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Natural aging as as a sequential poly-systemic syndrome

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1. ABSTRACT

We review the progression of aging as a sequential development of multiple syndromes analogous to other diseases. This generalized approach may allow practicing physicians to consider the signs of aging as manifestations of a poly-syndrome disease and facilitate prevention, diagnosis and treatment of common aging-related dysfunctions.

2. INTRODUCTION

The almost worldwide rapid aging of the population dictates a significant increase in interest in problems of gerontology, seeking the causes and mechanisms of aging, and the means for their control and reversal, to achieve active and healthy longevity for the population. Recently, a concept positing aging as a disease has been developing in gerontology (1–12).

The suggestion to consider aging as a disease was made long ago (13–14) and has been supported by many researchers (7–10, 12, 15, 16). The existence of partial progerias, presenting the development of particular aging syndromes, has been used as one of the arguments for the concept of aging as a disease (17). However, most gerontologists, philosophers, and clinicians do not accept the identification of aging (understood as a necessary period of life history, typical for the entire population) as a disease (understood as a manifestation observable only in a subset of the population) (1,18).

The rationale behind this concept is that aging, generally, is accompanied by a decrease in viability and development of common pathological states, especially the so-called "age-related diseases,"

together with reduced working capacity, adaptation ability, physical strength, and intellectual capacity. Moreover, to date a significant amount of experimental data on "anti-aging drugs" (or "geroprotectors") has accumulated (6, 11–12, 19–21). A new field of practical medicine, so-called "anti-aging medicine", is rapidly developing. It may appear appealing to refer to aging as a disease, as it could offer opportunities and incentives to look for treatments.

However, a disease is traditionally understood as a pathology depending on specific causes that only affects a part of the population and that can be treated by a therapy directed to the cause of the disease. Moreover, some typical pathologies are not considered as diseases, such as traumas, intoxications, and consequences of diseases and traumas (e.g. scars, lameness, etc.). The beginning (pubescence) and ending (menopause) of the reproductive period are not referred to as diseases, and even a debilitating climax is not considered a disease, but a severe climax. Also, a state characteristic of the whole population and being a part of the life cycle (ontogenesis) without a specific cause (etiology) cannot be referred to as a disease. The availability of many anti-aging drugs (geroprotectors) is also not a reason to consider aging as a disease, since the application of drugs may not be directly connected with a disease: e.g. the use of vitamins and minerals for the prevention of the spring-summer reduction in immunity, herbs-adaptogens, the use of caffeine in coffee and tea, etc. Such a typical medical approach as dietology is not directly related to the treatment of diseases, dealing with foods and not drugs.

However, besides the trivial association of aging with "age-related diseases," another approach to the relation of aging and diseases is possible. It could offer physicians additional opportunities to influence the aging process directly, while today they do not consider aging as a state requiring any special actions and in fact prefer treatment and prevention of "age-related diseases". The prevalent view of aging as a natural and inevitable process, not requiring special interventions, delays the development and application of drugs and other treatments against it. Our approach is based on the fact that during natural aging syndromes typical of common diseases and pathological processes develop. The availability of medical products that affect these syndromes, in particular anti-aging agents (geroprotectors), makes timely prevention and correction of aging reasonable and feasible. In other words, natural aging can be considered as a common poly-syndrome disease.

The multitude of known mechanisms of aging has led to the creation of hundreds of theories of aging and a vast variety of approaches to potential therapeutic effects against aging. The theories are usually categorized as variations of the stochastic damage theory or the reduction of tissue regeneration programmed during natural development (22–32). However, these purely phenomenological approaches did not lead to breakthroughs in solving the described practical and conceptual issues. The systemic approach that we are developing for the phenomenon of aging (20, 22) allows the transition from particular and phenomenological representations to a general model of aging, connecting its fundamental cause – the growth of entropy in a partially open system with a hierarchically organized system of its main interrelated mechanisms. It is becoming increasingly clear that well-known medical syndromes, which can be diagnosed and treated by common medical means, play an important role in the development of the natural aging process. Syndromes typical for common diseases are developed in the course of natural aging, including dystrophy, hypoxia, and tissue sclerosis, toxicity, oxidative stress, immunodeficiency, maladjustment, etc. Moreover, aging is accompanied by typical pathological processes or their precursor states: pre-diabetes, atherosclerosis, angina, tissue ischemia, osteoporosis, etc., requiring prevention and correction. This syndrome approach to influencing the natural aging processes, using available well-known medical agents that can affect these syndromes, provides physicians with a practical tool to make an impact on aging and makes such impact feasible and necessary from the scientific, practical, and regulatory points of view.

The objective of this article is to review the close relationship and even identity between the main natural aging syndromes and the typical syndromes of common diseases, as well as to show a possibility to affect the process of natural aging with modern medical means. This approach legitimizes research and practical application in medical practice of the so-called "geroprotectors" – a special class of pharmacological agents and other therapeutic methods, with the main intended effect being increasing healthy longevity (6, 11, 12, 19, 21).

Thereby, geroprotectors may be considered as agents prescribed under specific medical indications and may be entered into the pharmacopoeia as prophylactic and treatment agents for natural aging, which in turn can be regarded as a chronic systemic disease.

3. GENERAL SYSTEMS APPROACH TO AGING

3.1. Hierarchical model of aging

Modern scientific principles of systems analysis make it possible to apply methods of phenomenological analysis at an abstract level, replacing the consideration

of the material system structure with the consideration of the essential interrelations between its structural parts. Thus, the study of the endless particular manifestations and mechanisms is replaced by the consideration of general laws and principles.

It is now quite clear that the necessary and sufficient definition of "aging" must involve the general phenomenon of reducing viability (increasing probability of death) with aging. The basic cause and mechanism of aging may be posited as an increase in degree of chaos at all structural body levels, which manifests in a general reduction of the body's resistance and adaptability to all internal and external factors, and it is registered as an increase in the probability of death from all causes during aging. This process is fatally determined by a fundamental law of nature – the second law of thermodynamics for semi-open systems, which includes the human body, comprising stable (or semi-stable) structures and elements. Based on these fundamental concepts, a general model of aging of a living body can be constructed (20, 22).

According to the fundamental cause of aging, the basic approach for its inhibition and reversion is a reduction of chaos, i.e. elimination of accumulated impairments and disorders by their replacement or repair both from the outside (replacement of damaged organs and cells) and from the inside (enhancing metabolism, cell division, regeneration of organs and tissues). It is very important to keep in mind that the body components of different hierarchical levels – genes, subcellular structures, cells, and supracellular structures (e.g. alveoli, nephrons, and organs) – cannot be fully renewed. These components accumulate damage with aging and become a major cause of age-related reduction in the body's viability, providing the morphological basis of aging. The accumulation of damage takes place randomly (stochastically). This mechanism is the first major *stochastic aging mechanism*.

On its own, the process of active functioning of a living organism (the life-sustaining process) requires an exchange with the external environment and complex metabolism inside the system. The side effects of almost any process are waste and contamination. This mechanism is the basis, for example, of the well-known "free radical theory of aging". This mechanism causes body contamination with external intoxicants and internal metabolites. Not all substances entering the body are useful, and not all internal and inert toxins can be excreted. This "contamination" with external intoxicants and internal metabolites cannot be fully compensated for. This process of contaminant accumulation is the second major *toxic aging mechanism*.

The more complicated a system is, the greater is the share of its components and processes relating to the regulatory system, in particular, to the system managing the process of growth and development, which is responsible for the presence of the third major mechanism of aging – *the regulatory aging mechanism*. Insofar as cell proliferation completely renews such structures as skin, mucous membranes, and parenchyma of organs, so their aging can only be a result of reducing the regulatory factors (presumably, growth factors). This is a fundamental aging mechanism that is specific for living systems only. Stochastic and regulatory mechanisms are the main recognized aging mechanisms.

Figure 1 shows a hierarchical flow chart of the development of the aging process in a biosystem: from a single cause via the major mechanisms to specific manifestations of aging. Whereas the total cause of aging is manifested through three major aging mechanisms, the specific signs of aging are grouped by general mechanisms into syndromes.

3.2. Prospects and pathways to affect aging and significance of the syndrome approach

The impacts that can be produced on the major aging mechanisms are limited. The stochastic death of components is a fundamental limiting mechanism for the aging of biosystems, and it can be adjusted only by prosthesis (a classic example is dentistry). The regulatory aging mechanism is perhaps the most susceptible to intervention. Therapeutic impacts can be achieved by affecting the specific regulatory centers and regulation factors. The impact on the cell self-renewal mechanisms can be optimal, using, for example, blood growth factors and central regulation mechanisms, e.g. immune mechanisms of cellular growth control and hypothalamic control mechanisms of growth and development. Impact on the toxic aging mechanism is limited by the extent of stimulation of excretion and toxin metabolism systems.

Impacts on the natural aging syndromes may be much more varied and effective. The syndrome description principle is one of the fundamentals of medicine, and it is studied in detail in pathophysiology, where typical pathological processes are indicated. The body responds to any external and internal impacts, producing changes in its internal structures and functions, which are not unlimited, but are determined by a well-defined and limited number of standard reactions – or syndromes. These syndromes and the therapeutic interventions into them are well studied in medicine (20, 22). Many of the syndromes are characteristic of natural aging, and physicians are very familiar with them. The major natural aging syndromes are shown in Figure 2.

These syndromes interact. Therefore, a corrective action on one syndrome positively affects others and the entire manifestation of aging.

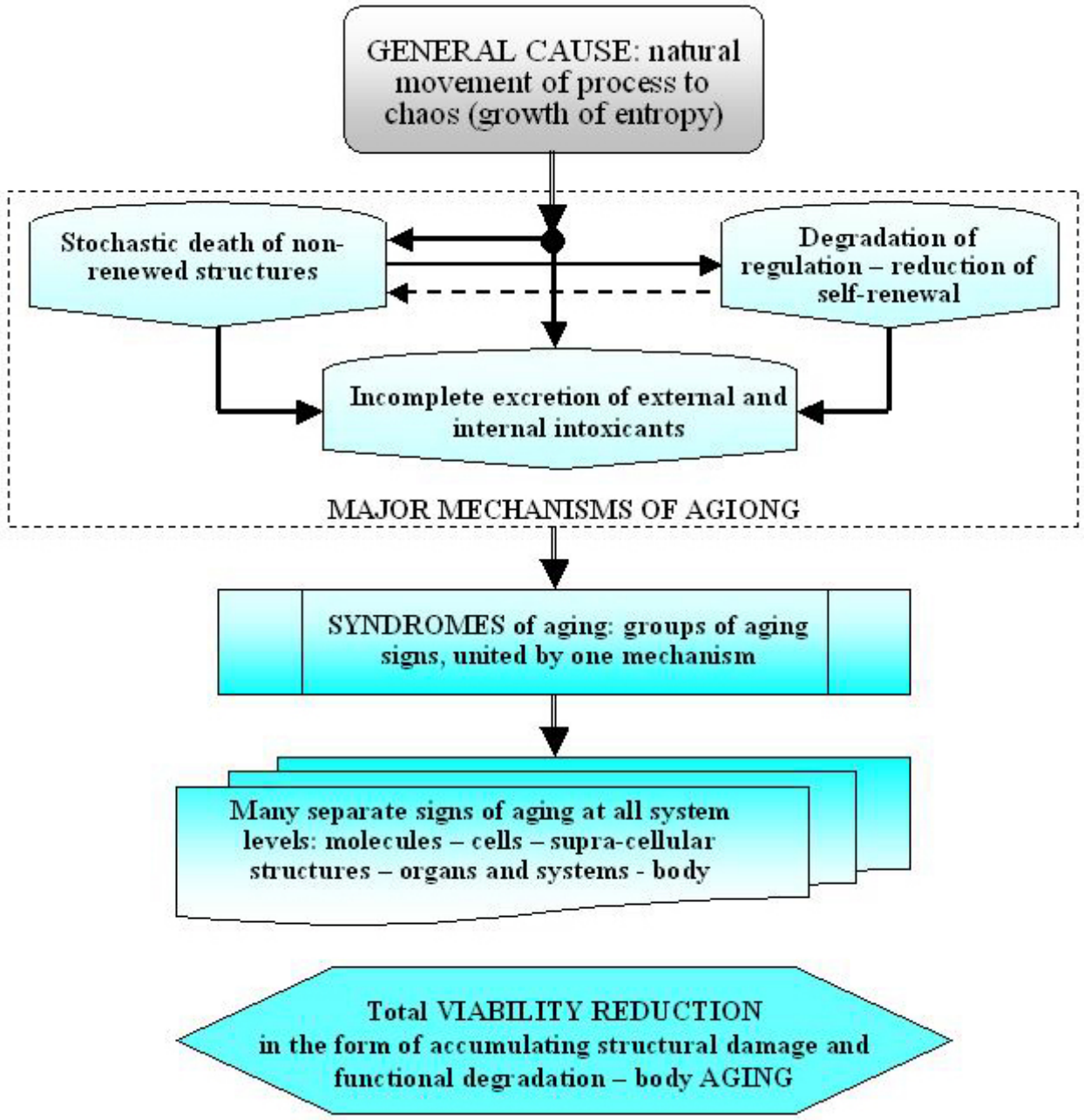

Figure 1. Hierarchical structure of aging mechanisms.

In most cases, in animal trials and some human studies the effect on aging is limited by the impact on the lowest level, i.e. the particular manifestations of aging. For example, for low level of enzymes in the intestinal tract, oral drugs are prescribed; for low level of hormones, hormonal drugs are prescribed, etc. However, the most effective impact on aging could be produced by interventions at a higher level, i.e. at the level of syndromes, insofar as syndrome therapy is well developed in medicine and employs a great number of therapeutic and prophylactic medications.

3.3. Syndromes of natural aging and their possible correction

Aging syndromes are groups of aging symptoms that are interconnected by a common mechanism. The central ones are the mechanisms of growth and development termination, manifested in reduction in metabolic rate and cell self-renewal. A typical example of the development program is the beginning (pubescence) and end (menopause) of the reproductive cycle, which is associated with the

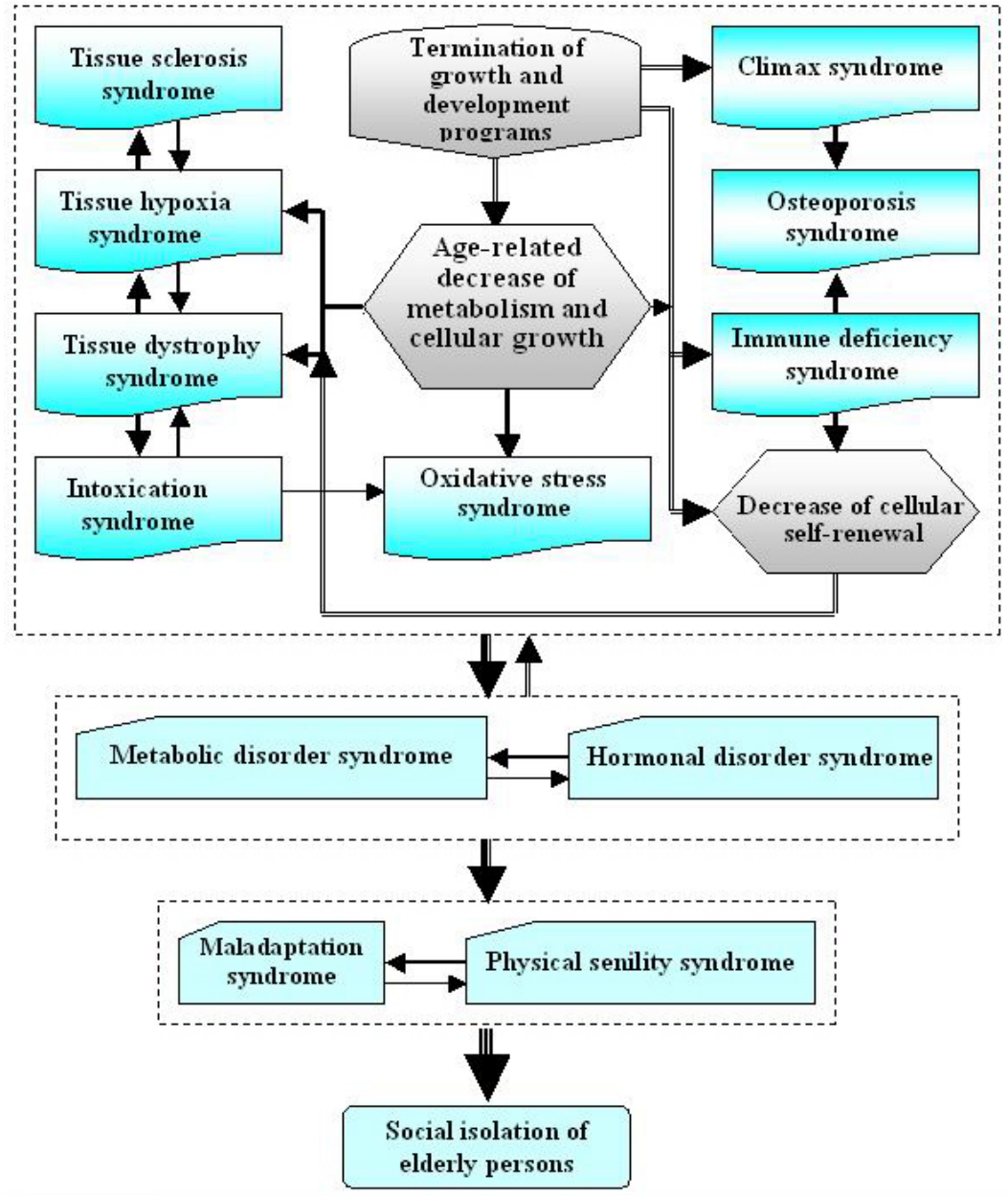

Figure 2. Major syndromes of aging and their links with the main aging mechanisms.

development of osteoporosis. The prevention and treatment of climax and osteoporosis syndromes may be good examples of the prevention and treatment of natural aging at the level of specific aging syndromes. Besides climax and osteoporosis syndromes, which have long been included in medical practice as separate diseases, some other syndromes developed during aging are also very well known to physicians. Some of the most important syndromes are discussed below, considering their relationship with natural aging and the possibility to therapeutically affect them. Some specific syndromes (such as dystrophy, tissue sclerosis and hypoxia, intoxication, oxidative stress, immune deficiency) are manifested in the form of common syndromes of metabolic and hormonal disorders and constitute general syndromes of maladaptation and physical senility, which are the most important causes of social isolation of elderly persons.

3.3.1. Tissue dystrophy syndrome

The age-related reduction of metabolism, the termination of growth and development processes, and the reduction of cellular self-renewal produce the most typical syndrome of aging – the age-related dystrophy of organs and tissues. This is accompanied by a decrease in muscle strength, decrease in organ parenchymal functions, thinning of mucous membranes and skin, atrophy of glands and hair follicles, and many other manifestations. Atrophy of capillaries causes the reduction of tissue nutrition, age-related hypoxia, and sclerosis.

Reduction of muscle strength with aging (sarcopenia) is a typical manifestation whose study is presently developing as a subfield of medicine and gerontology (33–35).

Correction of this syndrome can be achieved via the activation of cellular metabolism and growth by anabolics, growth factors, stem cells and their activators, as well as general training of functions, causing their activation and inhibiting tissue dystrophy.

3.3.2. Tissue sclerosis syndrome

This mechanism has been known for a long time and it underwrites one of the well-known theories of aging, namely, reduction in the speed of growth and self-renewal of cells and tissues with aging leads to tissue dystrophy and compensatory growth of connective tissue.

Proliferation of connective tissue is an active process and may be passively transferred to young animals via administering growth factors of connective tissue (including brain glia) from old animals (36). It causes vascular sclerosis and hemodynamic disorders, alongside with the interruption of tissue nutrition.

Correction for this syndrome can be achieved through the activation of the self-renewal and growth of cells, including fibroblasts regulating the state of connective tissue.

3.3.3. Tissue hypoxia syndrome

The depletion of the capillary network, age-related sclerosis, hemodynamic instability, and alveolar gas disorders, as well as changes in the metabolism of old cells, are the basic preconditions for age-related hypoxia.

The correction for this syndrome can be accomplished by applying oxygen therapy, hypoxic training, pressure chamber, and agents for blood flow improvement and capillary growth stimulation.

One of the treatment methods that has been tested against aging-related tissue ischemia is oxygen therapy, in particular hyperbaric oxygen therapy (37). This method can be beneficial for aging-related cardiovascular diseases (38) and can produce neuroprotective effects (39). The therapeutic effects of this type of therapy have been related to activation of antioxidant mechanisms, such as the activation of genes of the antioxidant defense system (40) as well as stem cell mobilization (41). There are also indications for effects of this therapy on skin rejuvenation (42).

3.3.4. Intoxication syndrome

The intoxication syndrome is always present to some extent in modern humans due to environmental factors (environmental pollution, pollution of food and water) and due to endogenous intoxication (the concept going back to the classical aging theory of Ilya Mechnikov that suggested aging to be due to “poisoning” of the body with its products, mainly from the large intestine). External intoxication symptoms are not always dependent on the level of the body’s “contamination,” because the toxic elements are accumulated in a depot (primarily in fatty tissue and bones) and clinical manifestations show the depletion of this depot. The “contamination” of the body is observed at all levels and for all cell types (a well-known example is deposits of lipofuscin in nerve cells).

Intoxication is manifested as neuro-vegetative symptoms, both general and specific for the type of organ and tissue (e.g. accumulation of lipofuscin in nerve cells reduces psychoemotional brain functions), and symptoms which are specific for the type of intoxicant (e.g. intoxication with lead, arsenic, nitrogen oxides, sulfur, and carbon dioxide contained in exhaust gases).

The diagnosis of intoxication is based on the clinical history (general and specific signs of intoxication) and interpretation of biochemical data, including indirect tests (examination of functions of liver, kidney, blood, immunity) and specific tests (examination of content of toxic elements in blood and/or urine), as well as on diagnostics of the states of nonspecific protective systems, in particular the antioxidant system.

Therapeutic interventions into this syndrome may include enterosorption, hemosorption, administration of specific antitoxic drugs and detoxifying agents (e.g. excretion of lipofuscin from nerve cells with the aid of centrophenoxine), stimulation of the purification organs – kidneys, liver, sweat glands – and stimulation of cell regeneration.

3.3.5. Oxidative stress syndrome

Oxidative stress is an important subject in modern medicine and gerontology (28, 32). The classic free radical theory of aging and the chronic stress theory are consolidated by this syndrome. Both closely connected phenomena (stress and changes in the antioxidant system) sooner or later cause the maladaptation syndrome, which is often present to some degree in modern humans. This syndrome is closely associated with various forms of immunodeficiency appearing in the clinic. The application of antioxidants for correction of this syndrome is a classic method of anti-aging therapy.

3.3.6. Immune deficiency syndrome

Immune deficiency is a common phenomenon in aging: thymus involution is the earliest sign of aging; the function of T-lymphocytes and blood lymphokine concentrations decrease with age; the function of T-helpers and natural killer cells usually decreases with the preservation or even activation of nonspecific T-suppressors; the function of B-cells and immunoglobulin concentration is preserved; the level of immune complexes and autoantibodies increases (autoaggression in elderly persons). However, perhaps the most important is the reduction of the recently described new T-dependent lymphocyte function for maintaining cell growth in somatic tissue, i.e. the implementation of the functions of tissue self-renewal and damage repair (43). The application of immunomodulators is one of the common means in aging therapy insofar as they impact one of the main aging mechanisms – the regulatory mechanism (20–22, 30, 43).

3.3.7. Maladaptation syndrome

Maladaptation syndrome is almost always present to some extent in modern humans due to environmental causes and mental stress and due to the intoxication syndrome (exogenous and endogenous). Permanent overloads (often psychoemotional) damage adaptive mechanisms, manifested as symptoms of the initial stages of stress or as the stage of stress decompensation. The theory of chronic stress is one of the general theories of aging, including the theory of oxidative stress. Maladaptation is manifested, among other phenomena, by general neurovegetative symptoms; specific stress symptoms (such as psychoemotional excitation alternating with lethargy, blood content changes, primarily in lymphocytes, changes of blood epinephrine, norepinephrine, DOPA, the “adaptation hormone” melatonin, reproductive hormones); changes in antioxidant system state (lipid peroxidation, enzyme activity, blood antioxidant content); changes in immunity (e.g. number and ratio of various forms of blood lymphocytes and cytokines).

Aging is manifested as a general decline in viability and a corresponding general increase in vulnerability leading to increasing incidence of many diseases (44). Over 2000 genes supposedly influence the aging process, while many of those genes are at the same time involved in age-related diseases (45). One of the most typical manifestations is the age-related increase in the incidence of cardiovascular diseases and cancers, while several selective anticancer agents can also act as geroprotective (anti-aging) agents (46). Also, typical for the elderly is the development of tissue amyloidosis (47), Parkinson’s disease (48), chronic inflammation, etc. Chronic inflammation is common for the elderly, and according to some authors it provides a link between aging and aging-related diseases (49). On the other hand, inflammation may be involved in reparative processes and stimulate tissue regeneration (50).

Psychoprophylactic and general tonic actions, including healthy lifestyle, are the primary actions against this syndrome.

3.3.8. Physical senility syndrome

Causes of physical senility in aging are mixed. These may include general decline of viability, reduced integration of organs and systems operation, reduced cardiovascular function, malnutrition (including absorption of vitamins and total reduction in calories), damage to hormonal balance (including somatotropic hormone, melatonin, testosterone, thyroxine, and other hormones), detraining, etc. Physical senility is perhaps the most important sign of aging, although it has been known since ancient times that physical strength, often exceeding the average strength of young people, can be preserved up to extreme old age. In modern society, mental capability, reproductive function, and appearance are often more important. However, in modern humans, the hypokinetic lifestyle, without special physical training, causes a progressive aging that reduces these important functions. The most common mistake is replacement of natural physical activity with chemical bio-stimulants that may be effective only together with physical training.

3.3.9. Metabolic disorder syndrome

Aging is characterized by changes in lipid metabolism, often manifested in obesity, atherosclerosis, and ischemic heart disease. The causes of disorders of lipid metabolism, in most cases, are the diet and physical detraining accompanied by mental stress. A background process is a change in metabolism involving

a sharp decrease in lipolysis in fat tissue and changes of reproductive hormone and dehydroepiandrosterone (DHEA) levels.

Disorders of *carbohydrate* metabolism are typical for age-related changes. Old age is often accompanied by a prediabetes state requiring dietary or medical correction. Intervention should consider the type of diet and habits, the state of the gastrointestinal tract, liver and pancreas, altogether serving as a basis for diagnostic procedures and correction.

Disorders of *protein* metabolism are not typical for age-related changes, but old age is often accompanied with a common dystrophy syndrome.

Changes in *water-salt* metabolism are typical for aging. They are based on changes in the levels of hormones (reproductive, adrenal, thyroid, melatonin etc.), local hydrophilia of tissues, general and local blood circulation and lymph flow, and renal function. These changes can be corrected by symptomatic drugs.

Disorders of vitamin and mineral metabolism in the form of *dis(a)vitaminosis* are quite common in old age (even though young and middle age persons are often characterized by a vitamin C deficiency). Such disorders are often associated with a decrease in caloric need, while maintaining the need for vitamins together with their decreased resorption. Presently, almost everyone suffers from a form of vitamin C deficiency (because of its increased consumption under stresses). A deficiency of the following vitamins is often observed: vitamins E, A (oxidative stress); vitamin D, whose deficiency is associated with the development of osteoporosis in women just after the age of 35–40 years old; B vitamins and niacin, which are important for prevention of cardiovascular diseases; folic acid, which has been recently considered as an important component for preventing the homocysteine forms of atherosclerosis (up to 40% of all cases of atherosclerosis by some estimates). Usually there is a deficiency of salts and microelements: calcium in osteoporosis; potassium, essential for prevention of cardiovascular disorders; zinc (immune-corrector, antioxidant); sometimes other factors. A common solution is to optimize the diet and, if necessary, provide biologically active food additives.

3.3.10. Hormonal disorder syndrome

Disorders of hormonal balance are typical in aging and are usually associated with the termination of the processes of growth and development, as well as with appearing metabolic disorders.

Dysthyroidism is frequently manifested in the elderly, revealing itself as a reduction or increase in thyroid function. Typical symptoms of this disease include psychoemotional changes, as well as changes of thyroid gland structure.

Sexual disorders are typical for elderly persons. This syndrome is known as the climax, which is often accompanied by age-related osteoporosis.

Termination of growth processes with age and reduction of growth (somatotropic) hormone (STH) level is the basis for attempts to use growth hormone therapy for biostimulation and life prolongation. STH therapy may be indicated in cases of a sharp decline in the growth hormone level and it uses various types of STH (including genetically engineered forms). This therapy is often accompanied by complications, including the growth of bones in hands and toes, and metabolic disorders. However, in many cases bioactivation effects and improvements in physical and psychoemotional status are observed.

Interest in the *epiphysis* (pineal gland) and therapy using epiphyseal extracts and melatonin periodically has increased dramatically. This is related to the important role of the epiphysis in the processes of growth, development, immunity, regulation of biorhythms and general resistance, as well as the rapid involution of the epiphysis with aging, comparable with the involution of the thymus.

3.3.11. Social isolation of elderly persons and psychological age-related changes

The termination of working activity and reduction of social contacts of elderly persons are often accompanied by pronounced changes in mental health, development of senile psychoses, depression, and emotional instability. The basis of this syndrome consists of multiple factors: neurophysiological changes, in particular the impairment of cognitive and sensory functions; cerebrovascular disorders; chronic stress; physical detraining; sleep disorders; social conditions (displacement of elderly persons from active life).

3.4. Geroprotectors as a natural part of the pharmacopeia

Doctors now use a variety of drugs whose main indications for application are disorders closely associated with the patient's age, including anti-ischemic, anti-atherosclerotic, nootropic, immuno-stimulating drugs, etc. However, these are still considered as therapeutic agents prescribed according to the diagnosis of particular diseases. The possible impact of these agents on the aging process is commonly beyond the interests of medical practitioners. However, animal trials have shown a

characteristic effect of several popular pharmacological agents, demonstrating an increase in longevity, i.e. the inhibition of aging or "geroprotective effect" (5, 11, 12, 19, 21). This effect is shown, in particular, for aspirin (51, 52), metformin (53), rapamycin (54), and some other drugs (11, 12, 19).

Increase in longevity and duration of the reproductive period in mice was observed after adding DOPA catecholamine in high doses (500 mg/kg) to the food of earlier generations. There are data indicating that using the well-known inhibitor of monoamine oxidase – deprenyl, increases the longevity of mice, rats, and dogs. Administration of growth hormone to long-living Balb/c mice (30 μg/mouse twice per week), starting from the age of 17-months, for 13 weeks, increased their longevity and reduced mortality of the animals during the whole injection period, from 67% in the control group to 7% in the test group (55). The popular antidiabetic agent metformin is considered to be a mimetic drug for calorie-restricted diet, which remains the most recognized gerontological effect for life prolongation (56–58). An increase in longevity was also shown due to the administration of α-fetoprotein in old mice (21).

4. CONCLUSION

Our hierarchical model of aging allows us to specify four levels of generalization/ detailing of the causes and mechanisms of aging: 1) the fundamental cause of aging of living and nonliving systems – the law of entropy increment in partially open systems; 2) the major general mechanisms of aging (stochastic death of non-renewed structures of the body, incomplete excretion of external and internal intoxicants, reduction of body function regulation and regulatory reduction of self-renewal); 3) the level of age-related syndromes; 4) the level of particular manifestations of aging. The higher is the level of exposure, the larger and more comprehensive can be the effect of aging inhibition.

The impacts on aging syndromes can be the most effective, because natural aging is manifested by many characteristic syndromes that are typical for modern clinical medicine. There are standardized means of their diagnosis and correction.

The syndrome approach to therapeutic interventions into the natural aging processes, with well-known medical treatments affecting these syndromes, primarily those with geroprotective properties, legitimize and inform timely prevention and correction of aging. Crucially, considering natural aging as an ordinary poly-syndrome disease makes it possible to apply timely prevention and correction for deteriorative aging using officially authorized drugs that are routinely available to practicing physicians.

The approach to natural aging as a poly-syndrome disease justifies using the most effective means for correction of this disease – the geroprotectors – in modern pharmacopoeia.

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