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On the Rostrum of the RAS Presidium

A new scientific trend—senescence prophylaxis—which regards natural aging as a superpathology and the basic cause of chronic diseases and death in humans, is emerging dynamically. V.N. Krut'ko, Dr. Sci. (Eng.) and one of the founders of this research trend, told a meeting of the RAS Presidium about the fundamentals of senescence prophylaxis, its technologies, obtained results, and prospects for its development.

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Senescence Prophylaxis as a Systemic Technology

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Russia and many other countries are facing such pressing problems as a drastic aging of the human population, leading to a rapid increase in individuals with limited biological and social functions, and, as a result, to a decline in the efficiency of society, as well as the problem of a radical increase in the active human life span. An essentially new class of medical technologies—natural senescence prophylaxis technologies—is suggested for solving these problems and surpassing the life span limit of *Homo sapiens* as a species.

Population senescence as a global modern problem. This process is a heavy strain for the economies and society as a whole and for each aging individual, his family, and his inner circle. The scale of the process is characterized by the following UN and leading demographers' estimates: in 1975, 5.3% of humans on the earth were over 65; in 2000, the share of individuals above 65 in developed countries was already 10–14% of the entire population; and by the 2020s, this value will double (Fig. 1). The share of very old people aged 80 and over will increase most rapidly. Their number will increase by 300% in the next decade. It is not accidental that big cities in developed countries turn into "geriatric homes" [1]. Many of these people are chronic patients; they are immobilized, cannot serve themselves, and require constant nursing and care, which needs vast financial expenditures. However, an increase in the ratio of dependants to workers—the so-called demographic load coefficient—is considerably heavier for society. An increasingly large proportion of the capable population is diverted to nursing severe patients.

Humankind is preparing for this situation. The UN aging program envisages several serious measures; however, we consider it passive to some extent. The human race seems to reconcile itself with the inevitability of the growing number of sick people in society and has to allocate considerable funds to somehow mitigate the situation by building more geriatric homes, training nurses, etc. Certainly, such measures are highly essential and make their contribution to the solution of the aging population problem; however, there is yet another, *active position of society*, which, unfortunately, has not been reflected in the UN program. It is necessary to concentrate efforts and funds on decreasing the share of functionally disabled people in society under the same age structure. This is achievable by a relative increase in the active working state of each person and a respective decrease in the period of limited capabilities, as well as by minimizing as far as possible the decline in the level of life activities of elderly people. According to the data of many Russian and foreign authors, including ours, these measures will considerably decrease the severity of the problem of global aging. Note in advance that the new sphere of science that we are developing—senescence prophylaxis—is exactly oriented at solving the task of *senescence processes control* to increase the period of an active, full-value, and working human life.

The systemic crisis of health care and ways to overcome it. It would seem that the process of rapid

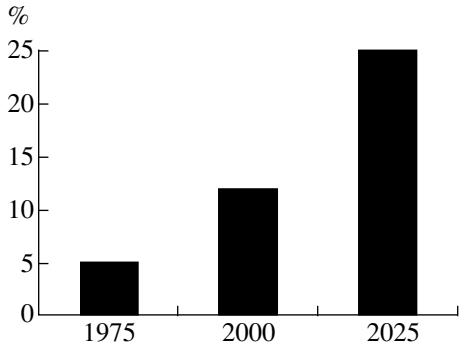

Fig. 1. The change in the share of people over 65 on the Earth.

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global aging of the population must be closely related to the adequately rapid and noticeable increase in life span. Indeed, life span is increasing but not as rapidly as specialists have expected. The point is that the quality of life is determined by many socioeconomic and culturological characteristics of a country, but the level of health ranks first. Its role is specific and incomparable to other components of the quality of life. The following expression is one of winged words: "Health is not everything, but without it, everything is nothing."

A modern approach to the quantitative assessment of the quality of life is based on calculating the *human potential development index*. This index was recommended by the United Nations in 1990 to rate countries by quality of life. One of the three main components of this index is the most informative integral characteristic of human heath—*life expectancy*. It is assigned a rather high importance. There is a fairly justified point of view, according to which this index can be used as the main criterion of the development of Russian society.

Naturally, billions of dollars and the potential of world science are invested in health care, especially in developed countries where health is highly valued. However, in the second half of the 20th century, the *systemic crisis of health care*, especially noticeable in developed countries where, paradoxically enough, vast funds are allocated to health care, has become a reality. The essence of the crisis is a steady decline in longevity growth rates despite increasing intellectual and financial investments into health care (Fig. 2). A striking example of the consequences of this global phenomenon is the fiasco of B. Clinton who, as President of the United States, promised his nation that the life span of 78 years by 2000 would be attained. He failed to keep his promise, although billions of dollars were invested into the US Nation's Health 2000 program for this purpose.

Our analysis indicates that by the end of the second millennium, due to the overall socioeconomic development and the progress in health care, in particular, humans have approached the biological limit of the mean life span of 85 years for women and 79 years for men. Near the biological limit, technologies that control pathogenic environmental factors, as well as individual disease prophylaxes and treatments, common for health care, make a relatively small contribution to the increase in the mean human longevity. In this case, a new class of medical technologies—*natural senescence prophylaxis technologies*—should be used. "Natural aging" must be regarded as a superdisease and the general risk factor of the main chronic diseases and deaths of humans, rather than an eternal God-given norm.

Senescence prophylaxis—a new trend in medical science and practice. According to the laws of science studies, a new trend in science should be characterized by its unique subject, method, and concept of the truth. For senescence prophylaxis, the subject is a combination of the processes of natural (normal) aging of a living organism; the method is a complex of unique preventive methods, technologies, and means of slowing and turning back the processes of natural aging (geroprotectors and revitalizers); and the concept of the truth involves a combination of effects that suppress the processes of natural aging of an organism, which are established using a special convincing basis. The latter includes, in particular, an experimental assessment of survival curves, as well as the mathematical methods of analysis and prognosis.

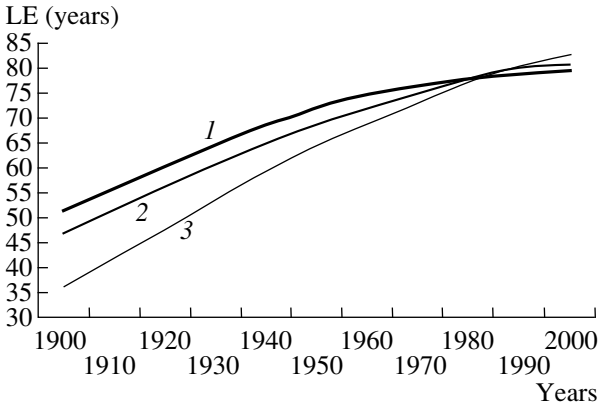

Fig. 2. The dynamics of change in life expectancy (LE) in the United States (*1*), West Germany (*2*), and Spain (*3*) throughout the 20th century.

The basic definitions of this new sphere of science—senescence prophylaxis—are the following:

• *senescence*—a decrease with age in the orderliness of the structures of an organism and an increase in the extent of their wear expressed in a decrease in the viability of an organism (a decrease in the functional potentialities and capacities for adaptation, as well as an increase in the probability of diseases and deaths from various causes);

• *biological age*—an index of the level of development, change, or wear of the structure or function of an element of an organism, a functional system, or the whole organism expressed in units of time; and

• *senescence biomarke*—a "biological event" or a value of a biological sample that represents an estimate or prognosis of one or more aging processes.

The cause and mechanisms of senescence. The extent of chaos (entropy) in the world is determined by one of the fundamental laws of nature—the second law of thermodynamics—stating an inevitable chaos accumulation over time in any partially open system isolated from the environment. Therefore, the discreteness of the forms of existence of modern organisms on the earth—essential isolation from the environment as a form of existence—can be regarded as a common cause of senescence. Thus, taking into account its global cause, we can counteract aging only by increasing the extent of openness of a system, i.e., an organism.

The common cause of senescence is specifically manifested under particular conditions, and the number of aging mechanisms is almost infinite, since it is determined by the number of various structures and functions of living beings. However, we can distinguish some general mechanisms—*main common types of senescence*, to which particular mechanisms of senile phenomena can be reduced [2]. They involve:

• the "pollution" of an organism over time as a result of essential insufficiency of the openness of any systems isolated from the environment, even if they self-renew within themselves;

• essential insufficiency of the forces of selection to preserve only the "required" structures within a certain system, if the information for self-preservation is only within a system;

• a decrease in the number of any nonrenewable structures in a system (the majority of complex organisms have nonrenewable structures at all levels of their organization); and

• control disturbances induced by most various causes of general and particular patterns, including a decrease in the pressure of evolutionary selection with age (after sexual maturation) on the factors of the quality and harmony of control systems, as well as the presence of the ultimate programs of development (growth, tissue differentiation, sexual development, immunity, etc.).

Distinguishing the four types of senescence makes it possible to orient oneself in the extent of manifestation of various aspects of the aging process in each individual and to select some impacts for life geroprophylaxis, bioactivation, and prolongation.

A systemic theory of aging. Recognizing the scientific and practical importance of senescence prophylaxis, several leading organizations of the Russian Academy of Sciences, the Russian Academy of Medical Sciences, and the Russian Ministry of Health, according to the initiative of the Ministry of Science, pooled their scientific potentials in the National Gerontological Center in 1996 to elaborate and promote technologies of natural senescence prophylaxis. The center has the status of a nonprofit partnership, and the specialists of the RAS Institute of Systemic Analysis, the Sechenov Medical Academy (Moscow), the Moscow State Medical Stomatological University, the Russian Research Center of Rehabilitation Treatment and Balneology, the Russian Research Institute of Gerontology of the Ministry of Health and Social Development, etc. are involved in its programs.

Modern gerontology has accumulated an immense potential of experimental data generalized in a great variety of senescence theories. We attempted to elaborate some common conceptual basis and mathematically formalize diverse senescence theories from a single standpoint, i.e., to develop a *systemic theory of senescence.* This theory is based on the fundamental laws of nature and the concepts of the basic mechanisms of functioning of living organisms [2]. It relies on the following laws of nature: the law of an entropy increase in partially open systems, which is one of the basic laws of the universe, true for living and nonliving nature, and the laws of systemology (a mechanism for the chaos control and the extension of the spectrum of the adaptation strategies of an organism through a systemic integration of specialized elements), since senescence is a disintegration of an organism as a system. The systemic theory of senescence regards life as a combination of active processes and interactions intimately related to the processes of wear and damage, which is true also for machines and mechanisms. All these processes have an efficiency <100%, which results in the "production wastes," typical of the majority of technological processes.

The consequences from these laws can be used as recommendations for geroprophylaxis. For example, from the law of entropy increase in partially open systems, involving an increase in the extent of chaos, deformation, and disturbance of the orderliness of organism structures at all levels, accompanied by the deterioration of the quality of their functioning, the following common mechanisms of geroprophylaxis can be inferred:

• an increase in the openness, the normalization of afferent and efferent fluxes of matter and energy (ancient people believed that health is a "normal introduction of substances into an organism and a normal excretion of substances from it") and

• maintenance of the processes of correction of altered structures or a replacement of structures that became unfit by new, normal ones.

As for systemological laws, in obeying them, it is recommended:

• to elaborate systemic technologies of geroprotection based on systemological models and

• to intensify control impacts promoting the systemic structure of an organism.

A few words should be said about systemology alone. To comprehend a phenomenon in physics and chemistry is to describe it, using accurate mathematical formulas, generalizing empirical data, and expressing the laws of nature in a strict particular form. Further, using these formulas, it is possible to solve optimization tasks, etc. But in biology where the object of cognition is an organically integral system whose complexity is determined by developed feedbacks, a simulation model of a system is an equivalent of a mathematical formula expressing laws in physics. Previously, before the appearance of computers, the whole class of systems, namely, of organically integral systems, which also include living organisms, could not be learned and studied completely. In their striving to study nature comprehensively but narrowly, humans has reached the very bottom—they decoded their own genome. We are now aware of the structure of the entire combination of molecules comprising a living organism, but we are yet

unable to control the organism. The next qualitatively higher step of cognition will be the elaboration of a simulation model, explicitly representing a hierarchical system of the contours of organism control.

We studied experimentally how systemological properties of an organism change with time. As expected, a systemic pattern decreases with time; in women it proceeds slower than in men. Women have a wider spectrum of potential of adaptive rearrangements with age, which, in particular, can be responsible for a greater life span in them. The general theory of health was developed as an attempt to uniformly and descriptively formalize the laws of the norm and pathology, formulated by the classics of medicine. A mathematical model of functional harmony has been developed and studied; according to it, an organism is a combination of interacting functional systems, each of which provides by its functions both inner systems and external needs of an organism, as well as compensation and adaptation models. The monograph *Mathematical Foundations of Gerontology* [3] was based on these materials. (Analogous concepts and models were actively developed slightly later in the school of Britain's leading gerontologist T. Kirkwood.) Subsequently, based on the general theory of health, a classification of types, syndromes, and basic mechanisms of aging was performed, which made it possible to develop a systemic technology of senescence prophylaxis.

A systemic technology of senescence prophylaxis. It is natural to ask the question why, despite an immense amount of knowledge accumulated by humankind on senescence mechanisms (several billions of dollars are annually allocated for gerontological studies in the world), no distinct technologies of controlling senescence with a correctly proven effect have yet been developed. In fact, there is a sufficient pool of experimental data obtained on animals and several studies on humans with a proven geroprotection efficiency of the action of a diversity of factors (Fig. 3).

We elaborated both the general architecture of the systemic technology of senescence prophylaxis (Fig. 4) and several of its important components, including the *methodology of senescence diagnostics and prophylaxis*. Gerotechnologies can (and must) be based on the data of direct experiments on animals aimed toward a radical (with surpassing the species level) increase in longevity. A comparative analysis of these studies suggests a potential use as geroprotectors of nootropic and neurometabolic compounds, antioxidants, enterosorbents, means of endoecology, and low-calorie full-value rations; special physical exercises, means of psychic status correction, hormonal replacement therapy, and tissue and cellular preparations.

Our variant of gerotechnology involves computerized procedures of assessing the rate of the natural aging of an organism as a whole and of its individual subsystems, the determination on this basis of the human life expectancy, the selection of an individual configuration of the means of controlling the aging process, and help in using these means in everyday practice.

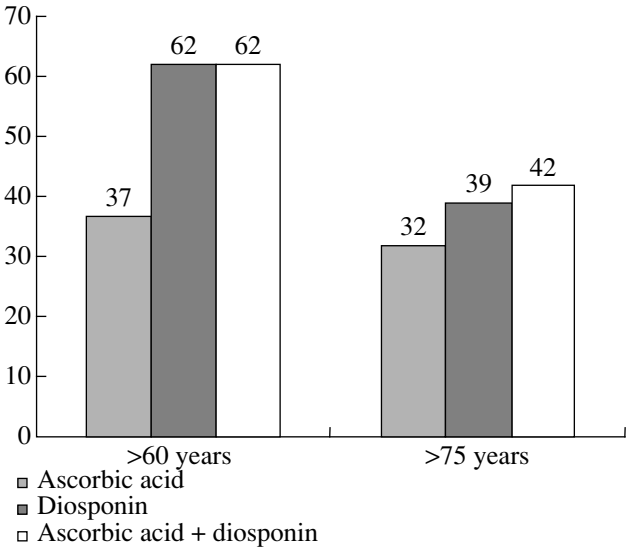

Fig. 3. The number of months lived by the inhabitants of the Veterans' Home (Peredelkino) above the control level using some technologies of senescence control—orthomolecular and geroprotection therapy.

An essential novelty of the technology is its orientation at the in-depth processes of the wear and exhaustion of the functional reserves of an organism in the course of normal life activity, rather than the diagnostics and correction of individual diseases. The technology surpasses the available foreign analogs in general methodology (the author's elaboration of systemic aging theory), the diagnostic algorithm (the possibility of determining both the integral biological age and the partial ages of individual systems of an organism and the calculation of life expectancy), and the methodology of selecting and using the configuration of senescence-slowing means (an integral technology of simultaneous impact on the main processes at different levels).

The National Gerontological Center systematizes the test panels of the assessment of the biological age and develops new and more efficient methods for its determination. The results of this study were the methodical recommendations *The Quantitative Assessment of Mortality, Senescence, Longevity, and Biological Age Indices* [4].

Of great significance is the elaboration of experimental schemes and mathematical algorithms aimed at minimizing the time and volumes of experiments on animals and humans and at maintaining the statistical significance of the results obtained. These schemes and algorithms help obtain life expectancy forecasts from individual fragments of the curve of the time left to live. For instance, we plotted and checked by tables of the

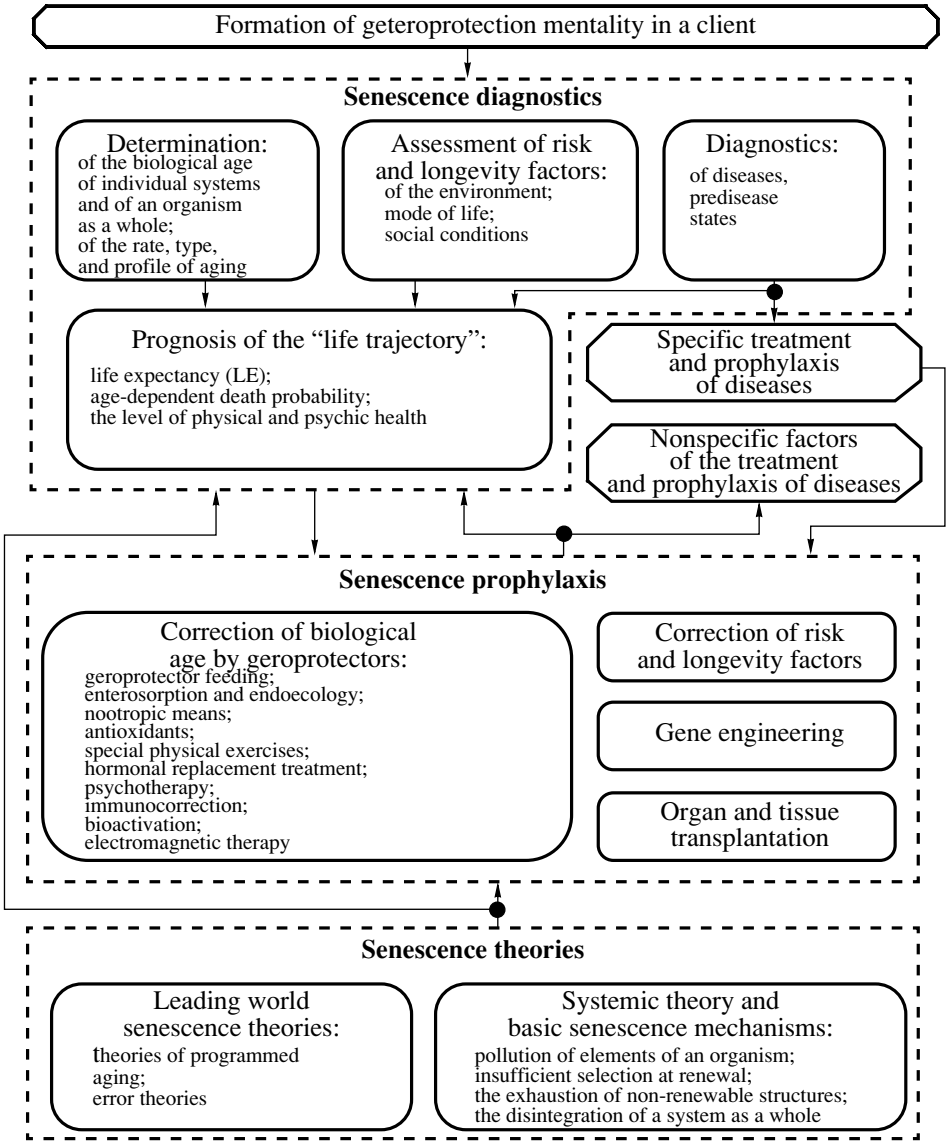

Fig. 4. The architecture of the systemic technology of senescence prophylaxis.

time left to live for rats and humans an algorithm of extrapolating the time-to-live curve with an accuracy of 0.1% and a decrease approximately by 30–50% during the period of research [5].

For a clinical use of geroprotectors on humans, we elaborated a convincing basic concept that proves that the probability of negative side effects of geroprotection is negligibly small in comparison with the scale of the positive effect—an increase in the healthy life span. Here is the basic structure of a geroprotection technology:

• convincing data on a pronounced geroprotector effect on animals (ideally, a double blind multicenter randomized unengaged experiment);

• a clear understanding of the mechanism of senescence at which a geroprotector is oriented and data on the identity of this mechanism in animals and humans;

• the results of pharmacokinetic analysis: the substantiation of course dose–time schemes, as well as the provision of side-effect control schemes;

• the consideration of the experience of using a geroprotector on humans with other purposes in short- and long-term schemes in the allied spheres of science and practice;

• a reliable scheme of current health control (the biological age, the parameters of homeostasis, etc.);

• the use of dosages that are, as a rule, considerably lower than pharmacological; and

• a statistically significant mathematical estimate and forecast of changes in the dynamics of biological age and life expectancy.

The technology of forming a credible basis of and scientifically substantiated conclusion on the possible

mass use of geroprotectors is ideologically new and uncommon for health care. On the other hand, it closely correlates with the expert procedure of passing from preclinical to clinical tests of a drug. This procedure should be officially promoted; otherwise, we shall be swept over with a wave of uncontrolled means of rejuvenation and life prolongation, which, as practice shows, decrease it, in fact.

We consider aging diagnostics methods, risk and longevity factors, bioactivation and biocontrol, geroprotector nutrition, cerebral aging diagnostics and correction, psychotherapy, hormonal therapy, immunocorrection, oxidative stress diagnostics and correction, enterosorption and endoecology, geroprotector multisystems, gerontological informatics, methodological support for a network of senescence prophylaxis centers, and the formation of a geroprotection mentality in physicians and the population the most important in senescence prophylaxis. Medicine already has approaches and methods useful for senescence prophylaxis, which were elaborated by the prophylaxis of noninfectious diseases, hygiene, valeology, balneology, recovery medicine, reservometry, donosological diagnostics, reflexotherapy, etc.

One of the central problems of geroprophylaxis is the elaboration of accurate quantitative methods of aging diagnostics, precisely, methods that would ensure a differential approach to individual senescence prophylaxis. Another important task is to computerize and provide information support for a complex process of forming and then tracking a scheme of individual senescence prophylaxis. We elaborated a computer complex to solve these tasks. It was initially designed for gerontology; however, due to the universality of incorporated approaches, the complex can be successfully used for a wide spectrum of tasks of assessing and correcting human health. It consists of the following four systems.

Senescence Diagnostics: Biological Age

Purpose: maintenance of a database of examined patients to determine the markers of biological age; the calculation and graphical presentation of an individual senescence profile; the calculation of biological age by the methods of the National Gerontological Center and the Kiev Research Institute of Gerontology; and the presentation of reference materials on age standards; samples of blanks, forms, and maps for the work of a physician; and methodological recommendations and materials.

Senescence Prophylaxis

Purpose: support of the individual selection and use of a system of senescence-slowing means and measures and bioactivation dependent on senescence profiles, habits, risk factors, and chronic diseases, financial capabilities, and other individual characteristics of a client. The provision of a physician with comprehensive information on senescence mechanisms and means of its slowing.

The System of Assessing Psychic Efficiency

Purpose: Testing the main characteristics of cognitive and sensorimotor functions in humans—perception, operative memory, stability of thinking, attention switching and distribution, operative thinking, logical thinking, spatial thinking, dynamic eye, and response rate and accuracy.

Nutrition for Health and Longevity

Purpose: The assessment of actual nutrition; developing individual norms of nutrition based on physiological parameters, physical and psychological load, ecological conditions, habits and modes of life; exercising a computerized elaboration of optimal therapeutic, prophylactic, and geroprotector rations corresponding to individual norms and taking into account the financial possibilities and preferences of clients.

The sphere of the use of computer systems embraces medical aspects (changes in weight, the assessment of the impact of biologically active additives and other means of correcting diet deficits), health-improving centers (sanatorium-and-spa network and medical–prophylactic institutions whose aim is to actually increase the efficiency, rejuvenation, and prolongation of active life in humans), and a system of graduate and postgraduate training of specialists in prophylactic medicine.

The expected effects of geroprophylaxis. Elaborated gerotechnology makes it possible to practically set the task of a radical prolongation of the period of active life in humans. The target program Geroprotectors (the means of senescence control) has been developed at the National Gerontological Center. Its main aim is to experimentally work out dose–time schemes and compositions of geroprotectors called to maximally increase life expectancy. The realization of this program can provide several considerable effects.

The first effect is *bioactivation.* The functional status and the efficiency of humans increases; they leads a more active mode of life. The correction of oxidative stress by antioxidant therapy yields the same effect.

The second effect is the slowing of the in-depth aging processes or *geroprotection* itself. It leads to a drastic increase in the working potential of Russia and to a considerable decrease in the coefficient of demographic load on society. Incidentally, according to demographic forecasts, the coefficient of demographic load in Russia will increase to 0.9 by the middle of the current century, i.e., there will be one dependant per worker, which will overload the already crisis economy of the country.

The third effect is an increase in the *life efficiency coefficient*, in other words, a considerable increase of

the ratio of periods of healthy life to periods of a low-quality life. Strictly speaking, the main goal of state activity is to increase this ratio.

The fourth effect is the *harmonization of aging*, i.e., more worthy and comfortable senility. This effect is attained by an early determination of the rates of aging of different organs and systems of an organism and the support of weak links.

The fifth effect involves a considerably *higher socioeconomic efficiency of geroprotector technologies* in comparison with traditional approaches where the efficiency is determined by the ratio of the number of years added to a healthy active life to unit of financial expenditures. For instance, an increase of 10–15 years in the mean life span in Russia by traditional means is possible only if it turns into a developed capitalist state of the level of Sweden, for example, by all main socio-economic indices. It is clear how many efforts and means it will require and how much time it will take.

Finally, the leading development of geroprotection technologies in Russia will enable it to occupy a worthy place on the world market of the health industry, which by its scale exceeds the weapon market.

The importance of geroprophylaxis technologies for Russia. Currently Russia is assigned to countries with the most unfavorable tendencies for population survival. The acuteness of the demographic situation of the last decade in Russia has no analogs in the previous history of either our country or other countries, including those that experienced severe social upheavals in the 20th century. Beginning in 1992, the Russian population has decreased annually. By the end of 2000, in comparison with the beginning of 1992, the population decreased by 3.52 million, despite a migration gain of 3.27 million over the same period. Thus, a natural increase of the population over eight years (that should be more likely called an unnatural loss) comprised an impressive negative value of 6.79 million; the result was determined by both a decrease in the birth rate and an increase in mortality. According to a forecast of the RAS Institute of Sociopolitical Studies [6], by maintaining or achieving a small improvement of the current tendencies of birth rate and mortality, the number of the population in Russia by 2025 will be dependent on the migration level within 108.8 million–123.3 million and by 2050, within 74.1 million–89.6 million, which will inevitably lead to radical changes in the state and society.

The government is now intensively searching for ways to overcome the demographic catastrophe, relying mainly on measures for a birth rate increase. However, a famous demographer N. Keyfitz in his fundamental work that generalized the experience of different countries to increase the birth rate, convincingly demonstrated that artificial governmental measures stimulating this process lead to only short-time insignificant increases in the birth rate and do not solve the problem as a whole. One has to rely on measures for a decrease in mortality. However, as we tried to show, a real solution of this issue is impossible without the intensification of fundamental and applied studies in senescence prophylaxis. Therefore, one of the ways to overcome the demographic crisis in Russia is the realization of the target program Geroprotectors elaborated by the RAS Institute of Systemic Analysis and the National Gerontological Center. Gerotechnologies proper open up new avenues for a radical increase in the period of functionally normal human life with a high level of efficiency and social activity.

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