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PLASMAPHERESIS FOR PREVENTIVE OF PREMATURE AGING

***Voinov, V.A.**

I.P. Pavlov First Saint-Petersburg State Medical University, Russia

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ABSTRACT

Old age is an inevitable biological process for all living organisms, including humans. However, the involution processes mechanisms are still not quite clear. Life expectancy of people is very variable and not all people live up to their predetermined age. And what can be considered to be this kind of deadline? In this review we aim to analyze the basic mechanisms underlying premature involution. Many studies show significant immune and metabolic disorders occurring in the elderly. In this case, there is a gradual accumulation of large-molecular metabolites and autoantibodies, which cannot be removed by the kidneys, and the medicines used often poison the body even more. Apheresis methods can be of great benefit to remove them from the body. In this case, plasmapheresis is considered to be the most simple, safe and effective method.

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INTRODUCTION

Preface

There is no doubt that the biologically predetermined human age is not less than 110 years, and according to some reports should reach 150 years, although in reality the average life expectancy does not exceed half of that period. It is difficult to say, whether there has ever been a so-called golden age of mankind, when people live to this age, as is evidenced by the Bible sources. On the other hand, there are evidences that ancient man lived in average about 40 years. Of course diseases and injuries of peace- and wartimes significantly shorten the period of life. So, according to insurance companies of Europe and the USA (and they deserve the greatest trust) 2% of population perish aged under 1 year, 5% - under 40 years, 15% - under 60 years. 65% of population dies up to 80 years, 90% - up to 90 years, and only the very few pass a centenary boundary. Even if a person avoids diseases and injuries for the lifetime, anyway, they will inevitably die due to *"old age."* But why in some cases the *"old age"* affects 60-year-olds, and in other cases spares 90-year-olds? What underlies the aging? Many authors dealing with these issues are limited to the findings concerning *"slagging"* of the body during lifetime, a kind of *self-poisoning*.

***Corresponding author:* Voinov, V.A.,**
I.P. Pavlov First Saint-Petersburg State Medical University, Russia.

What are the mechanisms of subsequent disorders? How does the immune system function, being our main guardian of *Health*, which largely influences the quality of our lives? The aim of this study is to try to answer these questions.

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, and Schiff bases are accumulated. Concentration increase of these natural metabolites leads to disorders and other metabolic processes, in particular, to excitation of proteolysis. So, for example a number of toxicants (heavy metals, combustion products, pesticides, etc.) can cause the neurodegenerative processes leading to disorders of the brain functions and even dementia [1]. Even more serious disorders of homeostasis occur in certain diseases. Thus, in acute inflammatory processes mediators of inflammation play an important role associated with increase of kininogenase-kinin cascade products in the blood such as biogenic amines (serotonin, histamine, kallikrein), contributing to shock-producing reactions worsening. Upcoming biochemical disorders of the internal environment inevitably affect the protection system - organs of detoxification, immunity, and excretion. Developing "toxic

burden" causes a cascade of subsequent disorders with 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 the immune system that can be subdivided into three main groups - stress, depression and immunity distortion. Immunity effort contributes to autoimmune pathology. There are possible increased formation of autoantibodies and immune complexes, and disorder of their degradation and excretion processes, 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 lead to development of fibrosis, granulomatosis, etc. Thus, different manifestations of connective tissue, glomerulonephritis, rheumatic fever appear. Immunity depression reduces resistance to 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 course, and to some extent incurability. These common features are disorders of the internal environment - homeostasis - due to either increased revenues or xenobiotics, including toxic and outside, or disorders 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 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 eliminating the reasons of the immune responses depression or distortion it is difficult to rely on a persistent immune correction. Without sanitation of the 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 burden" on the immunity, it is difficult to count on its recovery with only medical stimulation, and without which it is impossible to achieve a breakthrough in the disease course. 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 the organs and body systems.

Age immune disorders

Indeed, advancing with age, there are changes in the immune system as well, affecting all of its elements – stem cells, T- and B-lymphocytes, macrophages [2]. Since early childhood, there is a gradual deceleration of the "thymic hours" that manifests in reduced proliferative activity of T-cells, and a decrease in their effector and helper functions predisposes to infections and malignancies, the frequency of which is known to increase with age. There are decreased number and quality of the stem cells responsible for updating the basic functional elements of the body, maintaining health and life expectancy [3]. In old age increased susceptibility to infections does occur, which are some of the main direct causes of death [4-7]. There are especially frequent respiratory infections, pyelonephritis [8]. Even the effectiveness of vaccination wanes with age [9]. With age, the incidence of many other diseases also increases, such as cardiovascular diseases and cancer, diabetes and dementia [10]. Such changes in the body are often referred to as "age-related", "appropriate for the age."

The immunodeficiency weakens control for emergence of abnormal mitoses – cell fissions and emergence of tumor cells. They appear constantly and rather often in the body, however, possessing alien anti-gene structure, they at once get to *"field of vision"* of the immune guards and are destroyed right there. If these guards have missed the moment of their emergence and didn't destroy them in due time, soon their anti-gene structure is admitted to be their own one, which according to the all-biological laws blocks the corresponding antibodies development and predetermines the outcome of this antagonism of the body and a tumor. The main role in the removal of tumor cells belongs to cytotoxic lymphocytes, but the functions of T-cells are suppressed with age [11]. Therefore the most terrible consequence of an age-related immunodeficiency in elderly people is the increase of tumor growth probability [12] that is also confirmed in special researches of oncologists [13-16]. Moreover, there are findings that the cells, which are growing old, can affect the microenvironment and tissues due to allocation of the senecent-associated secretory phenotype (SASP) causing secretion of pro-inflammatory cytokines, which can stimulate emergence and growth of age-related tumors [17]. Removing these cytokines by means of a plasma exchange, it is also possible to prevent development of tumors. General immunostimulation, and, thus, antineoplastic effect of plasma exchange also promotes it. The most striking effects of immunodeficiency are manifested in a specific viral syndrome of acquired immunodeficiency – in AIDS, in which patients die either from infections or from malignant neoplasms. And senile immunodeficiency differs from AIDS, being its counterpart, only by the scale of immune disorders, maintaining the same essence. Slowing the rate of B-lymphocytes formation in the bone marrow also weakens the formation of antibodies to combat viral-bacterial infection. With age even antibodies the blood group (α and β) become weak.

The immune system function depends on the diversity of lymphocytes antigen receptors. With age, the general decline in the thymus and bone marrow lymphocytes ability to generate antigenic stimulation is combined with their clonal expansion. This leads to the emergence of monoclonal antibodies, and the direction of their reactions shifts from the external (foreign) to autoantigens. Accurate correlation between the age-related decrease in the thymus gland depressor function and development of autoimmune disorders is found. But the greatest danger has the weakening of T-cell suppressor function, which is accompanied by appearance of "forbidden" under normal conditions lymphoid cell clones reacting to self-antigens of the organism that causes different types of *autoimmune pathologies*, which is consistent with a higher prevalence in the elderly and senile various autoimmune diseases [12, 18-20]. However, there is evidence

of the fact that autoimmune diseases contribute to the acceleration of aging [21]. More than in 50% of the elderly different autoantibodies can be detected, but not in high concentrations of [22]. In particular, the content of antibodies to cyclic citrulline peptide associated with rheumatoid arthritis increases with age [23]. Therefore, rheumatoid factor causes the signs of arthritis, which are not as pronounced as in true rheumatoid arthritis, but a rare person in old age does not suffer from joint pain, considering them to be just the consequence of *"salt deposits."* There is evidence that "physiological" or "age-related" immunosuppression predisposes to rheumatoid arthritis development, and premature immunosuppression contributes to its development at a younger age [24]. Antinuclear antibodies can often be detected. With age, the concentration of anti-retinal autoantibodies increases, leading to senile macular degeneration [25-27]. There are characterized by the appearance of antibodies to *thyroglobulin*, causing autoimmune thyroiditis with hypothyroidism. On the other hand, thyroid hormones are necessary to maintain proper immune system activity, and hypothyroidism only aggravates immunodeficiency in old age. Interestingly, autoantibodies to three major thyroid antigens – *thyrolobulin*, *peroxidase* and *thyroid-stimulating hormone* are found in healthy individuals aged 18-24 years 10.6-14.9% of cases, but in the age of 55-64 y/o, this frequency increased to 24.2-30.3% [28]. Even healthy donors showed anticardiolipin antibodies with frequency 27%, of anti-DNA antibodies – 17%. Even senile dementia is a consequence of the appearance of autoantibodies to the elements of the central nervous system. In Alzheimer's disease mutations in genes may contribute to the appearance of autoantibodies presenilin-1 and presenilin-2 protein detectable by immunochemical methods in relation to the nerve fibers postmortem studies of the brain of these patients [29].

Mutations in DNA and RNA contribute to the appearance of protein molecules that differ from normal, and further leading to metabolic disorders. In particular, during Alzheimer's disorder there is a cascade of successive disorders, leading to deposition of amyloid plaques on the vascular walls, infiltration of microglia cell, apoptosis and ultimately increasing neuronal loss. One reason for this is the mutation of presenilin-1, which depends on the increase of amyloid-β deposits. There are also signs of a cerebral amyloid angiopathy, which is an important pathogenetic factor for the brain vascular disorders and even intracerebral hemorrhage in the elderly, having Alzheimer's disease. Both reasons and methods of treatment of this severe brain pathology are unknown; however, the above-stated facts testify the autoimmune nature of this "accumulation" disorder and do raise a question to use apheresis therapy methods. They are needed at least to delay the progression of this serious illness with the unpromising forecast and in recent years successful experience of plasmapheresis with replacement of the deleted plasma with albumin has been already described [30-32]. It is proved that 90% of the circulating beta-amyloid are connected with albumin and after a plasma exchange the donor albumin will mobilize amyloid from the brain, thereby promoting improvement of the cognitive functions in these patients [33]. As a result of autoimmune processes there are symptoms of Parkinson's disease, but not as intense as it is observed in Parkinson's disease. Its etiopathogenesis is not entirely clear, though there is evidence of autoimmune disorders presence. Elevated levels of cytokines and complement are revealed; in the cerebrospinal fluid there is an increase of T-cell autoantibodies (anti-alpha-synuclein and anti-GM1-ganglioside) and of vasoactive peptides in the peripheral blood [34-36]. It points to the possibility of using plasmapheresis in the treatment of this disease [37]. It was successfully performed courses of plasmapheresis in 29 patients with severe manifestations of Parkinson's disease with a decrease in the index of neurodeficiency from 28 to 8 units of Webster scale and autoantibodies levels [38]. Carrying out preventive plasma exchange may be able to prevent emergence of symptoms and this disease as well, for the risk of its development increases with age. Autoimmune processes underlie the formation also demyelinating diseases associated with widespread sclerosis of multiple sclerosis type and muscular dystrophy of myasthenia type. Appearance of paraproteinemia signs associated with accumulation of monoclonal immunoglobulin M-components resembling myeloma is characteristic for the old age.

Age metabolic disorders

Such metabolic disorders as disturbance of a cycle of uric acid, a remetylation, copper metabolism (*Wilson's illness*), a homocystinuria, cerebrotendinous xanthomatosis, an adrenoleukodystrophies and many others are also the reason for many neurologic and mental disorders [39-41]. True amyloidosis resembles amyloid deposition in the intercellular spaces, including formation of the so-called senile plaques that is the characteristic sign of old age in 60% of population. Amyloid deposition in the myocardium is also common in the elderly. Hypertrophic obstructive cardiomyopathy is the cause of about 50% of heart failure in elderly patients. It develops only due to diastolic dysfunction with the systolic function of heart ventricles preserved. Consolidation of the central arteries with increase of the vascular impedance promotes hypertrophy of the left ventricle in elderly subjects, even without development of arterial hypertension and other cardiovascular diseases. This pathology can come to light subjects over 50-60 y/o seen on Echo-Doppler-cardiography. One of the leading causes of gene mutations is accumulation of contractil proteins, such as cardiac β-myosin, cardiac troponin T, α-tropomyosin and C-myosin heart protein [42]. Restrictive cardiomyopathy results from infiltration and fibrosis of the left ventricle walls, resulting in its rigidity with earlier increase of diastolic pressure during its filling. It leads to increase of diastolic pressure in all of heart cameras with stasis of both pulmonary and systemic blood circulation, with small heart stroke volume syndrome. Amyloidosis is the most frequent primary cause while the less frequent one is sarcoidosis, sclerodermia, hemochromatosis, and tumors. The forecast in such cases is extremely unfavorable and depends on the pathology manifestation degree. Considering the left ventricle wall thickness less than 12 mm, the life expectancy averages 2.4 years, and the thickness over 15 mm – only 0.4 years [42]. Thus it must be kept in mind that there are a lot of medications for the disorders of the coronary circulation; in extreme cases stenting and shunting of such vessels is performed, but there are no reliable methods to manage a restrictive cardiomyopathy. And it is plasmapheresis that hopefully is able to remove such immunoglobulins or the amyloid proteins from the myocardium. In the recent years attention is drawn to the condition of the liver parenchyma in old age. The liver size, hepatic blood flow and perfusion of the liver are reduced by 30-40% between the third and tenth decades of life. The frequency of hepatitis C virus detection is growing from 10% in subjects under 35 y/o to 42% (!) those over 60 years old, though there was no correlation with such risk factors as

intravenous drugs, tattoos, acupuncture and surgeries [43]. Many elderly people even after 20 years after HCV infection identification had no symptoms of the liver damage; however, biopsy showed these signs rather frequently. Up to date the correlation between aging and autoimmune damages of the liver has been ignored. In this case, with age the prognosis in chronic hepatitis and cirrhosis becomes much worse. If in subjects under 60 years old the mortality rate after a year after these diseases detection accounts for 5%, and after 3 years - 24%, in subjects over 60 years old - 34% and 54%, respectively, and in subjects over 70 years old – as much as 75% die in a year. Half of those over 70 y/o developed hepatocellular carcinoma, usually associated with cirrhosis [44]. With age, worsening and autoimmune disorders are accompanied by systemic lesions of various organs, including the kidneys especially in case of different types of systemic vasculitis with renal vascular lesions. Cryoglobulins content Increases. All this is largely accompanied by disturbances of microcirculation, including that in the glomeruli [45]. With age, the frequency of viral hepatitis C infection increases, in which autoimmune hepatitis is observed, which is often also accompanied by the kidney damage. In addition, in the presence of chronic kidney disease the thymus suppression occurs associated with decrease in the number and activity of lymphocytes and a kind of "premature immune aging" with a decrease in functional and structural tissue reserves and disorders of homeostasis [46, 47].

On the other hand, there are vascular disorders associated with atherosclerosis due to narrowing of the lumen of the blood vessels, including the renal ones, and also not always amenable to drug therapy. And stenting or bypass surgery of the coronary vessels cannot be used for correction of the small renal vessels. Amyloid deposits are common in the intercellular spaces, including formation of so-called senile plaques. All the above mentioned is accompanied by renal amyloidosis as well. With age, worsening and autoimmune disorders are accompanied by systemic lesions of different organs, including the kidneys, especially in different types of systemic vasculitis affecting the kidneys vessels. It is typical for the old age that the signs of paraproteinemia appear associated with accumulation of monoclonal immunoglobulin M-components resembling myeloma. It increases the cryoglobulins content, too. All this largely disturb microcirculation, including that in the glomeruli. With age the frequency of hepatitis C virus infection increases, including autoimmune hepatitis, which is often accompanied by renal outcomes. With age the risk of renal lesions associated with disorders of biochemical and immune homeostasis increases. In particular, the growing number of patients suffering from the metabolic syndrome with disorders of lipid metabolism, hypertension, and type 2 diabetes. All this is accompanied by development of diabetic nephropathy, which is often so severe that it requires hemodialysis. Despite the maintenance of blood sugar levels, there is a microvascular endothelial damage and substances accumulation, which are not amenable to drug therapy. Metabolic syndrome or insulin resistance syndrome is naturally accompanied not only with impaired glucose tolerance and development of diabetes mellitus type 2, but it is also accompanied by dyslipidemia with visceral obesity, hypertension, and prothrombotic status. Furthermore, the metabolic syndrome is practically an early stage of type 2 diabetes development. It has spread in 2.5 to 3.8% of population, doubling the number of patients every 10-15 years. If at the end of the XX century there were 135 million people with diabetes in the world, by 2025 this number will increase to 300 million [48]. Diabetic patients can develop severe cardiomyopathy associated more with disorders of microcirculation in the myocardium than with atheromatous narrowing of the coronary arteries. It has non-specific functional and morphological changes including: cardiomyocyte hypertrophy, interstitial fibrosis, arteriolar thickening, decreasing capillary microaneurysms of their network, and disturbances of the left ventricle diastolic function followed by systolic dysfunction as well. The risk of coronary lesions in diabetics is 10-20 times higher and the death rate after myocardial infarction in these patients is 2 times higher than in those without diabetes [49]. Occlusive vascular diseases associated with disorders of both central and peripheral circulations are almost constant and rather severe satellites of diabetes, especially in the elderly. According to the U.S. National Commission for diabetes, these patients is 25 times more likely to go blind, 17 times more likely to suffer from kidney disease, 5 times more often affected limb gangrene, 2 times more likely – heart disease, and life expectancy is 30% shorter. Diabetic retinopathy results in permanent loss of vision. Diabetes generally is a leading cause of blindness among the working-age population. In the United States the number of newly blinded patients with diabetic retinopathy increased by 8,000 people, and in Germany as a result of diabetic retinopathy blindness rate reaches 2.01 per 100,000 of population [50]. The retina changes at different time from the onset of diabetes are found in 98.8% (!) of cases [51]. Upcoming polyneuropathy accompanied both by disturbances of motor and sensory nerve fibers, and by disorders of the autonomic system elements.

The presence of both immune and metabolic changes in this form of diabetes makes it reasonable to use apheresis therapy at all stages of the disease. Attempts to use drugs against hypercholesterolemia, can lead to a number of adverse complications. So, Clofibrate effectively reduced content of atherogenic lipids, but in patients with diabetes the mortality rate from non-cardiac diseases increased. Moreover, the treatment with statins in patients with type 2 diabetes more significantly decreased the content of antiatherogenic HDL and increased triglycerides than in patients without diabetes [52]. Plasmapheresis is essentially the only way to correct these complications meaning elimination of secondary metabolic disorders. Only by plasmapheresis one can remove many damaging factors such as autoantibodies, glycoproteins, lipids, uric acid, endothelins, antibodies against insulin and others. Plasmapheresis is needed in patients with advanced disease in order to prevent a number of secondary complications of diabetes. One of the manifestations of involutive processes in women is menopause. This period of adjustment of the hormonal status is accompanied by a number of specific menopausal symptoms – feeling "tide", "heat", sweating, irritability, which during a sufficiently long period disturbs women health and *"quality of life"*. Not only the ovaries function is disordered, but also the function of the other endocrine glands, in particular of the thyroid gland, followed by development of *autoimmune thyroiditis* symptoms. Metabolic processes are also broken, decreasing the level of enzyme activity, in particular, of succinate dehydrogenase, being the marker of mitochondrial and energy processes in the Krebs cycle. In cases when the usual therapeutic measures do not help, plasmapheresis allows in a relatively short time to achieve the disappearance of the above mentioned symptoms, especially in short "history" of

climacteric syndrome when these symptoms are still unstable and pronounced psycho-vegetative disorders have not developed yet. The positive effect of plasmapheresis lasted for 3-18 months. In 75% of such women the signs of hypercoagulation are observed and sets of plasmapheresis procedures in such cases promote normalization of a coagulogram, decrease in platelets aggregation extent, and disappearance of soluble complexes of fibrin monomers. In 67.5% of the women with climacteric syndrome hypercholesterolemia is marked and plasmapheresis procedures also help to normalize the lipid metabolism [53]. Thus, in the result of disorders of some parts of the immune system in old age there is a wide range of symptoms, more blurred than in the corresponding actual nosologic forms of diseases, but it is they who determine the shape of an old man – *slow response time, stiffness and incoordinate movements, muscle weakness and forgetfulness* etc.

With age, oxidative processes with the accumulation of free radical compounds are also disturbed, which also contributes to a more accelerated "aging" of the immune system [54, 55]. With aging discharging the electrostatic forces of the organism occurs, decreasing the membrane potential, ionization cytoplasm with coarsening of biocolloids particles, a decrease of their ability to swell, degradation and induration of protoplasm, its transition from a sol to a gel state [56]. During ontogeny hydrophilic colloids are generally reduced. So the content of water in the brain decreases from 90% in newborn to 80% in elderly that indirectly speaks about decrease of electric charge of colloids and deterioration of the tissue electroexchange. To some extent in some cases it promotes dehydration and decrease in feeling of thirst to compare with young that also causes accumulation of slag. Disorders of the physical and chemical state, and in fact aging of cytoplasm and cell nuclei, are the cause of inflammatory processes maintenance and spread of aging to other tissue elements [57]. Limiting the content of negatively charged ions in the inhaled air is one of the main factors accelerating the processes of biotransformation of cells colloidal state and tissues and premature aging.

There is no need to explain the role of atherosclerosis in the process of premature aging, too. Many researchers even consider atherosclerosis a natural process associated with aging. It also was declared: "You are insofar old as old your arteries are" [58]. However, the worst thing in atherosclerotic vascular lesions is that they are almost asymptomatic until the moment of the lumen blockage when it is late to think not only about prevention of these lesions, but even of a appropriate treatment. Therefore it is necessary to closely monitor the content of lipoproteins in the blood and the known slight signs of vascular disorders. Besides, it is also necessary to consider the inflammation role in pathogenesis of atherothrombosis associated with accumulation of a number of cytokins. In a large number of subjects who hadn't had cardiovascular diseases it was founded that in case of the IL-6 level increase over 3.19 pg/ml the risk of myocardial infarction development is doubled, increase in C-reactive protein over 2.78 mg/l is also connected with higher risk of death, and in case of both indicators increased the risk of death is 2.6 times higher [59]. During examination of older individuals, who in their average age were observed to have arterial hypertension and ventricular arrhythmias revealed a high rate of intellectual disabilities and depressive states with signs of the brain atrophy [60], With increasing age there is accumulation of toxic products of lipid peroxidation on the background of depression of the antioxidant defense system. Older people have higher levels of acute phase proteins with signs of oxidative stress, which confirms the special clinical value of apheresis therapy [61]. Recently, there is a growing interest to such autoimmune vascular disease as antiphospholipid (APL) syndrome that is manifested in development of recurrent thrombosis of the venous and arterial systems of various organs [62]. Antiphospholipid antibodies are a heterogenous group of autoantibodies with different properties, including different specific phospholipid-associated proteins, as well as reactive phospholipid molecules. These patients have a higher risk of thromboses and their recurrence. The same signs of autoantibodies increased activity (anti-DNA-IgM, anti-cardiolipin IgG and IgM, antibodies to microsomal thyroid antigen) were found in all elderly patients with inflammatory processes in the lungs [63]. There is the most dangerous thrombosis of the cerebral vessels leading to strokes. In 25% of young patients with stroke anticardiolipin antibodies can be found [64]. Some migraine manifestations are suggested to occur due to vascular disorders of the same origin. In particular, there may be repeated episodes of transient ischemic brain disorders, accompanied by headaches [65]. There can be a correlation between the antiphospholipid syndrome and amyloid deposits in the cerebral vessels walls, associated with a local weakening of the mechanical properties up to their rupture, being the cause of hemorrhagic stroke in 10-15% of cases [66]. It is believed that the age of cerebral ischemia onset associated with APL antibodies is a few tens of years younger than in the population with a typical cerebral ischemia. Venous sinus thrombosis may also develop. It cannot be excluded due to vascular dementia disorders caused by APL antibodies. The same applies to cases of late-onset epilepsy, which once again highlights the need for an immunological study of patients with neurological symptoms, especially young women [67]. Neurological disorders are described in the background of an increased level of anticardiolipin antibodies without causing visible vascular lesions [68]. There may also be some correlations between mental disorders and APL syndrome [69]. APL antibodies may be the cause of coronary heart disease and myocardial infarction, hepatic lesions. In this case, myocardial infarction caused by coronary artery damage as well as on the background of coagulation lipid metabolism disorders and hypercholesterolemia can occur even in young adults [70]. Anticardiolipin antibodies are detected in more than 70% of patients with coronary artery disease in young age.

APL antibodies impact on β_2-glycoprotein I, which is anti-atherogenic factor may play a complementary role in promoting atherosclerosis in patients with APL syndrome [71]. Patients with antiphospholipid syndrome have a greater tendency to atherogenesis [72, 73]. Oxidation of plasma proteins and endothelial oxidant-dependent damage reduce physiological anticoagulant endothelial function. Antiprothrombin antibodies increase the risk of myocardial infarction, and antibodies to β_2-glycoprotein I contribute to increasing platelet aggregation. It is possible that such antibodies occur as a result of systemic arterial inflammatory process and are the part of an autoimmune response to the appearance of different antigens, modified atherosclerotic vascular wall [74]. Nevertheless, in usual clinical practice it is unusual to correlate atherogenesis processes with autoimmune disorders. Even having the clinical picture of coronary or brain blood circulation disorders they pay attention only to

cholesterol level. And in case its level is increased only hypocholesterol medications are administered without paying attention to an autoimmune component of atherogenesis. Or the treatment is limited only to vasodilating drugs. At the same time, APL antibodies damaging the vascular wall lead to formation of lipid plaque even at the normal level of cholesterol.

Presenilation Prevention

On the one hand, one could regret that the Creator or Nature itself (depending on the philosophy of life) were not wise enough to provide more stringent ban on autoimmune processes formation. However, on the other hand, this may be the highest wisdom, because otherwise life would go on indefinitely long, and if it is impossible to completely avoid the accumulation of such *"micro-errors"* of immune and metabolic processes, it would create a number of other intractable problems. So, picture of homeostasis disorders, leading to progressive premature ageing, becomes much clearer. At the same time there is an accumulation of many pathological products, the size of molecules do not allow them to pass through the kidney, and the liver does not destroy them. On the other hand, the fact of their accumulation suggests that no drugs were able to help in their removal from the body. Even such disorders of homeostasis can lead to premature aging. Way back when Seneca said that *"old age is an incurable disease",* and therefore the attitude to it should be as to a *disease*. And disease can and should be treated! Mainly you should stop these vicious circles of interdependent disorders that can only be done by a timely removal of all the accumulated large molecular pathological products from the body. And it is apheresis therapy, mainly – plasmapheresis, that can completely solve this problem. The main task is not just an extension of life. If such a life will be extended with symptoms of dementia and helplessness in a wheelchair or in bed, then such work is not worth pursuing. It should be born in mind that the level of health including physical function and psychological status are more important for the elderly than duration of their lives. The goal is to increase the immune potency, which means extension of the productive middle age while maintaining the level of health and energy, i.e., quality of life, on which creative and physical performance depends, the opportunity to experience life in all its colors. The challenge is maintaining the "youth to the old age". The question is: when does the aging start and when to start its treatment? Should we wait for development of the appropriate age-related symptoms manifestation or prevent their occurrence? Of course, the last one is true!

As mentioned above, many diseases, as well as old age creep up unnoticed. For many months and even years micro-disorders of homeostasis compounds are growing until reaching a critical level when the symptoms of a particular disease appear [75]. Thus, according to the summary data of research pathologists who reviewed the results of 3000 autopsies of young people aged 15-34 years who had no clinical evidence of cardiovascular disease and died in the result of accidents revealed the following picture: all teens surveyed were found *fatty streaks* in some segments of the arteries [76]. These changes grew with age, with lesions of the coronary arteries were found in their walls leukocytes and circulating immune complexes; obesity increased the risk of vascular lesions; changes in the growth of abdominal aorta increased sharply *in smokers*; smoking and hypertension clearly correlated with the development of primary atherosclerotic plaques in young humans. Given that none of these young people was seen to have any manifestations of cardiovascular disease, it is clear that their primary prevention was necessary to begin without waiting for the manifesting symptoms. The same can be said about *micro-shears* and *mild signs* of other diseases. The task is to find these micro-disorders, not turn a blind eye and do not consider them a fluke. Attempts to cope with some rheumatoid manifestations by means of non-steroid anti-inflammatory medicines can lead to development of various damages of the mucous membranes of the digestive tract, especially in elderly. The risk of peptic ulcers and their complications developed increases. Salycylates lead to disorder of the transmembrane permeability, electric activity of ionic transport and metabolism in general, and cyclooxygenase inhibition.

In many cases, involutive processes in old age do not require medical treatment, and moreover, drugs can harm because even when used correctly, they can cause a number of other functional disorders. In the recent years, many authoritative experts note that "*pills strategy*", which is based on Western medicine, practically exhausted itself. It is not only practitioners, but even pharmacologists who have recognized that "tablets" are really effective in less than 30% of cases [75]. In order to delay aging they often resort to allogeneic bone marrow cell transplantation, but the developing to varying degrees "graft-versus-host" reaction can contribute to the development of severe elastosis with thinning of the skin and its numerous folds, that is, what one would like to get rid of [77]. In addition, it cannot be excluded that transplanted stem cells can transform into malignant ones. Timely primary prevention of diseases will serve as primary prevention of early aging as well. And the main point of such prophylaxis is apheresis therapy aimed at removing what can be seen now and of that, which is still not even manifested now [78-80].
Various cosmetic surgery is certainly justified, but after the elimination of defects in shape, posture, wrinkles, so called "*wrinkles of internal environment*" remain and all the reasons that have caused them. Therefore, these surgeries must be accompanied by reorganization of the internal environment, and some complicated plastic surgery should be performed only after the apheresis- and immunotherapy to prevent inflammatory complications, bringing to naught all the cosmetic effects.

Not only the reputation, but the old age is to be taken care of from one's youth, too! This means that there is no specific age when one should start to take measures to prevent senile disorders. We must realize that organic changes of the organs and tissues are resistant to reverse development, so an effort should be made before the onset of these lesions. These measures are indicated at almost any age, when there are mild signs, showing deviations from the normal state – excessive fatigue, unusual sensations and body aches, joint pain, and changes in the eyes sclera form, hair, nails, skin wrinkled face, hands; memory disorders and tinnitus, gait changes, elasticity and movement coordination, potency, and many others. Of course it is important to pay attention to the appearance of more than one of these symptoms, and their whole complex, especially if they retain for many days and weeks. One should not ignore rises in the blood pressure (assuming their being natural or age-related), heartache, even if they can be quickly eliminated by taking drugs for "there is no smoke without fire"! Thus, the developing atherosclerosis is one of the main

precursors of aging. Greek hero Jason can be considered the founder of apheresis therapy in gerontology who tried to restore youth of his father, replacing his blood with new red wine. Although this attempt failed, removal of pathological products together with part of the normal components of the body internal environment present in the blood plasma, results not only in its sanitation, but also a powerful impulse to renewal of its fresh, young ingredients. That is, the effect of *rejuvenation* is achieved simultaneously with removal of the gradually accumulated autoantibodies and other pathological metabolites of both exo- and endogenous origin. Thus, annual four procedures of plasmapheresis should underlie apheresis preventive therapy, and in case of immunosupression and allergy it is recommended to add photohemo-therapy (UVR or laser blood irradiation), too. One should not neglect aeroionotherapy, i.e., walking on the open air that is to help restore mechanisms to maintain electrostatic state of all the components of the internal environment, and to prevent pathological biotransformation of the cells cytoplasm. These measures can be considered to be primary prevention of malignant tumors, for removal of the "toxic burden" from the immune system is to promote its restoration, including systems of antineoplastic control. Even external laser radiotherapy in advanced age patients with osteoarthroses is reported to result in immunocorrective effect with increase of $CD3^+$ and $CD8^+$ lymphocytes to normal levels [81].

Naturally, apheresis therapy should not exclude a healthy lifestyle – exercise, proper diet (the main thing is not to overeat), and, of course, not to poison oneself by smoking, alcohol, and drugs [12]. It was noted that food restriction increases life span of mammals, reducing the frequency age-related pathologies including cardiomyopathy, and slows down physiological disorders associated with aging. Limitation of food leads to myocardial contractility increase. At the same time we must recognize that obesity is the most common disorder and its frequency increases with age. In particular, in more than 30% of Americans the body weight, at least, exceeds the "ideal" one by 20%, thus, the obesity incidence increases with age [82]. However, even in the old age plasmapheresis is also indicated, though, one should not expect a significant regression of the present organ and systemic lesions. Nevertheless, plasma exchange procedures lead to significant improvements even in case of marked clinical manifestations of the coronary heart disease, obliterating atherosclerosis of the lower extremities vessels and rheumatoid polyarthritis. It was reported that after a set of plasmapheresis and photohemotherapy in 91.9% of elderly patients improved their overall health, in 68.9% of patients with elevated blood pressure it decreased headaches and tinnitus, and improved their sight [83].

Plasmapheresis Methods

But if there is no doubt in the benefit of apheresis therapy in treatment of a variety of acute and chronic diseases now, then in case of a practically healthy person there may be doubts whether to apply this method or not. After all, there is no assurance that the expected health problems will inevitably arise. Virtually it is impossible to prove that we really have prevented the development of a disease, which has not been diagnosed yet. On the other hand, we must be absolutely sure that such an invasive procedure as plasmapheresis will not cause any complications.

We are confident in it for our experience shows that methodically correct operation of well-trained personnel, using only disposable needles and systems, virtually present no threat to the health of a patient. In addition, avoiding the use of donor plasma and other protein-based drugs to replace the deleted plasma gives an additional guarantee to prevent infection viral diseases and immunization of foreign antigens (donor lymphocytes, for example). The only obstacle can be a rather high cost of apheresis therapy. However, the most widespread devices and methods of plasma exchange demand special conditions for the application up to intensive care units. Besides, it is usually necessary to use the central veins with their traumatic catheterization. Moreover, from one up to two volumes of the circulating plasma (2-4 liters) is usually removed, which naturally, demands compensation by donor plasma and other blood preparations. It is fraught with transfer and transmission of viral diseases as there are no guarantees that the donor plasma has been examined for all possible causative agents of infections.

On the other hand, the portable "Hemofenix" device produced by the Russian company Trackpore Technology allows carrying out a one-needle membrane plasma exchange with use of any peripheral veins with catheters of smaller diameter, up to 1 mm (Fig. 1, 2 in the attachment). The small volume of filling (65-70 ml) allows carrying out a plasma exchange even in patients with hemodynamics disbalances, having had a heart attack and stroke [80]. Thus, it is quite enough to remove not all the volume of the circulating plasma but only a third of it that can be replaced just with a usual isotonic sodium chloride solution. However, for four such sets of procedures, which are carried out every other day, nevertheless, up to 1.5 of the circulating plasma volume is removed that is quite enough to achieve the clinical effect. Thus, there is no a slightest risk to transfer any viral infections. No special conditions are required to carry out such plasma exchange, which can be carried out in the procedure room of any hospital. Thus, the treatment can be in out-patient settings. After a short follow-up period the patient can be allowed to go home the same way as ordinary blood or plasma donors. So, such simple and safe plasmapheresis methods can easily be applied in out-patient conditions. And these conditions are most suitable for plasmapheresis for almost healthy people to provide presenilation prevention. The expenses on such procedures are low, respectively [84].

Conclusion

Human life can symbolically be divided into periods as in football – halftime - 40 years, second half - only 20 (!) years and then - "overtime" that the "Supreme Judge" will give you or not. And it entirely depends on the person. If during the first half one can afford much –drinking, smoking, and eating as much as you want, then at the age of forty people should stop, look back and around, and imagine how to live and for how long, and in what condition. And whether it is possible to "win" the extra time! Whether one will be able to be the mainstay of the family, children and grandchildren, and to oneself, or whether one will only be a burden to them, being in the best case in a wheelchair, or even bedridden. By forty years it is a kind of "equator of life" when there are so much "slag" accumulated in the body that it cannot be easily removed. These are the macromolecular toxic products, autoantibodies that the kidneys do not eliminate and the liver is not able to breakdown. And it is due to it we are deprived 50

years from our cradle-to-grave time, allotted by the Creator or Nature.

So, of course, we must suddenly "sober up", and in the literal sense:

- Stop poisoning oneself with alcohol, which has now become almost a surrogate. This saves the liver for it is the pledge of our health because it is able to destroy the toxic products;
- Stop smoking and thus save one's vessels free for the blood flow;
- Be more selective in the food - sweet and flour contributes to obesity and diabetes.

But not everything depends on the body. The accumulated macromolecular toxic products cannot be removed with help of "monitor intestinal cleansing", for if the kidneys are unable to filter them out they do not enter the intestine. They cannot be removed by various food additives, which also can be rather toxic. They can be removed only with plasma, which is the most liquid part of the blood. And such sets of four plasmapheresis procedures should be performed in the future, at least once a year. And then you can afford "earning" the "extra time." It doesn't mean you get an eternal youth and eternal life! But you can save your productive state, which will keep the working capacity as well. Save the mental power and emotions, as well as perception of Life in all its colors!!!

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