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Editorial

Towards realization of longer life

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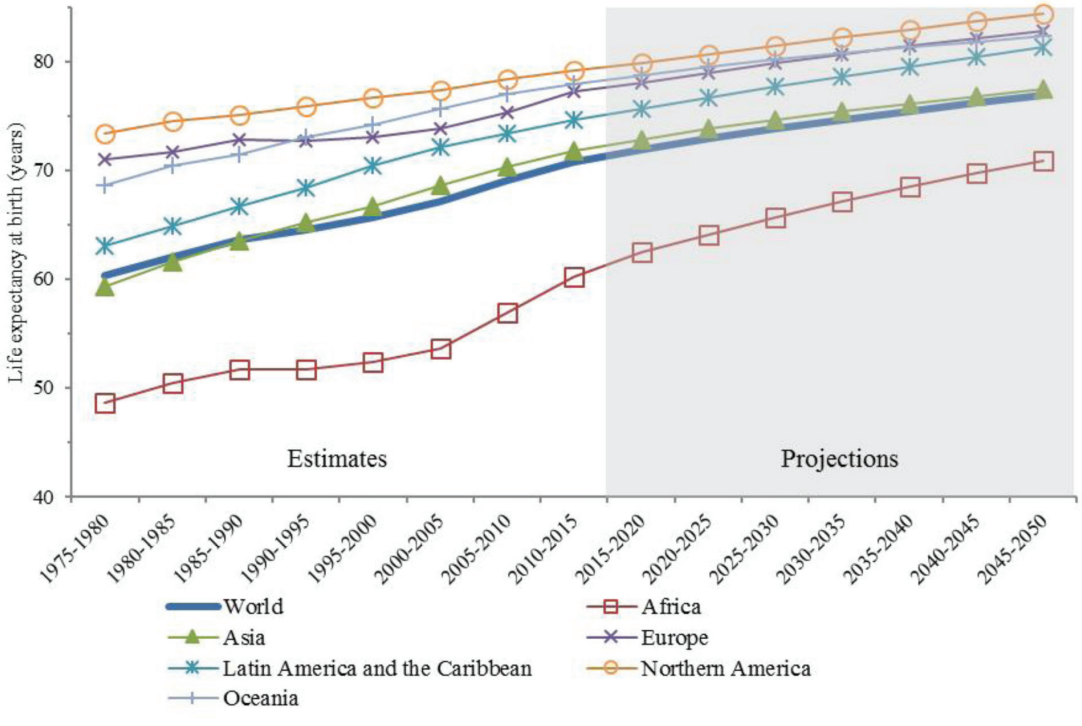
The current demographic situation in the world is characterized by an increase in average life expectancy, low birth rate, as well as an increase in the number of older and senior people, which is why our epoch is referred to as «the age of ageing».

The 2017 UN Report features data on the increase in life expectancy during the recent decades (1). On the global scale, life expectancy at birth has risen by 3.6 years during 2000-2015, i.e. from 67.2 to 70.8 years. The most significant rise was observed in Africa, where life expectancy during the considered period increased by 6.6 years. Thus, life expectancy in this region amounted to 60.2 years, while in Asia it is 71.8 years, in Latin America and the Caribbean, 74.6 years, in Europe, 77.2 years, in Oceania, 77.9 years, and in North America, 79.2 years (Fig. 1).

Notably, the share of population over 60 and older in the world is growing at a faster rate than that of other age groups, which is a manifestation of global population ageing. Thus, in 2017 the share of peo-



Source: World Population Ageing 2017 Report

Figure 1. Life expectancy at birth (years) by region: estimates 1975-2015 and projections 2015-2050

ple over 60 and older amounted to 962 mln, which is 13% of the total world population. The share of world population aged 60 and older is growing by 3% every year. Meanwhile, Europe is demographically the oldest continent in the world, whose share of population aged 60 and over amounts to 25%. Fast ageing is also going on in other regions. Consequently, by 2050 virtually everywhere, excluding Africa, people of 60 and over will make up a quarter of the whole population. According to UN forecasts, by 2030 the population of our planet aged 60 and over will amount to 3.1 bn people. The data from numerous foreign sources show that in developed countries there is a strong tendency to dynamic increase in the number of people aged over 80 in the total population structure; it is in this population group that the share of people in need of care is surging. From 2000 up to 2050 , this share is predicted to increase from 70 mln to 401 mln, respectively. The countries that have the largest demographic ageing rate are believed to be Japan and a number of European countries, including Germany, Italy, Sweden and Greece, with the population aged 65+ making up from 18 to 21%. However, other countries are also likely to show similar tendencies. For instance, by 2060 unprecedented population ageing is predicted in Latvia, Poland and Romania. The share of people over 65 will amount there to 35% and more.

«A large majority of the world's countries are experiencing significant shifts in the distribution of their populations by age, moving from the youthful populations associated with the relatively high levels of fertility and mortality of the past, towards the older populations associated with the lower levels of fertility and mortality of recent times. These changes are a manifestation of a demographic transition, characterized by long-term reductions in the mortality and fertility rates prevailing in a population, which brings important changes not only in the size of the population but also in its composition by age… Demographic transition is a universal phenomenon, even though its timing and speed have varied greatly across countries and regions... Considering these major global demographic trends and the way they affect further development, the Commission for Population and Development has decided that a special topic at its 50th session to be held in New-York on 3-7 April 2017 will be «Changing Population Age Structures and Sustainable Development» (United Nations expert group meeting on Changing Population Age Structures and Sustainable Development, Population Division, DESA UN Secretariat. New York, 13-14 October 2016).

The global demographic imbalance is getting worse. In 40 years period, the number of people over 60 will exceed that of people under 15. Low birth rates and increased life expectancy in many countries are certain to cause problems in the labor market, and lack of labor resources in particular. These processes are leading to substantial rise in the demographic load rate on the society, i.e. the proportion between its working and non-working members, which is aggravating the local economic situation causing significant structural changes in terms of employment and social support.

The main trends in population ageing and older people's living standard

- *The amount of world population aged 60 and over in 2017 amounted to 962 mil people, which is twice more than in 1980, when the number of old people in the world was estimated at 382 mil. By 2050, this figure is expected to double again to reach an estimated 2.1 bn people.*
- *In 2030, the number of elderly people is expected to exceed the number of children aged under 10 (1.41 bn against 1.35 bn); according to the forecasts for 2050, the number of people aged 60 and older will exceed that of the teenagers and young people aged 10 to 24 (2.1 bn against 2.0 bn).*
- *According to forecasts, the number of people aged 80 and older in the world has more than tripled in the period from 2017 to 2050, from 137 to 425 mil people.*
- *Two thirds of the elderly people live in the developing regions, where their numbers are growing faster than in the developed countries. It is expected that in 2050, 8 out of 10 elderly people will be living in developing countries.*

- *Population ageing, the inevitable increase in the share of elderly people caused by lowering birth rates and life expectancy growth, which are characteristic of the demographic transition period, is going on in the whole world. According to forecasts, starting from 2017, in all the 201 countries or regions of the world with the population of minimum 90 000 people, the share of the population aged 60 and older will be growing between 2017 and 2050.*
- *Although the ageing process is most evident in Europe and North America, where in 2017 there was one person over 60 per every five citizens, the population of other regions is also getting older. In 2050, the share of older people in Europe will amount to 35%, that in North America, to 28%, in South America and the Caribbean, to 25%, in Asia, to 23%, in Oceania, to 23% and in the countries of Central Africa, to 9%.*
- *According to the data submitted by 143 countries, the share of people aged 60 and older, who lead an «independent» life, that is, live alone or with their spouses, varied within a wide range, from 2.3% in Afghanistan to 93.4% in the Netherlands.*
- *In general, elderly women live alone more often than elderly men. Both in Europe and Africa, older women live alone twice as often as men.*
- *Data for 67 countries indicate that during the recent decades older people have become more willing to lead an independent life (around 37% in 2010 as compared to 24% in 1990), whereas living together with children has become less widespread (53% in 2010 against 65% in 1990).*
- *As the average population age continues growing, the governments should introduce policies directed at satisfying the needs and interests of elderly people, including the ones concerned with accommodation, employment, healthcare, social support and other aspects, contributing to the solidarity between generations. In view of this demographic shift, the countries should take active measures in order to adapt to the population ageing, which, in its turn, will be of great importance for achieving the aims of the Agenda for Sustainable Development for the period until 2030, whose slogan is: «Nobody will be left out».*

Source: World Population Ageing 2017 Report

Population ageing is one of the most important factors affecting politics in the multi-dimensional context of social and economic changes and transformations in the labor market. In this connection, the main reforms should be directed at using the potential of all generations and, particularly, that of the growing elder population.

The Madrid International Plan of Action on Ageing (MIPAA) is a new way of considering questions concerned with population and individual ageing. According to MIPAA, persons of older age are included into the productive population group (2). However, in order to attract this population group to taking part in social development, complex approach is necessary: mobilization of all efforts of the government, social services, mass media, as well as those of the healthcare system.

It is important to understand that the solution to the problems concerned with population ageing is only possible if all society members are aware that the citizen aged 65 and older constitute important potential for social development (3, 4). As a rule, healthy people of older age are able to work till later age, compensating for the work force deficit caused by lower birth rate, thereby providing for the continuity of knowledge and experience of older generations. It is necessary to realize that the enhancement of the physiological resources of human vitality and healthy longevity cannot be implemented unless modern technologies are applied; programs for encouraging healthy life style are developed and implemented; educational and wellness strategies for persons of all ages are introduced; realistic approaches are implemented to financial support at the later stages in life; programs and plans

concerned with ageing issues are coordinated. The definition of «unemployable age» should be cardinally reconsidered. The social and economic politics of the government should take account of the growing life expectancy. The equivalence of the notions of «ageing» and «disability» must be rejected. For many years the ageing phenomenon had been considered in terms of ethical and social problems. Now society has realized that the ageing process should be considered in different terms, as a special physiological body mechanism having certain evolutionary function.

The demographic change pattern is responsible for the special character of population ageing in Russia concerned with the increasing share of older people and biological ageing of people who formally do not belong to the elderly people category. These negative demographic trends are also closely linked with the increased disease incidence in people working in harmful conditions, including coal, power, oil, gas and nuclear industries, engineering, metallurgy, etc.

The ageing process must be considered not only in terms of ethical and social problems; it should be studied as a special physiological body mechanism that has a certain evolutionary function. The life expectancy limit for humans as a species is from 30 to 40% higher than the actual average life span. This is due to the effect of various unfavorable factors on human body leading to the changes in gene expression and structure, which is accompanied by protein synthesis disruption and reduction of bodily functions. Body ageing has many dysfunctional levels and can be classified as a systemic syndrome (5, 6).

The characteristic feature of ageing is reduction of the adaptive ability of the body, which is due to the symptomatic decline in the functions of cells, systems and organs. Among these, researchers are now expressing acute interest to the changes taking place in the major bodily systems, including the immune, cardiovascular, central nervous and endocrine systems. At ageing, a dissonance occurs in the well-regulated interaction mechanism of various organs and systems, leading to loosening control over the intrinsic environment of the body, reduction of immunological reactivity and self-regulation.

One of the priorities in modern gerontology is prevention of untimely ageing and age pathologies directed at increasing average life span, preservation of active life longevity and achievement of the species-specific human life span limit. Achievements in theoretical and applied gerontology allowed targeted age-related change regulation.

It is well-known that the ageing process is a gradual involution of organs and tissues, resulting in the disruption of bodily functions. Ageing symptoms become evident already at the end of the reproductive period and intensify with further ageing. In the late 19th century, I. I. Mechnikov proved that improvement of cell immunity contributes to life span increase. He developed the phagocyte immunity theory in the belief that the human body has an inherent capacity to withstand pathological ageing (Nobel Prize in Physiology or Medicine shared with P. Erlich, 1908) (7). A hundred years later, P. Doggerty and P. Zinkernagel accomplished detailed research of cell immunity specificity at viral infection, which largely confirmed Mechnikov's conclusions (Nobel Prize in Physiology or Medicine, 1996). In 1962, D. Watson and F. Crick received a Nobel Prize in Physiology or Medicine «for the discovery of the molecular structure of nucleic acids and its role in transferring information in live tissues». In 1961, F. Jakob and J. Monod proposed a genetic regulation model of protein synthesis involving low-molecular collagen, which displaces the depressor triggering allosteric conformational transition in the DNA structure and the bacterial cell (Nobel Prize in Physiology or Medicine shared with A.Lvov, 1965) (8). As a result of lengthy work, M. Nirenberg and H. Khorana managed to decipher the genetic code and determine the codons (nucleotide triplets) for each of the twenty amino acids (Nobel Prize in Physiology and Medicine shared with R. Holley, 1968). Fundamental research into the biochemistry of nucleic acids and determination of the RNA and DNA sequences were accomplished in the 60-ties and 70-ties of the 20th century by P. Berg, W. Gilbert and F. Sanger (Nobel Prize in Chemistry, 1980).

All these fundamental discoveries in molecular biology formed the basis for research into theoretical and experimental gerontology.

It should be emphasized that application of geroprotectors to physiologically stimulate an ageing body is scientifically founded on modern concepts of ageing mechanisms, which means that we can virtually influ-

ence and, to a certain extent, control the human ageing process (9, 10). Searching for new effective means of influencing an ageing body, finding the most rational combinations of geroprotective agents is a vital task. Against the general background of gerontological research, coming not the foreground is finding the means to affect the in-depth ageing mechanisms.

During the recent decade the achievements in theoretical and applied gerontology allowed implementing targeted regulation of age-related changes. Based on the latter, one of the priority tasks for modern gerontology is prevention of accelerated ageing and age pathologies, directed at increasing average life span, preserving active longevity and achieving species-specific human life span limit (4).

Application of the achievements of modern science in medicine has made us realize that the progress in clinical medicine is largely dependent on molecular medicine, i.e. the research conducted at the level of genes and biologically active molecules. Molecular medicine is also making wide use of the achievements in genetics, molecular and cell biology to develop new medicines and technologies.

One of the important directions in molecular medicine is research into the genetic mechanisms of ageing. By now, it has been established that there are genes which regulate the mechanisms of individual development and occurrence of many diseases (9).

As the cell proliferation and differentiation processes are reduced with age, there is a chance of correcting these dysfunctions by monitoring gene expression. Research into the genetic mechanisms of ageing and development of age-related pathologies forms the basis for regular therapy, involving application of transcription modulators, which hinder and reverse age-related genetic changes. Development of effective bioregulators facilitating achievement of species-related life span limit and preservation of the main physiological functions is one of the most urgent problems in modern biogerontology.

Notably, diet is one of the major components in supporting the homeostasis, which to a large extent determines the longevity and quality of life. The substances entering human body during the meals are further, through the gastrointestinal tract, blood vessels and various organs and tissues, involved in the metabolism, supporting functional cellular activity. Consequently, a balanced diet suitable for a particular age, as well as the physical and intellectual activity of the person, is an epigenetic factor of maintaining health and longevity. Thus, various pathological processes going on in the body, as well as ageing, can be considered in terms of disruption of organ, tissue and cellular level of living matter organization. Many products have hyper-protective properties, since their consumption can slow down the ageing processes and prevent development of age-related diseases.

Consumption of fruit, vegetables and fresh greenery can decrease the morbidity and death rate in older people due to their high content of polyphenols, carotinoids, folic acid and vitamin C (11). Besides, it was discovered that the so-called Mediterranean diet affects the length of telomeres. People who consume products pertaining to the Mediterranean diet manifested higher telomerase activity, which lowers the risk of developing hypertension, myocardial infarction, dementia, vascular diseases and cardiac failure (12). On the other hand, consumption of red meat could have negative effect on the ageing processes and increase the risk of cancer (13).

Mediterranean Diet was found to produce a protective effect against cognitive decline, Alzheimer's disease, Parkinson disease (14).

Of special interest is the restricted calorie diet (RCD). One of the most well-known studies is the work by L. Fontana et al. (15), which evaluated the reduction of calorie consumption in people who had been on this diet for 6 years on average, as compared to the healthy controls who had been on an ordinary diet. As a result it was established that the people who had been on a restricted calorie diet had lost weight, reduced the levels of general cholesterol, low-level lipoprotein, triglyceride, glucose, insulin, C-reactive protein, etc., as compared to the control group. These data suggests that RCD significantly reduces the risk of developing the metabolic syndrome and ischemic heart disease (15). It was also established that the people who voluntarily restrict their food, and hence calorie consumption live longer than those who do not (16).

Recent investigations manifested a decrease in cardio-metabolic risk factors in humans without signs of obesity who followed moderate calorie restriction. These data point out potential advantages and useful-

ness of the moderate caloric restriction for cardio-vascular health of young and middle-aged people (17).

One of the mechanisms providing positive effect of the restricted calorie diet is increased body sensitivity to insulin, which prevents development of a number of age-related diseases and ageing.

One of the popular accepted ageing theories is that of free radicals, proposed by D. Harman (18), who stated that over time, organisms accumulate macromolecular cell damage (of DNA, proteins and lipids), caused by free radicals, mainly by reactive oxygen forms. Accumulation of such damage causes cardio-vascular, neurodegenerative and oncological disorders, as well as age-related immunodepression and a number of other pathological changes. It is believed that reactive oxygen forms damage the membranes, collagen, DNA, chromatin, and structural proteins, and are also involved in epigenetic maintenance of nuclear and mitochondrial gene regulation, influencing the intracellular calcium level, etc. (19). The fact that the products of reactive oxygen interaction with macromolecules persistently occur in various organs and tissues shows that the anti-oxidative systems are not effective enough and that the cells are subject to oxidative stress. Enhancement of anti-oxidative protection could play a substantial role in the geroprotective mechanism.

Among the antioxidants, a special place is taken by resveratrol, which is a vegetable polyphenole. In experimental research it was shown that resveratrol increases the life span of yeast, worms and flies, as well as short-living fish (20, 21). *In vitro* research shows that resveratrol possesses not only anti-oxidative, but also anti-mutagenic properties, which is manifested in its ability to suppress development of neoplastic damage caused by carcinogenic agents in mouse cell culture (20). Much later, clinical test results of resveratrol effect were obtained. One of them stated that patients with type II diabetes who were receiving resveratrol (2×5 mg per day) showed significant improvement of insulin sensitivity, reduction of oxidative stress and improvement in the activation level of B protein kinase, as compared to the patients who were receiving placebo (22). The geroprotective antioxidation mechanisms of resveratrol effect are largely similar to those of the restricted calorie diet (23). This is testified by numerous studies, which describe the ability of resveratrol to prevent the development of type II diabetes, as well as some neurodegenerative disorders (Altzheimer disease), lower the protein biosynthesis rate and gene expression, reduce oxidative stress and prevent the development of cardio vascular (24) and oncological diseases (25).

In recent decades much attention in world science has been paid to the physiological role of melatonin, especially in the ageing process. It has been established that in many ageing people the level of melatonin, the pineal indole hormone, is significantly decreased. Melatonin regulates the sleep-wake cycle, changes in body motion and temperature, and influences seasonal activity cycles as well as reproduction. Most of the experimental research proves melatonin to possess geroprotective properties, since it both increased the animals' longevity and slowed down the ageing of their reproductive system (26). Melatonin has an anti-carcinogenic and anti-tumor effect, which has been demonstrated on the models of spontaneous and induced carcinogenesis in animals (27). The geroprotective and anticarcinogenic effect of melatonin is due to its anti-oxidative activity (28). There are reasons to believe that an important role in the geroprotective effect of melatonin is played by its normalizing influence on circadian rhythms. This suggests that the latter can be used as one of the reliable markers of accelerated ageing. Recent clinical studies depicted melatonin as a prophylactic and therapeutic remedy against neurological diseases such as Alzheimer and Parkinson diseases, Multiple sclerosis, Huntington disease, epilepsy, etc. (29).

In the studies concerned with this problem, much attention is paid to the role of peptides in preventing premature ageing. This approach is based on the existence of a bioregulating system in the human organism, which functions through cell mediators, oligopeptides whose main purpose is selective transmission of information during the interaction of the immune, nervous, endocrine and other systems (30). When the organism is in a pathological state, the information transmission process is disrupted. As a result, a number of endogenic compounds are released and accumulated, including peptides transferring distorted information, which hinders coordinated operation of the regulating body systems. Consequently, introduction of physiologically reactive peptides into to the human body contributes to the restoration of self-regulation of organs and systems.

Regulation of homeostasis through peptides takes an important place in the complicated chain of physiological processes leading to the ageing of cells, tissues, organs and the body as a whole (5). Morphological and functional equivalent of ageing is involution of organs and tissues, and primarily those that are concerned with the main regulatory systems including the nervous, endocrine and immune ones. There are data available testifying to age hypoplasia, and in a number of cases, to the atrophy of the pineal gland, thymus, neuronal cortex and sub-cortex, retina, vascular wall and genitalia (4, 31, 32).

For the first time in history, thanks to the development of a new concept based on application of a unique group of peptide geroprotectors, we have a realistic and affordable opportunity to prevent age-related diseases, by slowing down the ageing process and lengthening active life span. At present, with the existing level of knowledge, this is the only reliable way to affect the ageing process in humans (22, 33).

Analysis of *in vitro* research results concerned with the effect of peptides allows making a general conclusion about the possibility of targeted induction of polypeptide cell differentiation, which is the basis for achieving longevity up to the species-specific limit. Using the DNA-microchip technology, a study was carried out concerned with the influence of a number of peptides on the expression of 15247 genes in the heart and brain of mice. In the experiments, clones were used from the DNA library of the National Institute on Aging, USA (11). These experiments produced unique data on the expression of various genes under the peptide influence. An important conclusion was made about every peptide specifically regulating particular genes. The experimental results suggest the existence of a mechanism for peptides to regulate genetic activity.

Considering the data above, as well as *in vivo* experiments (9), which suggest high geroprotective reactivity of both natural tissue-specific and synthetic peptide preparations (34), research in the recent years was focused on studying the effectiveness of peptide preparations and peptides administered to old-aged people (35). Thus, annual course of treatment with thymus and pineal gland preparations resulted in credible reduction of mortality in patients during the period observed (15 years). This was due to the improvement in the functions of the immune, endocrine, cardio-vascular systems, and the brain, as well as that of the bone tissue density (6).

It would be reasonable to administer physiologically active short peptides to people of any age in order to support normal metabolic processes, as well as for prevention and treatment of various diseases, rehabilitation after severe illnesses, traumas, operations and slowing down ageing processes in the organism.

Health preservation and prevention of premature ageing of the available work force will allow to withstand excessive demographic loading in the context of global ageing tendency. The results of 35-year-long experimental tests and clinical research into the bioregulators developed at the Saint Petersburg Institute of Bioregulation and Gerontology by the staff of the leading Russian and foreign medical research institutions showed their high efficiency. Notably, administration of peptide bioregulators to over 15 mln people demonstrated their complete safety because they actually constitute organism's metabolites. The research results were published in numerous monographs, articles and dissertation; they are protected by over 200 Russian and international patents (26, 36).

To summarize, currently an opportunity is opening up for wide application of natural peptides in medicine with the aim of regulating various bodily functions. The most important direction is preventive application of peptide bioregulators for improving resistance to the effect of destabilizing factors. This allows lowering the ageing rate, the risk of age-related pathology development and facilitates increasing life span longevity, improving the life quality of older people.

The Concept of Healthy Ageing proposed by the UN experts as one of the priorities of the UN Research Agenda on Ageing for the 21st century focuses on people's life style (dieting habits, age of sex initiation, abstaining from alcohol and smoking, etc.), which can have a marked positive effect on the rate of age-related diseases and, hence, on general longevity. However, it should be emphasized that application of products normalizing age-related hormonal, metabolic and immunological changes and thus slowing down the genetic ageing process (by slowing down the ageing rate, rather than postponing its onset), is going to have a most significant geroprotective effect.

Development of the "Action Strategy in the Interests of Older Generation in the Russian Federation for the Period up to 2025" should be considered as a breakthrough that opened up a new stage in the development of gerontology and geriatrics in Russia (37). It took a large number of scientists, experts and public people a whole year to develop the strategy, a program document for forming a new approach to the social support of the older generation in Russia, which involves setting up a geriatric support system. Notably, the Strategy employs a complex, systemic approach to solving the problems of providing state support for people of older generation, which makes it different from all the previous normative acts.

One of the main Strategy directions is "improvement of the healthcare system for older-age citizen, developing geriatric services, including professional training and supplementary education of specialists in this area". In this respect, the following steps are planned:

- Development of a consistent and sustainable system combining medical assistance for people of all ages, from disease prevention to palliative medical help, which implies a complex approach to medical help for older citizen.
- Providing accessibility of geriatric assistance for older-generation citizen, which confirms the importance of geriatric help in the system of their medical support.
- Establishing early detection system for age-related chronic non-infectious diseases and their risk factors, which emphasizes the importance of "ageing prophylaxis".
- Arranging geriatric service as a joint system of long-term medical help involving continuity in patient treatment by different healthcare system levels, as well as the social support system, which manifests the systemic, complex and long-term nature of geriatric support, as well as the importance of inter-departmental integration. .
- Development of palliative medical help in the interests of older-generation citizen, which suggests the solution of the "expiring" problem in terms of geriatric help.
- Making use of the public-private partnership in the area of geriatric help provision for older-generation people conditioned by the need to extend medical support, which manifests the importance of attracting the service of non-commercial organizations.
- Popularizing the potential and achievements of gerontology and geriatrics as contemporary medical trends contributing to active longevity, which indicates the importance of public accessibility of the relevant information.
- Improvement of the professional training system, conducting research, providing medical personnel with contemporary knowledge in the area of gerontology and geriatrics, which emphasizes the importance of scientific, methodological and educational support of geriatric services.

Analysis of all the points listed above demonstrates an integrative approach used by the Strategy to solving the problems concerned with improvement of the healthcare system for older-generation citizen, highlighting geriatric support as a basic element in the system, which provides for the joint effort of the state institutions and non-governmental structures in forming a complex service, that of geriatric medical, social and psychological support for older-generation citizen. As a program document, the Strategy stands out for its high level of detailing.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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