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Evolutionary Genetic Mechanisms of Aging

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Abstract—The review systematizes the evolutionary genetic approaches to the problem of aging, basing on the concepts of different reliabilities of separate biological processes and of balance between the reliabilities of these processes at a level that guarantees survival and reproduction in aggressive environment. The basic concepts of the Kirkwood's disposable soma theory, according to which the viability potential is determined by a compromise in the allocation of the organism's resources between reproduction and repair and maintenance of the soma are discussed. The basic concepts of the balance evolutionary genetic theory of aging are presented.

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It is commonly accepted that gerontology operates by a variety of theories of aging. This is a deceit. All the theories, with single exceptions, postulate a correlation between age and damage in any structure or process and pay no attention to the principal questions of the biology of aging, specifically (1) why biosystems are subject to aging at all, (2) why different biological species age at different rates, and (3) how and why the aging rate is associated with other species parameters?.

A theory of aging is impossible to develop not developing "a theory of life," i.e. a general theory of biological organization. Naturally, growth, development, senescence, and death each has its own specifics. The task is to reveal common sources of biological organization and disorganization. Such synthesis can be based on the theory of systems and the evolutionary doctrine in its up-to-date perusal which combines the classical (Mendelian) and molecular genetics.

Resource Distribution Problem

One of the evolutionary physiologic models of aging is represented by the Kirkwood's disposable soma theory [1]. This theory is based on the postulate of competitive relationships between resourses an organism (species) allocates for reproduction (fertility) and for preservation of soma (body), which, in the end, predetrmines the rate of aging and the life expectancy. Since the body must budget its energy resourses, it must compromise their distribution, and the best variant is fixed by evolution [2]. Natural selection establish such compromises in resource distribution, which, in given environmental conditions, provide a maximum Fischer's adaptation index (proportional to the number of descendants capable of reaching the reproductory success). If the resources to be distributed in any fixed moment of life of a biologic species are substance and energy, the evolutionary vector adds information to them (information accumulation is theoretically unlimited). Resourse distribution can be compared with cake distribution [3]: Now we can divide no more than is available on our table, but, if we are progressing, we can expect increased cake production and improved cake cutting techniques.

Quite an important issue to focus on when exploring the problem of optimization of resource distribution is "life history" [4] which means mortality level as a function of age, initiation of the reproductory period (and distribution of reproductive episodes over the life course), as well as average reproduction in different ages [5]. The theory of disposable soma envisions that species and populations which, on average, have little threats from the environment, should spend much for protection of their soma than species and populations that have to expect a short life. Therefore, the first species have a low fertility and the second have a high fertility. Thus, the guppy populations living in an aggressive media (which is the reason for their high mortality rates) are characteristically smaller in size, grow faster, start to repoduce earlier, and give more descenders over the lifespan (per fertile unit) [6]. Long life in such conditions results in fast evolution of guppies to a shorter lifespan [7].

One more demonstrative research has been performed on two populations of Virgin opossums [8, 9]. The first colony resided on the Sapelo Island (Georgia, USA) and has no enemies among terrestial predators and the other resides in the continental region and has to share territory with mauntain lions and foxes. It was found that the island population has a smaller average number of cubs in a litter than continental and survive until the second reproduction season, thus having a new reproductive chance. The average and maximum lifespans of species belonging to the island population are respectively 25 and 50% longer compared to those belonging to the continental population.

Drosophila melanogaster flies which are widely applied for research managed the expections of gerontologists and gave evidence for the existence of a compromise between reproductory activity and duration of lifespan [10–13]. In this context of interest is to analyze human data. Here, too, enough evidence is available for the concept of disposable soma. Westendorp and Kirkwood [14] have studied the genealogy of British aristocratic families (19380 males, 13667 females, and 18125 marriages) to obtain confirmative evidence for the theoretical prognosis. The situation with a mixed (in social structure) population (Krummhörn Community, Northern Germany, 1720–1870). The whole group was divided into three groups, and reverse correlation was revealed between the number of children and the duration of life in the poorest population group [15].

Impetus to the appreciation of the concept of disposable soma was undeniably given by the publication of Kirkwood and his colleagues by the University of Manchester in their research on the cellular response of rodents with different lifespans on stress caused by a calorie-deficient diet [16].

The Kirkwood's concept advanced in 1977 proved to be quite useful for gerontology. First, its furmulation is simple and psychologically acceptable in our, modern, world with its resourse shortages, and it has stimulated interest in the problem of aging. Second, the Kirkwood's concept highlights unity of biological organization laws and identity of basic reasons for aging in different species. Third, the reverse correlation between fertility and longevity was supported by abundant experimental evidence, which favored methodical improvements and raised theoretical "subproblems," which is always useful.

However, the Kirkwood's concept has seemingly exhaused its potential as the principal paradigm of research on the evolution of aging. The concept of compromise (and competitive) distribution of resources for self-reproduction and soma (providing fertility and longer life) forms a wrong opinion that both characteristics of life are equal in value, whereas in natural selection fertility is of obvious priority. This misunderstanding arose since Kirkwood pays almost no attention to the evolution history of species and is based on an "immediate picture" of the behavior of organisms belonging to one or another species in aggressive or favorable media (and their associated possible life expectancy). Actually, the "immediate picture" metaphor keeps in the dark certain genetic factors which control situations recognition and reproductive behavior. Thus, the high territorial density of rodent population prevents hinders estrus in mature female animals. Predator's bacchanal, eating victims, and reduction of the population density of the latter favor accelerated sexual maturation and reproductive compensation of losses. In his speculations about the compromise, Kirkwood took into consideration the whole lifespan of species but neglected another important characteristic, namely the duration of the pre-reproductive period. This component of "life history" acquires great importance for reproduction in an aggressive (or turned aggressive) medium: reproduction initiates earlier, which ehances chances of a population (species) to survive. Therewith, accelerated sexual maturation decreases species size and stimulates ontogenetic (metaphoric) clocks, which, naturally, shortens the overall lifespan. Thus, enhanced reproduction and shortened lifespan are both consequences of accelerated maturation, and their negative correlation coefficient reflects a formal statistical (at least partially) rather than cause–effect relationship.

Based on these (and many other) reasons, 25 years ago the author of the present paper suggested his own interpretation of the evolutionary genetic mechanisms of aging.

Evolutionary Genetic (Balance) Theory of Aging

An attempt to systematize evolutionary genetic approaches to the problem of aging, based on the concepts of different reliabilities of separate biologic processes and of a balance between these reliabilities at an “excessively sufficient” level [17].

First of all let us note that speaking about reliability of biologic systems (and subjects) one most commonly focuses on theirability to maintain their functions under usual, as well as special (near-limiting or overlimiting) conditions.

Different researchers tend to develop different theories of aging, but quite natural is to search for a view of the problem, capable of joining all opinions. However, there is no theory of aging, which can be both general and special. The reproduction cost for cockoos (for instance, populational losses associated with the parent’s behavior) are lower than for birds feeding their foundlings, but one has to neglect such details. The balance evolutionary genetic theory focuses on general regularities and does not touch upon the biology of one or another species, senescence of one or another organ, and one or another reason for death.

For practical reasons, the balance theory is formulated as a set of separate principles; their number can be increased or decreased for the sake of detalization or generalization, respectively; in this review we give a more compact version.

(1) The lifespan comprises the growth, sexual maturation, mature, and senescence periods. The evolutionary regularities formed dirung each period cannot be the same. The maximum lifespan of white Wistar rats is 3 years and that of humans is slighly above 100 years. The factor which shows how many years of human life are equivalent to one month of rat life varies, at different evolution stages, from 1.78 to 5.94 [18]. The time distribution of human ontogenesis reveals a prolonged childhood. Whether there is a clear trend in the evolutionary control over the rate of growth and sexul maturation? Shpet [19] has considered this question with a large body of evidence for a great number of biologic species. His data show that the highest growth rate among insects is characteristic of phylogenetically young beetles, hymenopterans, flies, and butterflies, whereas cockroaches, raginflies, and dayflieswhich are the most ancient species grow very slowly. The slow development and low fertility are also characteristic of ancient fishes. Spurdog shark and certain sturgeons get sexually mature by the age of 12–18 years, whereas herring family fish species, according to thei phylogenetic youngsters, glow fast. Reptiles grow not as fast as evolutionally younger birds. The most ancient reptiles, tuataras, reach sexual maturation by 20 years, thereas the reproduction age of even the biggest birds is no more than 12 months. Of interest are to compare insect-eating mammals and rodents, since representatives of these families are similar in body size an structure. Phylogenetically younger rodents grow and matury faster that insect-eating mammals. Gray rat, house mouse, and guinea pig calve at 2–4 months of age, whereas common shrew, hedgehog, or muskrat mature by 1–2 years of age. Rodents use to calve 2–5 times a year, whereas insect-eating species generally calve no more than once a year.

Thus, an evolutionary shift occurred from slowly growing species to fast growing, which was accompanied by shortening of the relative duration of the prereproductive period and, at comparable body sizes, shortening of the lifespan.

Acceleration of growth and sexual maturation at a certain stage is the main line of evoltion. However, prosperous species are able to adapt to their environmental niche through the mechanism of secondary growth retardation. Evolutionally young cicadas grow slowly, like more ancient cockroaches; the growth rate of stag beetle is the slowest on record: this insect gets sexually mature at the sixth year of life.

The most considerable growth retardation and lifespan prolongation are characteristic of the evolution of hominids; the highest rate of these shifts (+ 14 years over 100 thousand years of evolution) took place 150–200 years ago at the final stage of formation of *Homo sapiens*. Speaking about contemporary mammals, the lifespans of species occupying extreme positions differ 40–60 times. The final result of acceleration and retardation shows what tendency has prevailed with a specific species.

For 195 mammal species a correlation was found between lifespan and body weight, cephalization factor (ratio of brain size to body size), pregnancy duration, sexual maturation age, number of cubs per litter, number of litters per lifespan, self-sufficiency of cubs, collectiveness of the way of life, and certain other parameters [20]. The contribution of an individual to the next generation is determined by the number of reproduction acts (proportional to lifespan) and the number of cubs per single reproduction cycle. The aim of natural selection is to maximize each of these parameters, but simultaneous maximization of all parameters is impossible. Thus, increase of the body weight of an adult specimen, which decreases the probability of accidental death, is accompanied by increasing fetal size, which prolongs embryogenesis and decreases the number of cubs and overall fertility. The inverse correlation between lifespan duration and number of cubs per litter reflects the result of interplay of genetic, physiologic, populational, and ecosystemic mechanisms which are potentially competitive but have to "bed in" on a compromise basis. Quite illustrative is the absence of correlation between the number of descendants born over the whole life and the duration of life. This implies the equality of mammals before selection (their equal adaptation to habitat conditions in their environmental niches), irrespective of how long is the individual life. Shortlving mice are equally well adapted to their living conditions as long-living elephants. On the other hand, the primitive echidna not yet experienced the evolutionary "acceleration" and chimpanze, a representative of "retarded" primates, have the same lifespan (about 50 years). These findings allow us to formulate the *first principle* of the balance theory of aging: *Mechanisms responsible for lifespan duration and fertility can function reliably at any level compatible with species survivability*.

This definition can be considered as one of the formulations of the Kirkwood's concept.

(2) Considering a group of species within a population, the processes underlying survival and preservation of population size can be considered as an intrinsic function and reproduction as an extrinsic function. Confining the consideration to an individual specimen, we can relate to the intrinsic function no other processes that those aimed at preservation of specific features of the living being and relate to extrinsic functions all kinds of its activity, such as hunting and reproduction. Survival of an individual or a population is based on a unity of these vital functions. The problem of vitality is a problem of balance betweel intrinsic and extrinsic functions. A cell cannot exist without housekeeping, a population (species) cannot exist without reproduction, and the evolution of aging and lifespan is a problem of consistency of these functions. Abrams and Ludwig [21] in their work on the effect of stimulated reparation on the lifespan of the worm *Paranais litoralis* came to a definition of aging, which is quite consisten with our suggested terminology, namely: Aging is "a result of an optimal resourse balance between reproduction and somatic reparation." The molecular genetic approaches have, to a certain extent, obstructed the subcellular, systemic physiological realization of intrinsic functions. At the same time, the evolution "did not take trouble" to organize such an embryon action as to place the mammal testis out of the peritoneal cavity, which can decrease the body temperature by 2–3°C, thereby decreasing mutation frequency. The perspiretory gland, i.e. the nephron shifted from kidney to skin, is an important evolutionary acquirement which had impact on the overall body. The thermoregulation system in humans is quite perfect: Under the threat of overheating, the organism generates up to 16 l of sweat; so, the term "homo sweating" contains as much sence as the term "homo sapience" [22].

All energetic processes in a body involve heat release, which provides a stable body temperature. The "pace of life" puts aging and lifespan in direct correlation with functioning the metabolic machine. The ratio of body weight to body surface area in mice is such that their daily energy exchange makes 160 cal/g, whereas the respective value for humans is 24 cal/g and for elephants, as little as 13 cal/g. In their "furnace" mice burn faster than elephants. Weight and size relate to the most important characteristics of an organism, including reliability of intrisnic and extrinsic functions: A big animal "burns" slower and has a lower probability to die for extrinsic reasons and a lower fertility. The ratio (balance) between the reliability of intrinsic and extrinsic fucntions is established and maintained by natural selection.

As far back as 1917, Severtsev [23] wrote that there is a correlation between the survival of an individual until maturation, suravival of adults, and duration of life. Unreliable intrinsic functioning enhances pre-reproductive mortality and is radically eliminated by selection. However, as an individual gets older, the efficiency of selection decreases. The first reason is that the number of accomplished reproduction acts increases, which decreases the threat that any of intrinsic functions will get imperfect and decrease the reproductive balance. Second, the number of individuals managed to survive in an aggressive medium decreases with age, and the populational material in which selection can fix mutations favoring more reliable internal functions gets unsuitable. The efficiency of informational and energetic expences for stabilization of intrinsic functions is the lower, the higher age in which such expenses can pay back. Any increase of the reliability of extrinsic functions (i.e. increase of the share of individuals attaining high ages) enhances this efficiency, but any decrease of the reliability of extrinsic functions (i.e. increase of the share of individuals attaining high ages) decreases it.

Summarizing the aforesaid, we can formulate the second principle of the balance theory: *The rate of aging is directly related to the probability of accidental death in the natural conditions of species habitat*.

Note the sentence of the prominent geneticist Weisman [24]: "..selection processes which induce changes in the lifespan could be even exactly calculated, provided the necessary data, physiological forces of an organism and relations to the external world, i.e. the probability in a certain moment to experience accidental death, are available" Referring to "physiological forces" as intrinsic functions and "relation to the external world" extrinsic functions of an organism, we obtain a thesis corresponding to the second principle of the balance theory.

(3) Selection is always realized in a material forming an ecosystem. Thus, the reproductive function of baboons depends on competitive relationships between species, established in their habitat zone. These relationships is one of the regulators of the distribution of resources for "maintaining," i.e. internal functions, and for reproduction [25]. Numerous examples of such relationships have been reported in papers devoted to the Kirkwood's concept (see above). Operating at a long time span, such regularities are fixed as mutual "adaptations" of co-existing species. For example, the body size ratios of two species belonging to a single ecosystem are close to constant, even though the absolute body weights in different couples vary [26]. At the same body size, stable coexistence of the pair predator–victim is possible only if the sexual maturation of the predator occurs later [27]. Such differences provide an optimum (in terms of ecosystem reliability, balanced) distribution of species over ecological niches.

From this we obtain the third principle of the balance theory of aging: *Allied evolution of species favors dissipation of balance points between reliability of extrinsic and intrinsic functions, which manifests itself in the differentiation of species within the ecosystems by fertility, aging rate, and lifespan duration*.

Getting back to the Kirkwood's concept, it will be remembered that the use of resources in different proportions within a single species depends on the pressure of the environment; interspecies variations reflect the "ecosystem balance of intraspecies balance points."

(4) Titmouse at home lives up to 9 years, but in the wild, in nature 3/4 adult birds dye over a year. The potential longevity of European redbreast is 12 years, but in nature 2/3 adult birds die over a year. To understand the evolution of aging, it is important to know that in nature a lot of species are characterized by age-irrelated mortality, i.e. death exclusively or predominantly for extrinsic reasons. Mammals and even humans, at a certain stage of their history, do not fall out of this regularity. In one of the upper paleolithic burials (the Cave of Taforalt in Morocco), the share of skeletons of people of the age 40 and above comprises no more than 1%. Study of remains of the Americal Indians Aricara (the burial dated 1750–1785) showed that only 4% lived 50 years and more.

Thus, senescence and its associated death are absent from the life cycle of many species in the natural conditions, in certain species they occur but not very frequently. As a result, higher age periods are obscured by the "evolutionary shadow" and hardly available for the "cleaning" natural selection. The existence of the "evolutionary shadow" makes possible active consolidation of factors enhancing spontaneous age-related organism's wearing out. This concept dates back to the gerontologic ideas of Mechnikov. It is explicitly contained in the Mechnikov's intoxication hypothesis of aging: Evolution resulted in a considerable development of the large intestine in mammals, since it is quite interested in the use of this anatomic entity but neglects its ability to bring a "putrifactive harm." The "plus component" ("useful" mutations) is addressed to young and mature species (and is a selective reality), whereas the "minus component" ("harmful" mutations) is addressed to higher ages (and is a hardly realizable potential, since only rare individuals manage to reach these ages). A new wave of interest in this idea was raised by the Medawar–Williams's concept [28, 29] later perfected by Hamilton [30]. The key point in the modern interpretation of this concept is pleiotropy, a phenomenon whereby a single genetic factor (gene) affects several traits.

Let us consider the fate of mutations whose pleiotropic effect are different (favorable, neutral, and unfavorable) and separated in time (reveal themselves in young or higher ages). Mutations that give selective preference to young individuals are fixed by natural selection; both their types ("plus/minus" and "plus/zero") results in that the vitality and/or fertility in higher ages are lower than in younger ages. In this case, the evolution, based on the "plus component" actively works to form senescence. The realistic approach leads to a concept according to which the pleiotropic effects of mutations arise in overlapping rather then in isolated age groups; important is that the pleiotropic effect will develop later.

If a limited stability of vital functions is a cardinal property of the biologic "microworld," and if the conflict, uncontrollability of the nature, and violent death are a cardinal property of the biologic "macroworld," then the strategy of life consists in that to "protect" one damage by another and minimize harm. Such strategy allows resource saving, delaying the effects of "harmful" mutations until higher ages which are seldom achieved.

This process occurs not "for what" but "why": Because the pleiotropic mutation whose favorable (from viewpoint of the Darwin's species adaptation) effect occurs in young ages, while unfavorable effect reveals itself in higher ages expels the wild gene, so that its related phenotypic affect becomes a basic characteristic of the species. If both pleiotropic mutation effects, favorable and unfavorable, take place simultaneously, selection separates them by moving the "minus component" away by means of modifier genes. The driving forces of such transformations are not always equivalent, and the wild gene is not expelled completely and fixed in the gene pool at a certain frequency. A balanced genetic polymorphism thus arises (this term, consistent and quite close in essence to other positions of the population genetics, is a long-held acquirement of the population genetics which, in general, does not deal with gerontological problems).

Thus, based on the existence of pleiotropy, we can formulate the fourth principle of the balance theory: *Aging is a consequence of fixing mutations enhancing the adaptabiliy of young individuals; the antagonistic pleiotropy is one of prerequisites of this process*.

(5) The hypothesis of programmed (adaptive) death, suggested by Weismann, reflects the ideas of the organization of live systems, associated with their single- and multicellular structure. Multicellular organisms in which sexual cells are isolated from somatic and can, in principle, live or die without any harm to the population (species). However, "eternal" animals compete with young, "don't let to live children and grandchildren," and eventually cease "progress." The absence of programmed death leads to overpopulation, and, therefore, the program of organism's self-elimination is an indispensable regulator of the population size.

The argument of overpopulation due to unaging and undying specimens is built on the substitution of notions: A lack of programmed death is treated as the lack of death at all, whatever is its reason. At the same time, limited resources of nutrients, as well as diseases and predator–victim relationships sufficiently control the population size. The main "concern" of wild animals and primordial human populations was to keep track of whether generations interchange too successfully, which poses the threat of degeneration. These arguments are not denied by atteptms to reformulate the Weismann's hypothesis in the terms of molecular biology [31] or to postulate concrete mechanisms of the suggested self-elimination [32, 33].

Thus, the postulate of programmed (adaptive) death should be considered not as an imminence but as a possibility of such death. Under certain conditions, the seld-destruction program is quite possible to develop. The case in point is that the enhancement of survivability in young ages at the expence of its reduction in older ages is only one of the consequences of the existence of the "evolutionary shadow." No less effective in terms of species adaptability can be the enhancement of fertility in young ages at the expence of its resuction in older ages. Let us imagine a biologic species whose population characterisctically sharply decreases due to a high probability of accidental deaths. Therewith, reproduction and parental behavior enhance the probability of death. In such conditions, the probability to survive until the second reproduction cycle is quite low. The traits affected by natural selection will become the following: (1) increase of the reproductive potential due to a still stronger switching vital resources to reproduction; (2) working out means for providing survival until the second, third, and further reproduction cycles. Eventually, one of the two strategies will be realized: single or multiple reproduction.

The force of natural selection is determined by the difference between the maximum (expected) and realized contribution into the next generation. This value is high in the prereproductory period and tends to zero with decreasing number of survived individuals and increasing number of completed reproduction acts. That means that the efficiency of natural selection in repeatedly reproducing species gradually declines with age, while in singly reproducing species it falls sharply. In the first case, an individual, having fulfilled one reproduction act, has a nonzero probability to survive until the next one (and nonzero reproductive value), whereas in the second, the first reproduction "depreciates" the an individual completely. In the first case, every reproduction act is one in series and cannot trigger the self-destruction program, and in the second, the reproduction is a unique event which can serve as such a trigger. It is not surprising that the advocates of the programmed death hypothesis refer to, as the main argument, biological features of singly reproducing species (monocarpic plants, certain insects, or fish dying immediately after spawning). However, the possible benefit from the elimination of the parent's generation is not determined exclusively by single reproduction and depends on other specific features of the species. Had chum salmon flocks exhausted by migration stayed in the spawning site and competed with the young generation for food, therewith having almost no chance to overcome again the river–ocean–river route, programmed elimination of adult specimens would have been favorable for the species. Adaptive benefits can be associated not only in elimination, but also in preservation of postreproductive individuals. In due time, Mechnikov discussed this possibility on an example of a solitary bee whose female does not die after the first and single egg laying but continues to live and looks after offspring. Obviously, the life cycle of chum salmon exerted a too strong impact on gerontology. Evidence showing that the conjugation of reproduction and death in a common "generation change" program relates to a functional rather than strategic level of the evolutionary control of life span comes from the biology of Atlantic salmon [34] with its flexible (changeable) ontogenesis. Female and male salmons can reach sexual maturation both at the age of 1 year and at the age of 3–4 years, and, therewith, specimens of both types are singly reproducing. The Australian marsupial mouse *Antechinus* illustrates the tactics of single reproduction, which is unusual in terrestial animals: Its postreproductive aging lasts a few weeks, which makes this animal a unique object for gerontologic investigations [35]. In any case, the style of reproduction and parental behavior correlate with lifespan duration (and "style of dying") according to the first principle.

Thus, the fifth and sixth principles of the balance theory can be formulated as follows: *In repeatedly reproducing species, aging is associated with fixing pleiotropic effects and gives no evidence in favor of an adaptive (programmed) death; single reproduction allows formation of a genetic self-destruction program associated with species specialization and not reflecting a general evolution strategy.*

(6) There is abundanary experimental evidence showing that age-related changes in different anatomical and physiological body systems occur at different rates (the phenomenon of aging heterochronicity). In humans, lenticular accomodation starts to decline as early as the age of 8–10 and falls almost completely by the age of 50, whereas lenticular opacity (cataracta) only starts to develop by the age of 50 and is progressing until the end of life. The reason for these differences consists in that these disorders have a different impact on vitality. Lenticular accomodation did not provoke incapacitation of primitive men, but lenticular opacity might prove to be even more tragic for them than for our contemporaries. The decline of accomodation, developing until sexual maturation, is impossible to associate with programmed self-destruction, immune clocks, or "death center" function: In the framework of the "near-Weismann" concepts, most gerontologists ignore glasses as if they are nonexistent

The different significance of stable functioning of different body systems implies that natural selection controls their reliability with different tolerances. No less important is that different body systems require different energy and information expences for maintaining their stable functioning. When it comes to a vitally important function, these expenses are justified and, therefore, inevitable; less important functions are supplied according to their rank based on the cost/benefit balance.

In this connection of particular importance is the fact that in a multicellular organism there is a different reliability of control of sex and differentiated cells. The safety of the genetic information passed from generation to generation is provided, in particular, by that division of sex cells is accompanies by DNA reparation (rejuvenescence): Homologous chromosomes serve as templates for each other, which allows to check up and repair damaged nucleotide sequences. Apparently, in most somatic cells this scheme does not function with sufficient reliability, but the differences between somatic and sex cells are only quantitative in nature. The problem of immortality of sex cells is a semantic rather than a biological problem [36]. One can give different definitions for death (loss of individuality), and, depending on this, sex cells can look as either mortal or immortal. The immortality of sex cells means nothing but that their mutation burden stays at a certain level. The Weissman's thesis about the immortality of germ plasm was formulated in the period of active fight with the concept of inheritance of acquired traits; the concept of "impairment" of somatic cells and "elitism" of sex cells, developed on this basis, has played its role in biology, but nowdays it belongs to history.

In the long run, the problem converges to the interrelationships between geno- an phenotype, rather than between sex and somatic cells. A mutant sex cell that gives rise to an unvital organism is genetically dead, even though a spermatozoon bearing a wrong information is quite vital by criteria applied to define normal spermatozoa. The late manifestation of the deleterious mutation is associated with that the accumulation of somatic mutations in a somatic cell has denude the latter of the ability to maintain homeostasis. On this background, the defective genetic information originating from a mutation in a sex cell of the parent's organism gets chance to "penetrate" into the phenotype. Mutations in somatic cells occur more frequently, whereas mutations in sex cells are more rigorously controlled and rejected; however, this, too, does not qualitatively differentiate one process from another.

The aforesaid allows us to formulate the seventh principle of the balance theory: *Reliability (aging rate) of different boy systems is balanced at a level directly related to their contribution in maintaining vitality and reproductive potential and inversely related to the energy and information expences for providing stable functioning*.

Discussion of the Problem of Programmed Aging

In 1993 Pisaruk [37] made use of computer simulation of the simplest ecosystem "plants–vegetarians–predators" to study the effect of lifespan on interspecies competition and sirvivability and also on the relationship between lifespan of a species and its reproductive ability. Five simulation experiments gave evidence, in the author's opinion, for the basic postulates of the balance theory of aging for different species. In their paper published in same year, Partridge and Barton [38] provided evidence for the concept that the evolution of aging is a consequence of a strategy when survival and reproduction in late ages are sacrificed to early reproduction and survival. Dasgupta [39] and Stauffer [40] performed a Monte Carlo simulation of the mutation process and obtained evidence showing that mutations provoking the "minus effect" in late ages are accumulated in the course of evolution. If the Kirkwood's concept sets sirvival against reproduction within "today," then the concept of a system of reliable balances interrelate these two functions in the "yesterday, today, tomorrow" dynamics. Both in terms of reproduction and in terms of survival, the "tomorrow" process is worse than "yesterday," and this is just what means aging as a result of evolutionary and genetic interventions in *a species*' biology. As judged, in particular, from the fundamental publication "Gerontology *in silico*: Establishment of a New Discipline" (2007), such ideas are percieved with understanding and form a basis for new speculation.

The criticism of evolutionary genetic concepts is built primarily on three agruments. (1) The concept of disposable soma is supported by a great body of evidence; however, experiments in animals with a low-calorie diet either provided no evidence for the alternative long life vs. active reproduction (male animals) or gave results much dependent on experimental conditions. (2) Up-to-date methodical potential allowed identification of "aging genes." Some of them were found in the genomes of phylogenetically remote eucariots (yeast, worms, flies, and mice), and, consequently, these genes are not associated with random mutations whose "minus effects" manifest themselves in old ages. (3) Some of "aging genes" enhance the reproductivity of young individuals (which fits in the scheme of antagonistic pleoitropy), but some of these genes could not be correlated with the "plus effects."

Thus, the evolutionary genetic theory of aging is not ruled out, but it fails to give an exhaustive explanation of the whole phenomenon. An intraorganismal mechnism has to be found, which is capable of destabilizing (or eliminating) a hypothetical individual with an "ideal" genotype, i.e. to eliminate an individual that has not accumulated "unnecessary" destructive traits. A good candidate for such an imaginary experiment is a toothless horse (which is doomed to death even in the absence of predators). However, for whale or Tasmanian wolf, lemur or humans we have to search for other models and, Comparative characteristic of basic biosystemic processes [44]

Phenomenology	Organizational essence	Name
Preservation of self-identity under intrinsic and extrinsic perturbations	Invariance of state	Homeostasis
Equifinal attainment of a state which provides self-reproduction	Stabilized flux	Homeoresis
Loss of reproductive function, longevity decline, death	System destabilization	Homeoclasis

moreover, different for different species. The position expressed in this context increased the number of advocates (explicit or implicit) of the Weissman's concept of species-specific adaptive (programmed) self-destruction [41–43]. As known, Weissman by himself gave up this idea and honestly admitted that he is able to imagine possible benefits of self-destruction but does not see mechanisms of their fixing in reality (when it comes to repeatedly reproducing species). Now it is time to discuss why self-destruction actually takes place.

Obvious facts and phenomena are not infrequently the last to be analyzed. Thus, in Weissmann's times, in attempts to prove inheritance of allogenetic traits people cutted off tails in infant rats and expected tail-less animals to be born in successive generation. However, no tail-less rats appeared. Why they cutted off tails in infant rats? No prepuceless boys were born in Jewish families, even though posthetomy is practiced since time immemorial. And all girls come into world virgin, even though the defloration of their mothers, grandmothers, great grandmothers, etc. is a prerequisite of pregnancy.

Thus, the complexity of living systems (successively increasing from the cellular level to the level of a physiologic system and an integral organism) is both a guarantee of survival (reproduction) and a prerequisite of self-destruction: Homeostasis gives way to homeoclasis, i.e. a destabilization of the biological system (see table) [44]. Provocing (poly)systemic response reactions, physiological perturbations are quenched by separate acts of homeostasis. A deficite of homeostatic potencies is a reasonable basis for aging models [45–48]. However, the homeostatic deficit is provoked by systemic generalization of local physiological perturbations, as a result of which the organism is destroyed as systemically (and inevitably) as it avoided destruction before.

This is the principal "minus" effect of the integrative complexity of biosystems; the "plus" effect is their very existence. On this funamental background, each species (or each individual) acquires its own life functions. The simplest analogy is the economic crisis in global world, triggered by an "overheated" economy in one country and propagated to other countries. The world will not die only because it is simpler than biosystem

To our knowledge, the only mathematical model of aging and death, based on global systemic concepts, was published by Voitenko and Pisaruk [49]. Since the reliability of systems psychologically targeted to simple machines and mechanisms, depends on wear, we not always recognize a "wrong" organizational essence of biosystems, based on irreversible reactions, nonequilibrium systems, and nonlinear interactions [50].

Homeoclasis as one the basic biosystemic concepts, casts hopes on indefinitely great successes in the fight against aging, but forces to accept death as inevitable. However, the same conclusion follows from the molecular basics of life [51].

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