessions during a day) during ECMO made it possible to provide regression of organ lesions in extremely severe stages of RDS. Out of ten such incurable patients it was possible to save seven [Voinov V.A. et al, 1985, 1995].

It should be noted that, according to G.J. Peek et al. (1997), for RDS treatment with ECMO on the average there were needed 207 hours and a lot of donor blood, plasma, platelet suspension and other drugs, which explained extremely high cost of such courses (over 100 000 dollars). But in our case, to relieve very severe RDS it took only 20 - 40 hours. The difference in the tactics of treatment was the only one - together with ECMO we performed intensive detoxication with hemosorption, which is ignored in America and Western Europe.

It is necessary to emphasize once again that during ECMO true therapeutic effect was created by detoxication, which would have never been achieved with the most adequate and continuous membrane oxygenation that we reckoned upon earlier, and that is still recommended in isolation (without detoxication).

Nevertheless, detoxification alone, achieved by means of hemosorption, is also insufficient for the full therapeutic effect, since the body remains in a state of immune suppression, due to which there has been created possibility of developing this severe complication. More stable result is achieved by performing plasmapheresis with replacement of removed plasma from the patient with "incompetent" antibodies, immunoglobulins, complement, opsonins to native plasma, above immune components of which immediately begin to fight against pathogens and other pathological products.
This provides more reliable results, particularly when replacing the plasma in volume close to patient’s CPV. In this case, to be fair, it is necessary to emphasize that this is actually not so much of plasmapheresis as plasma exchange. After all, in terms of hypoproteinemia it is impossible to remove even a small volume of plasma without its immediate replacement for the donor one at a ratio of 1:1. In recent years we have almost completely switched to this tactic [Voinov V.A. et al, 2007].

All patients received medication and traditional therapy, and the development of respiratory failure – artificial lung ventilation (ALV), in severe cases, with a positive end-expiratory pressure (PEEP).

There are 3 allocated degrees of RDS – moderate, severe and highly severe, focusing on the level of hypoxemia, medium weight oligopeptides (“middle molecules”) and to the area and intensity of lung shading on X-ray examination (table 2).

Table 2.

<table>
<thead>
<tr>
<th>RDS degree</th>
<th>Severity criteria</th>
<th>Middle molecule level</th>
<th>PaO₂</th>
<th>Area of lung shading in X-Ray</th>
<th>Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Moderate</td>
<td>350.0±22.5</td>
<td>68.2±1.8 (at FiO₂ 0.4)</td>
<td>Lower sections (or sources)</td>
<td>Self-maintained</td>
</tr>
<tr>
<td>II</td>
<td>Severe</td>
<td>444.2±45.3</td>
<td>60.3±0.8 (at FiO₂ 0.7)</td>
<td>Lower and middle regions</td>
<td>ALV+PEEP</td>
</tr>
<tr>
<td>III</td>
<td>Highly severe</td>
<td>680.1±52.6</td>
<td>44.7±0.9 (at FiO₂ 1.0)</td>
<td>Complete hepatization of lungs</td>
<td>ALV with PEEP</td>
</tr>
</tbody>
</table>

Allocation of patients according to the degree of evidence of RDS is presented in table 3.

Table 3.

<table>
<thead>
<tr>
<th>Degree RDS</th>
<th>Methods of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>I</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Among patients with moderate RDS there were no deaths, but the duration of the treatment using the methods of detoxicating was significantly shorter – 28.0±1.5 versus 40.3±3.3 days in the control group (p<0.05). The mortality rate for severe and highly severe degree of RDS is presented in Table 4. It should be noted that a subgroup of patients with a highly severe RDS treated with only traditional methods did not stand alone, because in such cases the mortality rate was 100%.

Table 4.

Mortality rate for different degrees of RDS depending on the methods of treatment

<table>
<thead>
<tr>
<th>Degree of RDS</th>
<th>Methods of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only traditional</td>
</tr>
<tr>
<td>I  Moderate</td>
<td>0</td>
</tr>
<tr>
<td>II Severe</td>
<td>73.33%</td>
</tr>
<tr>
<td>III Highly severe</td>
<td></td>
</tr>
</tbody>
</table>

As seen from the table, even with moderately-severe RDS use of detoxification allows faster and more reliable arresting of acute lung injury, but in severe cases it is reflected also in the overall outcome of the disease. It should be noted that the earlier methods of detoxification were used, the more expressed and evident was their effectiveness. Thus, as a rule, it was enough to have just one session hemosorption or plasmapheresis with UV or laser irradiation and indirect electrochemical oxidation of blood to provoke a turning point in the course of the disease and subsequently the body itself, and at a lower level of medical support, would cope with new complications. Severe cases of RDS often require repetition of two or three sessions of detoxification to achieve stabilization and regression of lesions of lungs, but their belated application is not able to save all the patients.

With extremely severe cases of RDS with almost total lung damage develop severe pulmonary parenchymal respiratory failure, not corrected by any means of mechanical ventilation. In these cases, ECMO provided a more rapid normalization of
gas exchange, and carried out in parallel intensive detoxification (up to three sessions per day) contributed to the elimination of toxic edema of the lung parenchyma with restoring the degree of "airiness" at lung X-ray examination after 7-15 hours, and by the end of ECMO they managed to recover quite a satisfactory level of gas exchange function of the lungs. Overseas ECMO became far more widespread and its performance in recent years has increased to 47-60% [Bartlett RH et al., 1996; Kolla S. et al., 1997], but to achieve stable restoration of gas exchange it usually takes from several days to two weeks of such treatments. And at the same time none of detoxification methods are generally used. In our practice, with parallel hemosorption it is sufficient to have 20-44 hours of ECMO [Voinov V.A. et al., 1995].

Endotoxemia, which determines the severity of RDS and the scale of destruction of lung parenchyma, is quite multicomponent. It consists of bacterial endo- and exotoxins, mediators of inflammation and tissue destruction, and proteolysis products as well as lipid peroxidation. All of these toxins disrupt cell membrane permeability, including vascular endothelial with access not only to interstitial fluid, but also to the protein. Such a toxic edema underlies the development of RDS, but to the same extent it affects other organs and systems, leading to multiple organ failure [Voinov V.A., 2007].

However, only detoxification, achievable through hemosorption is not enough for full therapeutic effect, because the body is still in a state of immunosuppression due to which at one time opportunity to develop this serious complication was created. More stable result is achieved through conduct of plasmapheresis with replacement of remote plasma of the patient with "incompetent" antibodies, immunoglobulins, complement, opsonized by native plasma, above mentioned immune the components of which immediately begin to fight against pathogens and other abnormal products.

It should be noted that this approach not only normalizes the humoral but also cell-mediated immunity since a complement does not occur without opsonization receptors of macrophages, without which it is not possible to capture and subsequently destroy pathogens. This provides more reliable results, particularly when replacing plasma volume approaching CPV of the patient. At the same time, in fairness, it should be emphasized that this is actually not so much of plasmapheresis as a plasma exchange. Indeed, in a hypoproteinemia we cannot remove even a small volume of plasma without immediately replacing it with a donor at a ratio of 1:1. Recovery of the level of immune protection is also facilitated by photohemotherapy and indirect
electrochemical oxidation potentiates detoxification. And in recent years, we have almost completely switched to such tactics.

An example of such a leading role of endotoxemia and immunosuppression on the emergence and development of life-threatening RDS and effectiveness of detoxification is the following clinical observation.

Total lung damage with severe multiple organ failure developed in a patient S., 40 years old, suffering from sarcoidosis, long-term history of use of steroids. Gradually deepening immunosuppression determined the scale and speed of progression of respiratory infection. By the beginning of efferent therapy the patient was in a critical condition. ALV with PEEP did not correct parenchymal hypoxic respiratory failure and coma. X-ray examination revealed an intense and almost total shading ("hepatization") of the lungs. Hepato-renal failure manifested by significant fluid retention in the body with an increase in serum creatinine, bilirubin and transaminases. Central hemodynamics was maintained by sympathomimetics, frequent group politopnye ventricular extrasystoles were detected.

Donor plasma was not available, so the first phase of efferent therapy aimed at detoxification included hemosorption of 6 liters of blood with its laser irradiation and indirect electrochemical oxidation. The next day the condition stabilized to some degree. 500 ml of urine was received. X-ray showed signs of airiness in upper parts of lungs. Almost recovered was the normal rhythm with single extrasystoles, sympathomimetics were cancelled.

At that, the repeated screening of efferent therapy was conducted - membrane plasmapheresis with exchange of 1500 ml of fresh frozen plasma to the donor, and with laser irradiation and indirect electrochemical oxidation of the blood. The next day, we observed recovery of consciousness and spontaneous breathing, followed by a more rapid recovery of lung function and other vital organs and complete recovery.

It should be emphasized that this patient was in one of the district hospitals of Leningrad region and detoxification on the road has been possible with the help of a portable domestic unit AMP-TT "Hemofenix", with which you can conduct both hemosorption and plasmapheresis.

Massive plasma exchange leads to a more rapid normalization of homeostasis. Unlike hemosorption, there is not only a more reliable and complete removal of all pathological products, regardless of their electrochemical activity, but also a full recovery of all plasma components – proteins with normalization of oncotic pressure.
and volemic balance, hormone-enzyme activity with recovery mechanisms of autoregulation [Nedashkovsky E.V. et al., 1999]. All this allows to completely prevent the dramatic scenario of RDS development and provides a more rapid and full improving, meaning the regression of a toxic edema of the lungs and other organ failures, a complete restoration of their functions and ultimately - recovery [Voinov V.A., 1995; Gromov M.I., 1996]. Use of plasmapheresis with photomodification of blood in cases of patients with acute pneumonia reduced the time of their stay in a hospital bed from 24.1 to 19.9 days, increased frequency of full recovery from 21.6 to 42.9% and prevented deaths [Karmanova I.V., Lujnova T.M., 2002].

The same positive effect was achieved with the use of detoxification (membrane plasmapheresis), in cases of respiratory distress syndrome or neonatal RDS, including seriously premature children with weight of up to 700g in which cases the surfactant deficiency is the main pathogenetic mechanism of lung lesions. At the same time without any additional surfactant for several hours on X-ray examination we could also see recovery of lung airiness [Voinov V.A., 2005].

Thus, no fully satisfactory results of using a surfactant on one hand, and the achievement of much better results in the application of methods of detoxification in cases of RDS, on the other hand, suggests that the true reason for the drop of surfactant activity is its inhibition by toxic substances penetrating into the alveolus with toxic violation of vascular permeability. This introduced exogenous surfactant, as well as the natural one, is affected by these toxic substances and stops its activity.

Use of detoxification, promoting the elimination of porosity of vessels is a more pathogenically reasonable treatment in cases of RDS, as after the termination of admission to the alveoli of toxic substances in the coming hours there is a restoration of reproduction of natural surfactant, which makes it unnecessary the need for the exogenous drugs.

This also applies to cases of RDS of premature infants, where there is indeed a deficiency of surfactant, but the most common case is development of RDS "adult" type - a toxic pulmonary edema as a result of infiltration into bloodstream of the fetus of endotoxins of the mother in cases of violation of pregnancy, which causes premature birth. Therefore, for such a newborn the use of detoxification is more justified - specifically developed method of syringe membrane plasmapheresis [Voinov V.A., 1996], after which there is no need for additional introducing exogenous surfactant.

The following clinical observation may serve as an example.
Child M. with body mass of 700 gr was born at the time of 22 weeks with severe pre-eclampsia in a critical condition. Apgar index was 4-6. On the second day after birth we observed remaining severe hypoxia, not interrupted by mechanical ventilation of lungs. X-ray reveals practically total shading of lungs in the degree of density equal to the shadow of heart and liver. Anuria. On the screen we can see only ECG complexes with a straight line of registration of microcirculation from the sensor on the finger. Started syringe membrane plasmapheresis with the help of plasma filter “Rosa”. After replacing 50% of CPV on the screen we can already see oscillations with a finger oximeter - start of recovery of hemodynamics and microcirculation. At the end of plasma exchange (1.5 CPV) diuresis appeared. The next day, the state stabilized and in about half of the lung X-ray fields were already aerial. In the future, there have been observed quite a fast recovery dynamics of the lungs, kidneys, liver and recovery of the child.

For a more complete restoration of immune mechanisms appropriate combination of hemosorption and plasma exchange with methods of phototherapy. Oxidative methods have also been successful, mainly indirect electrochemical oxidation, meaning addition to the infusion solution of 200-400 mL of 0.06% of sodium hypochlorite.

Described in more detail is an example that reveals the pathogenesis of RDS and rationale for the use of methods of efferent therapy in case of development of this complication, and reflects a number of other clinical situations arising in severe burns and trauma, acute inflammatory diseases of the abdominal cavity, etc. In all these cases efferent therapy, however, cannot provide stable effect without toxicity source elimination, usually by surgical methods. But sometimes without prior detoxification it is impossible to provide a secure environment for operative treatment, and after surgery efferent therapy promotes more rapid normalization of homeostasis, a more complete and permanent cure [Chanchiev Z.M., 2012].

One can often hear concerns that during plasmapheresis important antibodies are extracted that developed after vaccination (smallpox, measles, tuberculosis, etc.). In a special study U.Schöntrmarck et al. (2011) actually showed a decline in measles, however, in an average of 64 days after a course of plasmapheresis they were fully restored to their original level.
It seems more reasonable, an active detoxification – hemosorption or plasmapheresis. And, indeed, almost always after removing “toxic press” from kidneys restoration of their excretory function happened. The next day the urine output was no less than 500-700 ml. In parallel, improved was functional status of other vital organs - lungs, liver, heart, brain [Voinov V.A. et al., 1995, 2012]. Especially revealing was the treatment of a patient with RDS and full anuria with eclampsia, which lasted for a month after delivery. After the session of hemosorption, the next day diuresis was already 500 ml, and after repeated sessions it recovered fully followed by a rapid recovery of the patient.

Besides kidneys failure occurs in other vital organs to some degree. Upon accession of acute liver failure there is an increase of bilirubin levels much, and, even more, of enzymes - ALT and AST. And removing the “toxic press” from hepatocytes rapidly normalizes liver function. At the extreme hypoxia there is impact on structures of the brain, down to the deep hypoxic coma. Growing frustration at both the central and peripheral circulation is present.

Furthermore, toxic products circulating in the blood, not only damage the vessel walls, but also the cells of the blood itself. The first is excited platelet aggregation with the formation of platelet microaggregates, which is the first step in the development of DIC with all its consequences. The risk of bleeding rises, and not only from the lungs in the form of hemoptysis, but, even more dangerous, from profuse bleeding from erosions and acute ulcers of the stomach. Their appearance can also be associated with endotoxicosis and disorders of microcirculation at the level of the mucous membrane of the stomach. In places where there is tissue ischemia soon appear the sources of their destruction with the appearance of erosions and acute ulcers, of which at any time may cause bleeding.

Given the extremely severe cases of RDS along with multiple organ failure and hemodynamic disturbances occur, making it difficult to carry out any procedures extracorporeal detoxification. However, domestic device «Hemofenix» provide the possibility of plasmapheresis with plasma filter «Rosa» and hemosorption with any available hemosorbent, even with unstable hemodynamics, supported by a relatively satisfactory level only with sympathomimetics. This was possible when taking into account the small volume of prefilled extracorporeal circuit of this unit, not to exceed 65-70 ml, which makes it possible to provide treatment even for children up to the age of breast.
Therefore, treatment of patients with RDS in critical condition is a rather difficult task. Recently, we had developed a treatment strategy taking into account all sides of the pathogenesis of RDS and acceding multiple organ failure.

Given the large proportion of the probability of the circulation in the blood of a number of pathogens at the first stage it is advisable to resort to massive hemosorption, which in addition to a significant detoxification by passing through a molecular 1-2 bcc column provides and decontamination - a delay on the sorbent agents, both living and dead, which leads to stabilization of the patients. Functions not only light, but all other vital organs are improved.

In the second stage, the very next day, you can start plasmapheresis to remove at least 60-80% of CPV and substituting it with an equal volume of fresh frozen plasma donation. Thus, in addition to detoxification we have correction ("prosthesis") of the immune system with a reduction of not only humoral but also cellular immunity. Very often these sessions of hemosorption and plasmapheresis may be enough for the body itself to restore its autoregulation and end the critical state.

It should be taken into account that high risk of bleeding requires special tactics and use of anticoagulants. First of all, heparin is completely excluded, and the prevention of blood thrombosis in the extracorporeal circuit is provided by a solution of sodium citrate. The best of them is domestic solution "CPG" (citrate-phosphate-glucose), which is more efficient than imported solution ACD-A. In the first active principle - sodium citrate - concentration of 3.2%, and ACD-A is only 2.2% under similar other constituents.

The following observation serves as an example of a highly difficult treatment of RDS in development.

**Girl D., 2.5 years old, weighing 15 kg, suffered from acute lymphoid leukemia. After high-dose chemotherapy with stem cell transplantation severe RDS against septic conditions developed due to almost complete absence of circulating white blood cells. RDS was accompanied by acute renal failure with unstable hemodynamics and hypoxic coma. After hemosorption condition has stabilized somewhat, body temperature decreased, urine output activated. Plasma exchange with replacement of 1.2 CPV proceeded without significant hemodynamic disorders. However, the persistence of deep leukopenia again activated septic inflammation and 2 weeks later again we had to repeat the same course of extracorporeal blood correction - hemosorption and plasmapheresis, after which the girl's condition finally stabilized, recovered consciousness, as well as adequate gas exchange and function of other organs.**
This case shows possibility of success of extracorporeal detoxification and immunomodulation in extremely severe cases of RDS not only in adults but also children, among whom were 3-6-month-old infants.

However, we should not wait for such a critical condition and perform adequate treatment in the early stages of RDS when the negative dynamics of its development already emerges. Thus, it is necessary to take into account increase the severity of RDS, fairly rapid in some cases, where just a few hours you can "lose" these patients.
Membrane plasmapheresis

Daria, 2.5 years old (15 kg). Diagnosis - lymphoid leukemia. After high-dose chemotherapy and stem cell transplant respiratory distress syndrome, multiple organ failure and sepsis in the background complete lack of white blood cells developed. First hemocarboperfusion was performed, then plasma exchange with the «Hemofenix» device. Improvement, urine output recovered, the temperature returned to normal. However, because of leukopenia in 2 weeks new impairment, sepsis and hemocarboperfusion escalated again and plasma exchange has been completed, after which the recovery was evident.
The same girl a week after her final plasma exchange session.
Let us examine some features of the approaches in some different clinical situations.

### Acute renal failure

As noted above, adult respiratory distress syndrome is never isolated. It is often accompanied by a lesion in varying degrees, of other vital organs and, above all, kidney [Bolton WK, 2010]. Acute renal failure (ARF) is observed in one third of patients with acute pneumonia [Murugan R. et al., 2009]. It has long been observed that even in itself artificial lung ventilation, especially with a positive end-expiratory pressure (PEEP) reduces renal blood flow by 32%, glomerular filtration rate by 19%, and urine output by 34% [Annat G. et al., 1983; Ko G.J. et al., 2009; Koyner J.L., Murray P.T., 2010].

Often, ARF develops in the presence of sepsis or sepsis joins an already developed kidney disease [Schrier RW, Wang W., 2004; Bouglé A., Duranteau J., 2011; Mehta RL et al., 2011]. Risk factors include severe burns, pancreatitis and peritonitis traumatic shock syndrome and prolonged compression, eclampsia [Kirkovski VV, 1997; Mosier MJ et al., 2010; Serov VN et al, 2011]. Mortality is as high as 70-80% [Ko G.L. et al., 2009; Chou Y.H. et al., 2011].

However, as with RDS, with a variety of etiologic factors in the pathogenesis of ARF lies toxic damage of the renal parenchyma. Violations of the permeability of the vascular endothelium lead to perivascular edema with decreased renal blood flow, glomerular filtration, tubular necrosis, oligo-anuria [Bouglé A., Duranteau J., 2011]. According to the consensus reached at the conference of the working group on ARF (ADQI), the criteria for inclusion of patients “at risk” is decreased urine output to less than 0.5 mL / kg in 6 hours, to a group of "kidney disease" - less than 0.5 ml / kg 12 hours, the group "renal failure" - less than 0.3 ml / kg over 24 hours or anuria for 12 hours [Bellomo R. et al., 2004]. The risk of death in a group of "at risk" - 13%, in the "disease" - 40%, and "failure" - 80% [Stainvall I. et al., 2008].

But the survivors in a remote period, often showing signs of chronic renal failure. At the same time, despite the efforts methods of renal replacement therapy (permanent or preryvystoy hemofiltration), after discharge from hospitals mortality during the first year was 23%, and for the second year 7.6% more, which ultimately was 65, 7% [Van Berendoncks AM et al., 2010].

Such unfavorable prognosis in cases of ARF, of course, requires intensive care. However, as with RDS, when trying to treat respiratory failure through various methods
of artificial ventilation, in cases of acute renal failure of excretory function some tend corrected it through the measures of removing the accumulating fluid by hemodialysis or various methods of hemofiltration [Lins R.L. et al., 2009; Lo L.J. et al, 2009; Abe M. et al., 2010 Chawla L.S., 2011].

And in both cases, this approach was explained by the desire to eliminate the only visible disorders - breathing with RDS and diuresis in case of ARF. That is, it was actually symptomatic therapy not affecting the essence of pathology - endotoxemia, which is the basis of these organ disorders. And really - the mortality in these patients remained quite high - up to 50-70%, regardless of the choice of methods of "renal replacement therapy" - dialysis, intermittent or continuous veno-venous hemofiltration [House A.A., Ronco C., 2008; Russel J.A., 2008; Palevsky P.M. et al., 2009; Захаров М.В., 2010]. But the survivors in the long term often showed signs of chronic renal failure [Lo LJ et al., 2009; Hsu C.Y. et al., 2009; Chawla L.S., 2011]. In spite of the applied methods of renal replacement therapy (continuous or intermittent hemofiltration), after discharge from hospitals in mortality during the first year was 23% and in the second year of another 7.6%, which in the end was 65.7% [Van Berendoncks AM et al., 2010]. Using only hemofiltration we cannot remove macromolecular and no less toxic products, including fibrinogen, which causes the need to use plasmapheresis [Fülöp T. et al., 2011]. This confirms our belief that purely symptomatic therapy (removal of excess fluid) does not eliminate the problem of endotoxemia - a major factor tanatogenesis.

In particular, at high removal of cytokines such as TNF-α IL-1β, other cytokines - IL-6 and IL-8, more unfavorable in prognosis, were delayed in the body [Gromova E.G. et al., 2002]. A.M.Karas’kov et al. (2002) also noted that using hemodiafiltration can reduce the levels of TNF-α, IFN-γ and IL-4 with the correction of the flow of critical states, however, such a procedure did not influence the course of infection. That gave in correction only with plasmapheresis that contributed to the restoration of decreased production of INF-γ improvement of cellular and humoral immunity. Schmidt J. et al. (2000) used a combination of plasmapheresis with continuous hemofiltration.