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Prophylaxis of Aging: Contours of a New Science

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Abstract—The subjects of analysis are the fundamental scientific and applied aspects of a new sphere of biomedicine, i.e., prophylaxis of aging. It is shown that it presupposes a principally new class of medical technologies that enable physicians to set and accomplish the task of exceeding the limits of the average species life expectancy of the human.

Prophylaxis of aging is among the spheres of scientific and practical activity that is developing most actively and dynamically at present [1-23]. This is due to both the enormous complexity and socioeconomic importance of the problem of aging of the population of the contemporary world and particularly Russia with its economic and demographic crisis. Prophylaxis of aging presupposes new approaches and modern high technologies that improve the quality of peoples' life while reducing the real pace of aging and increasing the duration of active life and ability to work. These technologies are applied to deep fundamental processes of the natural aging of the body. It is very important that they open a substantially new, compared with the methods of correction of environmental factors, possibility to exceed the species limit of the average life expectancy of a human (according to contemporary estimates, 83 years), i.e., to radically increase the duration of active healthy life.

The present paper concludes the series of the author's publications in *Fiziologiya Cheloveka* on various questions of the analysis of the aging process and problems of its restraint [8, 9, 11, 16-18] and opens the next cycle of publications concerning the tasks of diagnosis and prophylaxis of aging. Studies are carried out in this field under the auspices of the National Gerontological Center (NGC) by the collectives of the researchers of the Institute of Systemic Analysis (Russian Academy of Sciences), Sechenov Moscow Medical Academy, Moscow State Medico-Stomatological University, and some other organizations. The investigations in the field of prophylaxis of aging are coordinated by the Commission for Applied Gerontology of the Interdepartmental Scientific Council for Gerontology and Geriatry (Russian Academy of Medical Sciences) and the Ministry of Public Health of the Russian Federation with NGC as its leading organization.

The work deals with fundamental scientific and applied aspects of a new sphere of biomedicine, i.e., prophylaxis of aging, whose subject is the complex of means and methods of restraint of the natural aging processes.

THE CAUSES OF HEALTH CARE CRISIS AND PATHS TOWARDS OVERCOMING IT

The main purpose of the activities of the state on the whole and, in particular, of health care is to increase the duration of maximally active full-value life for every member of the society.

This purpose is achieved by maximizing three basic characteristics: (1) human life duration; (2) working capacity and emotional status of the human; and (3) adequacy of the socioeconomic and natural environment of the human. Since two of these characteristics are of a basically biological nature, they are "farmed out" mainly to biomedicine.

Almost each impact on the human and his environmental niche leads to positive and negative changes in his health [4]. There may be thousands of such impacts of various character, and, therefore, particularly in the setting of an acute economic crisis, the question of comparative analysis of their efficiency, defined as the ratio of the number of additional man-years of life resulted by the impact to its cost, comes to the forefront.

Such evaluations are actively made and used in the developed countries, and it proves that the cost of an additional year of life may vary, depending on the kind of impact, from some dollars to some thousands of dollars, i.e., it can differ thousands of times. Analysis shows that prophylaxis of aging is among the most efficient ways towards achieving the main purpose of socioeconomic development.

The health care crisis observed in both developed capitalist countries and in Russia in the late 20th century manifests itself in the fact that it becomes more complicated and expensive every year to win additional man-years from death. Analysis of the dynamics of mortality and life expectancy in the 20th century shows that these processes tend to reach a plateau and approach a limit, i.e., the dead-end value [1].

Our comparative analysis of some epidemiological, demographic, and experimental biological results eluci-

dates the fundamental reason for this crisis and clarifies the paths towards overcoming it.

The following results may be noted in this series as most significant.

(1) The data collected by Gavrilov and Gavrilova[5], which testify that the "environmental" component of total human mortality changed catastrophically inthe developed countries in the 20th century, dropping from very high values in the beginning of the century toalmost zero in its second half, the "intrabody" biologi cal component remaining almost unchanged.

(2) The results of Marchetti's [21] calculation of the above-mentioned limits of the human life expectancy in comfortable conditions. This value proved about 85 years for women and 80 years for men.

(3) The data on the share of the health care budget spent in the last half year of human life in developed countries, which is from 40% to 80% according to different authors.

(4) The results obtained by Gundarov [6], McCormick and Skrabanek [22], etc., who compared dozens of vast and very costly research projects carried out in the USA, Canada, the USSR, and European countries with dozens of thousands of test subjects, aimed at decreasing the most important risk factors of the noninfectious diseases that are the main reasons for human death, such as hypercholesterinemia, arterial hypertension, smoking, excess weight, hypokinesia, and excess content of calories and animal fats in the diet. Great hopes were placed on these programs, but it proved that the substantial purposeful reduction of these risk factors was not accompanied by a decrease in total mortal ity, which even went up on some occasions. Most likely, the cause of death lies much deeper.

(5) Detailed multifactor analysis of the characteristics of the way of life, heredity, and environmental conditions of several dozens of thousands of men who reached the age of 95 years, made in the USA, Bulgaria, and Mediterranean countries. It did not demonstrate significant correlations of these indices with the fact of longevity, except for the factors of steadiness of the nervous system, kind character, and lack of gross deviations in the diet, i.e., the indices that are necessary but not sufficient conditions of long life.

(6) Analysis of the reasons of the age dynamics of morbidity and mortality showed it to have same exponential character for such different diseases as measles, pneumonia, cancer, strokes, and many others.

Comparative analysis of these and some other data, which seem heterogeneous only at the first glance, leads necessarily to the following conclusions.

In the second half of the 20th century, due to socioeconomic development on the whole and progress of health care as its component, the developed countries managed to create very comfortable life conditions and to ensure such a level of protection that the human closely approached the generic limit of the life expectancy characterized by the average values of 85 years for women and 80 years for men.

If the human has approached his biological age limit, reaching the condition that is expressed most adequately as "decrepitude" (becoming not old exactly but decrepit), no modern medical technologies can keep him for a long time on the verge of a grave.

A principally new approach is needed to accomplish the task of a radical increase in the duration of healthy active life. Its sense is to emphasize impacts on the fundamental biological mechanisms of the human body that determine the pace of its natural aging.

This approach may be realized within the framework of a new sphere of medicine, i.e., *Prophylaxis of Aging,* which is undoubtedly going to become one of the leading spheres of medicine in the 21st century [12].

PROPHYLAXIS OF AGING AS A SCIENTIFIC DIRECTION:

SUBJECT, METHOD, AND THE NOTION OF TRUTH

A really new sphere of science must have a unique *subject, method, and notion of truth,* which distinguish it from other spheres. The main *subject of prophylaxis of aging,* the point where its efforts are applied is *the totality of the processes of natural (normal) aging* of a living body. The *method* of this science is the totality of unique prophylactic methods and technologies of the restraint of natural aging processes. *The notion of truth* is the totality of the effects of the restraint of processes of the natural aging of the body found using the special demonstrative basis described below, which includes unique experimental procedures based on the analysis of life expectancy curves and special mathematical methods of analysis and prognosis. The basic notion of this analysis is biological age. The aforesaid effects have an integral manifestation in the increment in the average generic life duration (AGLD) on the population level and in the increment in the life expectancy (LE) on the individual level.

THE PATHS TOWARDS CREATING PRACTICAL TECHNOLOGIES OF PROPHYLAXIS OF AGING ("GERONTOTECHNOLOGIES")

Can gerontotechnologies be created and applied in practice today? If so, on what basis and how? The leading gerontologists and gerontological organizations of the world, such as the National Institute of Aging of the Unit-

ed States, claim that in recent years the world gerontology has accumulated sufficient knowledge, and the time is ripe to unite it in order to have a practical effect [1]. Such technologies may be based on two blocks of information.

Firstly, we mean the totality of modern aging theories, which generalize the achievements of fundamental gerontology and describe the leading aging mechanisms. Such theories number more than a hundred, and numerous works describe their different typologizations, systematizations, and generalizations [2, 7, 10, 18]. One can identify two main approaches to systematization. One of them is generalization and aggregation of profound particular analytical theories, which is more typical of the Western scientific school. The second one is a systemic approach based on the general fundamental laws of nature, which is characteristic of the Russian tradition. The National Gerontological Center paid its contribution to the development of this approach [7, 9, 10].

Secondly, gerontotechnologies can and must be based on the results of experiments with animals aimed at an increase in the life duration and exceeding the species limit. Comparative analysis of such works [7, 16, 17, 19, 23] permits one to conclude that the following classes of means have a potential prospect of being applied as geroprotectors: nootropic and neurometabolic compounds; antioxidants; enterosorbents and endoecological agents; low-caloric full-value diet; physical exercise; means for the correction of mental status; substitution hormonotherapy; etc.

How can all this be used in the real practice of the prophylaxis of aging?

Analyzing the approaches to the solution of this problem, one should pay attention to the key moment which is specific to gerontology and shows that the phenomenon of biological age plays a very important role in this field and it is impossible to accomplish the task without the active use of modern mathematical methodology.

Is there even a single work in the world literature that shows convincingly that this or that agent or aid is a genuine geroprotector for the human, i.e., increases both the average and the maximum life expectation on the population level? Clearly, there is none, and such a work will hardly be published in the next century, because, to get a direct and convincing answer to this question, one has to observe reference and experimental human populations for the life period (until they reach the maximum age) plus the period of the increment in the life duration caused by the geroprotector.

It seems a logical dead-end: on the one hand, as we tried to show above, it is the most prospective or even the only way towards a radical increase in the duration of active life, the main trend of the medicine of the 21-th century; on the other hand, the efficiency of these geroprotective technologies is not amenable to rigid control. The standard scheme of clinical medicine (preclinical trial-clinical investigation-mass application) cannot be followed here.

It is the objective reality and a specific feature of the object. However, there is a way out from this complicated situation. It consists in the diagnosis of the levels and pace of the processes of aging of the body on the whole and its individual parts, i.e., the characteristics of the biological age, and preparation of statistically significant forecasts of life expectancy using modern mathematical methods.

The technologies of prophylaxis of aging are based on two corner-stones: (1) methods of diagnosis and prognosis of the aging processes, as well as of the evaluation of efficiency of geroprotective impacts, and (2) methods and means of making impact on the aging processes.

Diagnosis of aging is based on the methods of the evaluation of a human's biological age. *Biological age (BA)* is an index of the level of the wear and tear of the structure and function of a structural element or a group of elements of the body and of the body as a whole, expressed in time units, by correlating the values of measured individual biomarkers with standard average population curves of the dependence of changes in these biomarkers on the calendar age.

This may be done both by direct imposition of a standard graph on the reference curve and by using a calculation procedure, e.g., a regression model of data evaluation.

Thus, *BA* is a characteristic of any process or biomarker that changes with age, but there are classes or groups of these processes and elements that have special names because of their specific features. Such classes may be overlapping; their definitions formulated by different authors may differ; therefore, we describe the system of definitions that seems to this author most acceptable from the viewpoint of, on the one hand, completeness of the representation of the aging processes and, on the other hand, specificity of classes of different processes.

The *calendar age (CA)* reflects aging of the body and its systems, on average, for a population and describes standard mean probabilities of death and life expectancy (LE), the objective index related only to the purely physical flow of time and is expressed in absolute physical time units.

The functional age (FA) reflects the age dynamics of physiological functions and functional reserves, a human's ability to function. Some of these processes may exert no substantial influence on the LE but determine the life quality, and some others may influence the LE. The FA may substantially decrease as a result of training. When the FA is evaluated, it is desirable to allow for the indices of muscular working capacity, cognitive activi-

ty, and the emotional profile of the individual.

The pathological age (PtA) reflects the time dynamics of the frequency and intensity of diseases and premorbid states of an individual that influence the LE. This characteristic determines the specific features of treatment, prophylaxis, and geroprophylaxis.

The *psychological age (PsA)* is a group of indices that characterize age-related changes in the state of mind.

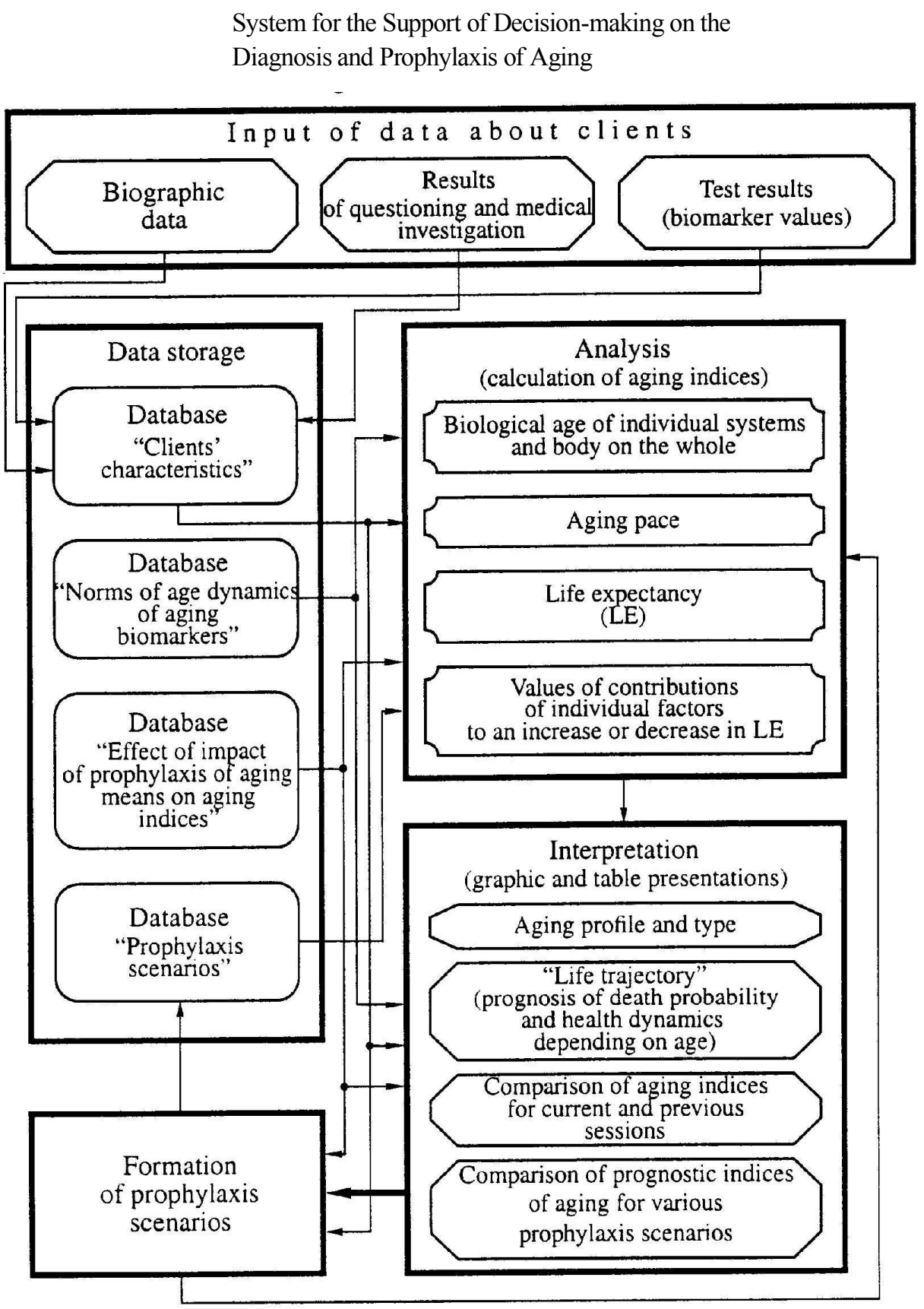

Fig. 1. Block-scheme of the System for the Support of Decision-making on the Diagnosis and Prophylaxis of Aging.

Apart from the bioage indices, a prognosis of the vital trajectory (determination of the LE and life quality) requires also the determination of risk factors (RF). These are the hereditary and acquired factors that decrease the life duration, which can be taken into regard and whose influence can be "rendered harmless" prophylactically, and longevity factors (LF), i.e., the genetic and environmental factors that increase the life duration, such as long-lived persons among the ancestors, balanced low-caloric diet, a kind and steady type of personality, etc.

To speak about bioage as a phenomenon and a scientific problem, Academician V.V. Frol'kis justly noted that it is among the central gerontological phenomena, which is as complicated and general as, e.g., health, adaptation reserve, level of the body functional capacities, etc. Therefore, it is unjustified to raise the question of a single and ideal method of measuring bioage. There may be many such methods, and different methods will be most suitable for different tasks.

For instance, the task of evaluating physical working capacity may require one or two biomarkers; to evaluate the

level of aging of the whole body, the optimum number of biomarkers should be sought in the range of 5 to 15; hundreds of them may be needed for the fine selection of geroprophylactic means. Each school suggests its own approach to the bioage evaluation and sets of tests aimed at it [3, 7, 11, 20]. Therefore, the generalization and comparative analysis of these works and an attempt to develop common approaches and standardize them for typical and practically most important classes of tasks, etc., are important and useful at present, because the fact that different schools use different sets of tests complicates the comparison of their results.

Efforts are made at the National Gerontological Center to systematize the test panels for the bioage evaluation and develop new, more efficient methods of its evaluation [7, 11]. This work resulted in the methodological recommendations concerning the quantitative evaluation of the indices of mortality, aging, life duration, and biological age.

Further, to overcome the above-mentioned dead-end, it is very important to develop experimental schemes and mathematical algorithms aimed, first of all, at the minimization of the duration and volume of animal experiments and tests with humans, preserving the statistical significance of the results. These schemes and algorithms will be used for the prognostic evaluation of the life expectancy curve and life expectation on the basis of fragments of the curve. For instance, working in this field, we found an algorithm for rats and humans and checked it by the life expectancy tables, which makes it possible to extrapolate the life expectancy curve with an accuracy of 0.1% and reduce the study duration by 30-50% [15]. We also created a special software for bioage evaluation [7].

Thus, prophylaxis of aging as a sphere of scientific and practical activities has substantial specific features both in its general ideology, which relies on the active use of the bioage phenomenon, and in the biomedical and mathematical features of the methodology of the preparation of prophylactic programs and analysis of the obtained data. There is vast room in this field for very interesting work, but there are reasons to believe that the procedure of reliable evaluation of the efficiency of the means that slow down aging and radically increase the duration of active life can be put on a strictly scientific basis. The efficiency of scientific and practical activities aimed at the prophylaxis of aging may be substantially increased using the means of modern informatics, such as the system for the support of decision-making — the "Diagnosis and Prophylaxis of Aging" developed by us (see Fig. 1.).

Now, let us discuss the second corner-stone, i.e., geroprotectors as practical means of prophylaxis of aging. Is it possible to start their practical application now? If so, how can it be done without waiting for convincing evidence of the efficiency of geroprotectors in humans? What is needed to this end?

Notably, there are some important differences between the technologies of prophylaxis of aging and of clinical treatment of diseases: (1) the means of prophylaxis of aging are applied throughout the life; (2) many years or even decades are required to test them in humans; (3) these technologies are applied, first of all, to healthy persons, although a disease is not, naturally, an unsurmountable obstacle to their application.

To continue the analogy with clinical treatment, the situation in the field of prophylaxis of aging is as follows: a number of means of prophylaxis are at the stage of preclinical testing; some means have passed through this stage; the clinical testing of some others has just begun. The reality and specific features of geroprophylaxis make it certain that we are going to live in this condition of transition from the preclinical to clinical stage, i.e., of permanent clinical trial, for dozens of years. Can the question of the sufficiently wide application of technologies of prophylaxis of aging be raised in this situation, or we should wait for many years, despite their potentially high practical usefulness? In our opinion, given a sufficiently serious basis for scientific argumentation about perspectives of a technology as a geroprotector, this is both possible and necessary, provided such a basis is sufficient for an argumented conclusion on the negligibly low probability of negative side effects in comparison with the positive effect, i.e., an increment in the duration of a full-value life.

The general structure of the demonstrative basis of prospects of the application of a technology as a geroprotector is, in our opinion, as follows: convincing data on a manifest geroprotective effect in animals (a double-blind multicenter experiment as an ideal); clear understanding of the aging mechanism at which the geroprotector is targeted and data on the identity of that mechanism in animals and humans; the results of pharmacokinetic analysis as the substantiation of the dosetime structure of the course; results of pharmacodynamic analysis, i.e., selection and approval of the schemes of side effect control; regard for the experience of the application of the geroprotector in humans with other purposes in short - and long - term schemes in the adjacent spheres of science and practice; a reliable scheme of current control of health condition (bioage, homeostatic parameters, etc.); use of doses that are, as a rule, much lower than pharmacological doses; and statistically significant mathematical evaluation and prognosis of change in the bioage dynamics and life expectancy.

The technology of the formation of this basis and of a scientific conclusion on the possibility of mass application of a geroprotector is, on the one hand, ideologically new and unusual in health care and, on the other hand, closely correlates with the technology of an expert conclusion on the permissibility of the transition from preclinical testing of a preparation to clinical testing. Such a technology must be sponsored officially, otherwise a wave of uncontrolled "means for rejuvenation and life prolongation" will sweep us over; actually, it has already

done so. Both scientific logic and practice prove that such means can only shorten a man's life.

The most promising fields of activities related to the creation and introduction of technologies of prophylaxis of aging are methods of the diagnosis of aging processes; risk and longevity factors; bioactivation and bioregulation; geroprotective nutrition; diagnosis and correction of cerebral aging; psychotherapy; hormonotherapy; immunocorrection; diagnosis and correction of oxidative stress; enterosorption and endoecology; geroprotective multisystems; gerontological informatics; creation and methodological support of a network of centers for prophylaxis of aging; and formation of a geroprotective mentality in the physicians and population.

Some fully formed fields of medicine possess approaches and methods that are very useful for the prophylaxis of aging. In particular, we mean such fields as prophylaxis of noninfectious diseases, hygiene, valeology, balneology, rehabilitative medicine, reservometry, prenosological diagnosis, reflexotherapy, etc.

Notably, some important features characterize geroprotective technologies on the whole.

On the one hand, these impacts are applied, as a rule, throughout life in doses below the pharmacological level; or, they may be nonpharmacological means that make, due to their essence and mechanisms, a mild supporting, stimulatory, regulatory, and health-improving impact. By the way, a constructive and useful mutual penetration of traditional and nontraditional medicine may be expected in this field. Mild means of popular medicine will be combined with rigid and standardized methodology of their application, which is characteristic of official medicine.

On the other hand, these methods pose a serious danger of detraining of the body's own systems, e.g., antioxidant or hormonoproductive systems during hormonocorrection, as well as the danger of taking an overload instead of a stable enhancement of functional activity or feeling distress instead of eustress. Therefore, unskillful use of "means of rejuvenation" (such as fat burners, ginseng-based adaptogens, etc.) may lead and actually do lead to serious disorders. The borderline is quite fine here, and medicine needs well-tested methods, individual approach, and rigid control of the body condition.

The technologies of prophylaxis of aging must rely on the potential of data accumulated by researchers of the whole world in the fields of gerontology and adjacent disciplines, but it is important that the Russian science has developed unique approaches in a number of fields, leaving the West behind, and is able to create competitive technologies.

In particular, considering the field of general methodology, one cannot overlook the vitauct theory and the stress-age syndrome concept developed by the Kiev school, M. Dil'man's regulatory theory of aging, R. Baevskii's and V. Kaznacheev's methodology of prenosological diagnosis, etc. Generally, Russia was traditionally strong in the synthetic, integrative, and systemic approach. Continuing this tradition, we developed new versions of the systemic theory of health and aging, which are considered the basis of integral geroprotective technologies [8-10, 13, 14]. Similar approaches are tested experimentally at Kursk State Medical University.

The following concrete studies, which are promising in prophylaxis of aging, deserve special mention: the methodology of treatment of the chronical fatigue syndrome (Moscow State Medico-Stomatological University, Ministry of Public Health of the Russian Federation; National Gerontological Center); the method of antioxidant therapy (Institute of Biochemical Physics, Russian Academy of Sciences; Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences); a new method of bioage diagnosis (Moscow State Medico-Stomatological University, Ministry of Health Care of the Russian Federation; National Gerontological Center; Institute of Systemic Analysis, Russian Academy of Sciences; Sechenov Moscow Medical Academy); cytamines and cytamedines (St. Petersburg Institute of Bioregulation and Gerontology); electrochemically activated systems (Moscow State Medico-Stomatological University, Ministry of Health Care of the Russian Federation); method of enterosorption in the prophylaxis of aging (Kiev Research Institute of Gerontology); mathematical algorithms of the optimization of studies in geroprotection (Institute of Systemic Analysis, Russian Academy of Sciences; National Gerontological Center); endoecological methods (Research Institute of Regional Pathology and Pathomorphology, Siberian Division of the Russian Academy of Medical Sciences); immunocorrective methods (National Gerontological Center; Institute of Immunology, Ministry of Public Health of the Russian Federation; Moscow State Medico-Stomatological University, Ministry of Public Health of the Russian Federation); methods of the evaluation of systemic disintegration of body functions (Kursk State Medical University, Ministry of Public Health of the Russian Federation); methodology of the system of sociohygienic monitoring of Russia (Institute of Systemic Analysis, Russian Academy of Sciences; Sechenov Moscow Medical Academy).

CONCLUSIONS

Real progress in the works aimed at the creation of modern technologies of the prophylaxis of aging requires organizational and financial support on the state level at the present time. Wide introduction of these technologies promises enormous socioeconomic effects, including the following:

increase in the present level of activity and full value of an individual's life;

increase in the society's labor potential and reduction of the demographic load rate;

increase in the "life volume" and "efficiency factor" of an individual's life;

"harmonization of aging" and comfortable senility.

Russia's worthy place in the world market of the "health industry".

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