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REVIEW

# Aging Is a Simple Deprivation Syndrome Driven by a Quasi-programmed Preventable and Reversible Drift of Control System Set Points Due to Inappropriate Organism–Environment Interaction

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**Abstract**—There are two well-known but opposing concepts of the reason for aging. The first supposes that *senescence is programmed* similarly to the genetic program of development from a zygote up to a mature organism. Genetically determined senile wasting is thought to be associated with the necessity to renovate the population to ensure its adaptation and survival. According to the concept of the *stochastic aging* (due to accumulation of occasional error and damage), there is no built-in program of aging. There is only a program of development up to the state of maturity, and then the organism should be able to maintain itself limitlessly. However, although the efficiency of repair systems is assumed to be rather high, it is less than 100%. Just this has to result in aging because of accumulation of various errors. We have continued and developed another approach that considers both programmed and stochastic concepts to be incorrect. Aging is a simple deprivation syndrome driven by preventable and even reversible drifts of control systems set points because of an inappropriate "organism–environment" interaction.

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According to data of the World Health Organization, the rate of human aging depends 10% on the living standard, 20% on the genotype, 20% on the environment, and 50% on way of living. Thus, ecological factors and activities induced by them significantly influencing the way of living are the major contributors to the genetic potential of longevity. It is known that only less than 5% of Alzheimer's disease cases and about 5% of some malignant tumors are associated with particular alleles, whereas the remaining 95% are associated with negative influences of the environment and the way of living. Therefore, even the possible elimination of deleterious influence of the above-mentioned alleles will give only an insignificant effect. In progerias the effect will be still less because of their very low frequency. Therefore, it is rather reasonable to consider environmental influences and reactions of organisms to them as a promising modifier of longevity potential. Also, although it is difficult to assess the aforementioned longevity potential, nevertheless the potential immortality of cell populations composing a higher organism is compatible with the limitlessness of this potential and the finiteness in time of its bearer due to randomness.

Analysis of regularities of survival kinetics of cohorts and of statistics of their mortality depending on environmental conditions and life activity regimens induced by them [1] allows us to understand "why the organism consisting of potentially immortal cells is aging" [1, 2]. Moreover, it is quite reasonably to think that it is aging not according to a "program" and not because of the postulated limitedness of the repairing systems, but because of functioning in non-optimal regimens of life activity dictated by inadequate life conditions [3]. If this is so, the strategy of intensification and extensification of searches for "inner mechanisms of senescence" discussed in the overwhelming majority of the works may be fruitless. However, upon generalization of the bulk of available data using approaches of systems biology, this strategy has finally to lead to the same conclusions: it is useless to search for the initial cause of senescence inside the organism.

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## BIOLOGICAL REASONS

A decrease in activities of the organism's systems with age is one of the major traits of senescence. Many researchers believe that senescence is associated with changes in gene expression, e.g. because of age-related shortening of telomeres (the programmed aging variant postulated and then rejected by A. M. Olovnikov [4, 5]) or with accumulation of free-radical damage to macromolecular complexes, especially of mitochondrial ones (the stochastic aging variant supposed by D. Harman). However, both the use of the powerful mitochondria-tropic antioxidant SkQ1 [6] and an increase in telomerase expression [7] failed to result in a significant increase in the maximal life span [6, 7], although in the case of SkQ1 a two-fold increase in the median life span was observed for some species. Moreover, probable noncanonical functions of the chromosome telomeric regions are discussed, including those located inside the chromosome in maintaining its integrity, shape, etc. [8]. It is known that mouse cells in culture under physiological concentrations of $O_2$ constitutively express telomerase and are not subordinated to the Hayflick limit [9]. Nevertheless, mice advance in age. On the other hand, the experimentally observed reversibility of many manifestations of senescence allows us to regard skeptically the postulate about the inevitability of aging.

Thus, it is known that the replicative activity of cells, even of stem cells, decreases with age. However, maintaining or reconstructing adequate conditions prolonged this activity or recovered it up to the level of youth under both *in vitro* [10, 11] and *in vivo* [12-16] conditions.

In addition to so-called replicative aging, chronological aging of cells in stationary culture is also known [17, 18]. Experiments of A. N. Khokhlov generalized in his monograph [17] were performed on a compact monolayer in culture with absence or minimal proliferative activity because of contact inhibition. Within a short time (one-two weeks), the cells began to manifest traits of senescence similar to those in aged organisms [17, 18]. During this time the cultural medium became exhausted, which could model a decrease in the levels of growth factors and nutrients on the aging of organisms. However, if nutritional medium enriched with fetal calf serum was renewed two times a week, no irreversible traits of proliferative aging were observed in the cells after their being in the stationary state for a year [19, 20].

Similar results about the reversibility of traits of senescence were obtained for mitochondria *in vitro* [21-23] and *in vivo* [24-26]. Bruce Ames generalized the results of his numerous experiments on recovery of mitochondrial and general physiological activities of old rats and presented, in particular, data on improvement of these activities virtually up to the level of youth using a mixture of acetyl carnitine and lipoic acid [24], whereas D. Sinclair et al. reported similar results on increasing the level of NAD(+) [25, 26].

These data and others have revealed a high potential of the organism to withstand aging and suggest possibilities to control this potential.

## SIGNALING ROLE OF THE ENVIRONMENT IN MANAGING SENESCENCE AND REGULARITIES OF MORTALITY STATISTICS

It is well known that living organisms are self-adjusting systems sensitively reacting to environmental conditions and capable of changing the activity level and actions depending on arising situations. And even if the organism's components are potentially able for self-maintenance for an unlimitedly long time, they can realize this potential only under conditions of an adequate environment [3]. Just the environment causes the responding regimens of life activity optimal for the organism's functioning with a complete recovery cycle. Deviations from limits of the ecological niche optimal for a given species inevitably lead to an incomplete recovery cycle moving the organism toward aging. This regularity is known also for such non-aging organisms as hydras. Their aging can be obtained by changing the environment.

In this connection, it is interesting that such statistical laws as the Gompertz law and Strehler-Milwan's correlation are compatible with the concept of senescence because of the non-optimal influence of the environment and the life way induced by it [1, 3, 8].

The genome can directly influence the duration of life and the character of aging both through the realization of the genetic program (if it exists) and the genetically-conditioned "designed" reliability of the organism's construction, which worsens during life's activity because of incomplete recovery of this reliability after constant stochastic events and of these causes combined. Note that normally the influence of the genome is significant *only* for interspecies differences in lifespans (several orders). Moreover, the contribution of heredity to the variability of intraspecific life duration under comparable conditions is *only* about 20%. However, many data have accumulated showing that changes in the environment and/or readjustment of systems responsible for the management of the organism can significantly increase longevity potential influencing the deceleration of aging and even its termination and reversal. This reduces the complex process of aging of representatives of the majority of species with multiple reproduction cycles to a simple deprivation syndrome driven by the drift of set points of the control systems because of inadequate "organism–environment" interaction [1, 3, 8]. A minority of species with repeated reproduction, the so-called "negative aging" species [27, 28], can be characterized by an elevation syndrome. Due to some causes, the drift of set points of the organism's control systems occurs in the opposite direction and does

not decrease adaptive and other potentialities of representatives of such species after maturation, but rather it continues to increase these potentialities for a long time.

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