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Review

Old age as a privilege of the "selfish ones"

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ABSTRACT: In the past couple of centuries, scientists proposed great number of aging theories but neither of them appears to be fully satisfactory. In the statistical sense, we are dealing with an even greater challenge because large array of factors affects the aging process. Although at this point the most of these factors are well known, it is the very fact of their innumerability that complicates approaches to the issue at hand. Both in life and in medicine, the cause behind an effect can rarely be unequivocally determined. Thus, it appears that through out human history longevity has been primarily affected by eradication of diseases, especially by eradication of infectious diseases and introduction of the vaccines. For that reason, maybe we should not be referring to this issue as the «fountain of youth» but rather as the «vaccine of youth». The postulate that genetic instability is the precipitating factor both of aging and cancer has withstood many tests and keeps on being reaffirmed. For this reason, it is legitimate to pose a question of whether long-lived individuals may be those with «selfish» genes and more stable genetic material. They certainly cannot avoid aging, but aging in such individuals could be delayed due to steady character of their genome, which is less susceptible to mutations. On the population level, they constitute minority because stable genome would represent an obstacle to successful evolution of the species. If this was not the case, we might not be writing all these texts today.

Key words: aging; genetic instability; elderly; longevity; intra-individual variability

We are certain that we do not need to start by saying that "aging is not an illness." However, we are not so certain that we do not need to add, "Aging is a problem for the human kind only." Overall, the cure for aging or reaching immortality is simply not realistic.

Changes during aging are manifested at the level of cells, tissues and of the body as a whole. Throughout human history, finding the cause of aging was a major challenge. From the aspect of its universality, best way to discuss the aging process should be based on exploring causal relationships between various factors and systems that are present in all living organisms subject to the aging. There is no doubt that evolution makes exceptions, as judged by the factors and cellular mechanisms found in certain species only (special neuro-humoral factors and organ systems, etc...).

Hayflick argues that "the forces that produce age changes are entirely different from those that drive longevity determination" [1]. This implies that "why we age?" is entirely different question from the "how we age?" Investigation of this area is rendered difficult by the fact viewed on a molecular level; there

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is hardly any single manifestation of aging which does not occur at any other period of life.

Biological and evolutionary significance of aging ("why do we age?") mainly tries to answer the question in what way is the evolution of species (and its survival) benefited from the aging process. The second argument ("how do we age?") relates to mechanisms involved in this process, and manifestations that can be attributed to occurrence of age related changes. This latter issue constitutes what is often referred to as biological aging theories. The importance of the statement given above lies in the fact that it reconciles various overlapping issues implied by the theories of aging, usually coming out as nature vs. nurture debate.

In the past couple of centuries, scientists proposed great number of aging theories but neither of them appears to be fully satisfactory. In the statistical sense, we are dealing with an even greater challenge because a large array of factors affects the aging process. Although at this point most of these factors are well known to us, it is the very fact of their innumerability that complicates approaches to the issue at hand. Factors that are known to affect aging in the positive sense involve starvation, Mediterranean diet, certain life styles, regular physical activity, and so on. In the negative sense they comprise mainly "unhealthy" life styles, including absence of the positive factors listed above.

Dynamics of the aging process

If we attempt to sum up everything we know today about factors that can affect the aging process, as much as such simplifications can be dangerous, we would probably come up with only the following two statements:

1. *Starvation*: most of the authors today agree that starvation can positively affect longevity, but it is species dependent [2].
2. *Delayed reproduction*: this can also prolong the life span, in a similar species dependent pattern. Delayed reproduction shows these effects only in those species (or mostly in those species) that reproduce following a season with ample amounts of food (i.e. those species whose reproduction is positively correlated with the environmental causes that can increase survival rates for the young) [3]. In addition, some studies seem to indicate that high-predation risk in one group of the guppies might also prolong their reproduction and general life span [6].

However, these two general remarks cannot be carried over in any simple way into existing numerous aging theories. «If starvation leads to delayed reproduction, and if the expenditure of energy relative to the sustainability of the species is not too large, then depending on the species the life span will be increased» [7]. Clearly, such a statement with numerous conditional clauses cannot be regarded as particularly informative. In addition, it seems that even within a single species, the spectrum of these conditional circumstances may be too broad, and therefore the effects of starvation and delayed reproduction are not going to be the same.

Genetic make up of each individual further affects these complex interactions. The mechanisms involved which operate between starvation, delayed reproduction and longevity are, according to genetic studies, numerous and variable [4]. Just as we have a whole plethora of theories, there are also a great number of implicated mechanisms at work.

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The postulate that genetic instability is the precipitating factor for both aging, and cancer has withstood many tests and keeps on being reaffirmed [5]. For this reason, it is legitimate to pose a question of whether long-lived individuals may be those with «selfish» genes and more stable genetic material. They certainly cannot avoid aging, but aging in such individuals could be delayed due to steady character of their genome, which is less susceptible to mutations. On the population level, they constitute minority because stable genome would represent an obstacle to successful evolution of the species. If this was not the case, we might not be writing all these texts today.

Some authors are trying to explain the unknowns in understanding of these issues by hypothesizing that there are two subgroups existing in the general population. This is not in contradiction with other basic postulates outlined in this paper. The hypothesis could explain numerous cases that cannot be otherwise accounted for or fitted into basic

observations about caloric restrictions and delayed reproduction [8].

Is old age a privilege of the selfish genes?

Genetic instability was implicated as the main reason leading to various manifestations of senescence. Some authors reported relatively low percentage of chromosomal aberrations in the "oldest old" (aged 80 years or above), as compared to the levels found in younger controls [9]. Thus, the relatively low level of chromosomal aberrations in the "oldest old" is likely to be a consequence of their genetic stability conducive to attainment of advanced old age. In addition, this may offer an explanation to the finding that successfully aged population segments are genetically stable as their middle-aged counterparts [10].

Thus, we hypothesize that two subgroups exist in the general population: the first with "normal" genetic make-up and aging pattern, and the other one with postponed aging – "the privileged group" [11]. Identification of those two groups would allow us to seek more realistic goals in aging studies, as well as more efficient treatment for certain age-related diseases [12]. This hypothesis does not contradict the aging theories, or the fact that there is a large inter-individual variability among the elderly.

The genetic trait of having more stable genome would play a more significant role than the genetic variability itself, as intra-individual variability is present in all age segments, not only in the elderly . Recent research in humans reported a number of genes with potential role in longevity and in age-related diseases. Thus, these findings have a potential of developing tools, which would enable us to identify the factors involved, and possibly correct such genetic instability with "vaccine of youth". This would potentially make human race living up to 30 years longer with an excellent quality of life.

Two presently known factors of prolonging life (namely starvation and delayed reproduction) are applicable to the majority of general population. To "selfish ones", however, as much as it might seem awkward, this is not the case, as they can be considered as intrinsically privileged. The first group, i.e. the majority, is principally responsible for the evolution of human species. In other words, there would not have been successful evolution without them. The privileged group, on the other hand, is genetically more stable, and evolution would have taken much longer time to operate. If "selfish ones" were the majority, human race would not have gone down the same evolutionary path [13].

Disscusion

Biochemical aspects of aging, as universal as they are, remain poorly understood. A number of diseases are associated with aging either as a cause or as a consequence of the aging process. Many physicians consider aging unavoidable and essentially unalterable process. Most of the opposite evidence comes from non-human material. This has led to nearly 300 different theories of aging explaining its biochemical, molecular, neurological and functional aspects. Among them, there is a high degree of mutual complementarities [14].

Aging Theories – The Role of Genetics

Biological theories of aging are divided in two main groups: programmed aging theory, and theory of cellular aging. Programmed theories explain the phenomenon of aging as a primary disorder instigated by inner coordination and control mechanisms. Reduced secretion of sex hormones in old age, particularly estrogen in women after menopause creates conditions for osteoporosis developing.

Second group of theories tends to explain the aging process at the cellular and molecular levels [14]. Basic postulate of these theories is that primary disorder occurs within the cellular DNA. Thus, variable expression of different genes can cause changes in cellular metabolism and functions. This leads to activation of certain enzymes that are involved in important cell mechanisms. [15]. Biology of aging is based on a time-specific gene expression sequence, taking place as a result of changes in DNA activity, and caused by the action of either primary or secondary influences, both endogenous and exogenous ones.

Among many theories developed over past few years, free radicals gained particular importance [16]. DNA is constantly affected by the action of various environmental factors. It is estimated that approximately 74,000 molecules can damage DNA in mammalian cells every day due to oxidative action, hydrolysis, alkylation, deamination, radiation or toxic chemicals. In general, we can say that gene expression is dependent on the presence or absence of DNA methylation gene promotor region, its structural and

regulatory genes. Methylation of genes is considered part of the regulatory mechanism, which drives the aging process. All human cells in tissue culture lose their methylated gene fragments with an increased number of cell divisions. DNA methylation rate in the liver of the young mice is higher than in the liver of old mice [17, 18]. This process will reduce the amount of methylated DNA in the lymphocytes, liver, heart, brain, and the spleen of older people.

The fact that the cytosine hipomethylation increases in old age opens new perspectives to the possible changes that accompany cell aging. At current state of knowledge, it can be assumed that reduced methylation of DNA in old ages leads to increased activity of genes responsible for the aging process. It also means that increased methylation of DNA in the cells protects young organisms from the appearance of degenerative processes that are integral part of aging. A gene or a set of genes that are expressed in a wide range of tissues, and which exhibit an age-dependent, easily quantifiable increase in their expression, represent possible molecular biomarkers of aging.

Studies have revealed that the chromosome telomere shortens on each cell division [19]. This process begins as early in the embryonic development. The telomeres at birth are thus twice shorter than those of the eggs are prior to conception. It is thought that chromosomal telomere lose an average eight sub-sequences of TTAGGG on each cell division. Interestingly, it has been demonstrated that tumor cells show no telomere shortening. This may be the very reason for their longevity.

Increased oxidation of macromolecules is another good biochemical marker of advancing age changes [19]. The Sun UV radiation breaks down water molecules and creates new oxygen radicals, which can damage the cell DNA. These changes are common in the skin and in the eyes. In addition to degenerative changes of the skin, the eye cataract and retinopathy are thus frequently found amongst people aged 65 years and older. It should be pointed out that in the cell culture of people with multiple accelerated aging syndromes, increased oxidative proteins damage exists [20].

For all of the above reasons there is little dispute on the importance of genetic component in aging. Prior to work of Puca et al., familial aggregation of exceptional longevity was mainly investigated in candidate gene(s) polymorphism studies. This group however carried out a genome-wide scan for longevity predisposing loci – "linkage analysis", which revealed how likely it was that a region of the genome is associated with a particular trait. Using 308 individuals belonging to 136 sib ships demonstrating exceptional longevity (where one sibling was at least 98 years old and had a brother aged at least 91, or a sister aged at least 95), their results pinpointed to significant linkage at the chromosome 4. This finding is strongly suggestive that on this chromosome exists a gene or genes that exert a substantial influence on longevity [21].

Not all cells of the human body are, however, subject to aging process. Lepperdinger thus reviews some of the current issues on the cell senescence. Main focus relates to the question of whether is immortality exclusively inherent to the germ line. While all somatic cells are subject to aging, germ line links generations, and pluripotent germ cells are considered potentially immortal. Biological significance of this mechanism would be that somatic cell proliferation comes at the expense of acquiring and propagating mutations. For this reason, cancer affects complex organisms, while "somatic maintenance evolved at the cost of certain tumor suppressor mechanisms" – same as the ones involved in aging process. Embryonic stem cells (ES cells), derived from the inner cell mass of a blastocyst, are also bearing 'the immortal germ line' properties. In order to have their pluripotent character maintained the somatic program has to be properly repressed in these cells. This raises the question whether pluripotency itself endows immortality. While answer is not a straightforward one, nuclear cloning experiments unraveled some mechanisms, which cause the epigenetic conversion of the somatic program into the embryonic fate - pluripotent stem cells (iPSC).

Finally, what remains to be answered is "what resets 'age' in germ line?" Every time a stem cell copies its chromosomes, it puts itself at risk of generating mutations in the new chromosomes. The immortal strand hypothesis [Cairns, 1975 cited in 22] implies that "Placing chromosomes with recently synthesized DNA strands into the daughter cell and keeping those with the original strand as an error-free ('immortal' template) would minimize the risk of accumulating harmful genetic changes". Experimental evidence for non-random segregation of chromosomes that would reserve the mutation-free stability of the genome has been confirmed in several stem cell types, indeed [22]. Obviously, the above discussion has

profound effects on understanding the mechanisms of aging process in general.

Successfully aged population

The difficulties of establishing informative biomarkers of aging originate from wide scale of biological variation between individuals, which makes generalizations difficult. Other factors include overlapping between aging and disease processes, uncertainty regarding benign versus pathological age-related changes, identification of cut-off point at which a process begins to damage the organism, and if so, when does it occur, as well as many others. Leading biologists and clinicians thus convene to discuss and establish the biomarkers of aging.

Participants of a population based study of adults in Beaver Dam, Wisconsin, were classified by the current age or age at death of their parents as reported in 1988–2000 (baseline examination). Selected biomarkers of aging included hand grip strength, chair stand, gait time, peak expiratory flow rate, visual acuity, and contrast sensitivity, which were again measured 10 and 15 years later. Gait time, peak expiratory flow rate, visual acuity, and contrast sensitivity were found to have been significantly better in participants whose parents lived longer. In addition, lower scores of an index, which included poor measures of all the biomarkers combined were highly associated with increased parental age. In other words, greater attained parental age was indeed found to be associated with better functional status of adult children as reflected by the levels of aging biomarkers, and suggests that persons whose parents were long-lived may enjoy not only a longer life but also the one relatively spared from frailties associated with older age [23].

Despite the finding that substantial proportion of cardiovascular diseases remains undiagnosed until death in very old people, functional activity patterns do not seem to follow the same trajectory. This could be partly explained by the fact that diagnosis itself does not immediately express the extent of its severity. At the same time, it also reaffirms great variability of aging patterns.

The Danish 1905 cohort data were used to assess the loss of physical and cognitive independence at the ages 92 and 100 years. Multiple functional outcomes studied included independence (defined as being able to perform basic activities of daily living without assistance from other persons and having a Mini Mental State Examination (MMSE) score of 23 or higher. Only a modest decline in the overall proportion of independent individuals between the first and final assessment was recorded: 39%, 36%, 32%, and 33%, [95% confidence interval (CI), 1–14%]. When only those who took part in all four examinations were considered separately (that is those who survived until 2005), the prevalence of independence amongst them was reduced by more than double: from 70% on initial examination in 1998 to 33% in 2005 follow-up (difference 37%; 95% CI, 28–46%). The discrepancy between the population trajectory and individual trajectory is explained by increased mortality among dependent individuals, suggesting that implications of increased survival to the advanced age may be different at the population level from an individual [27].

Similarly, siblings of centenarians experience mortality advantage over their non-centenarian counterparts. Analysis of 444 pedigrees of centenarian families, which included 2,092 of their siblings, was used to compare their survival compared to the U.S. 1900 birth cohort. The centenarians' siblings were found to experience mortality advantage throughout their lives relative to U.S. 1900 cohort survival data from the U.S. Social Security Administration. The male siblings were at least 17 times more likely to survive up to the age of 100 years, while the female siblings were at least 8 times more likely. In addition, female siblings at all ages experienced death rates roughly one-half of the national level. The same was true of the male siblings at most ages, although their advantage was somewhat diminished during adolescence and young adulthood. The survival advantage becomes most pronounced at older ages, when their relative survival probability increases markedly, probably reflecting cumulative effect of their mortality advantage throughout life [28].

Finally, some pharmaceutical drugs and some life style behaviors also appear to have beneficial effect on two or more major manifestations of aging. Thus, statins are useful in treating heart diseases and they appear to have an anti-cancer effect [24]. Aspirin appears to alleviate several symptoms of aging [25]. As previously discussed, caloric restriction is generally conducive to living longer. Exercise is reported to delay incidence of many symptoms of aging. Some studies even suggest that it is more important to life span than obesity [4]. Resveratrol, a constituent of red wine and grape skins has been also found to extend life span in animal studies and may

have favorable effect on course and development of heart diseases, cancer, and diabetes [26].

The aging process

Despite the importance of the genetic component, there is no single gene responsible for aging. There exist, however, a large array of genes that have more then one function. In other words, in addition to their known function, many genes can act as modulators of the aging process, for the purposes of survival of the species. Modification of gene expression and their effects seem to represent a promising prospective intervention. Currently, there are no more but a few successful ways.

Another relevant point concerns the genetic instability of humans that allows us basic evolutionary advantage as compared to other species [10]. Primates have a similar genetic makeup, and yet the reparation capacity of our genome is twice as good. Would it be possible to return it to a more stable genetic structure and make our species less susceptible to aging and to age-related diseases? All of the current advantages of scientific progress, e.g. vaccines, played an important role in preventing illness and prolonging life. What remains to be answered is how sure we are that there is no "privileged" group within our species, which is already genetically more stable, and thus less susceptible to complex set of changes that manifests as an aging process? We should ask ourselves if the dolphins are truly inferior to us, or whether they have already known this and chose a simpler and better life. Nature seems to be cyclical in its essence. It acts as a sum of births, existences and deaths. Human civilization seems to follow the same pattern. However, just like individuals in all other species, every one of us is constrained by its own survival instinct. Further, it is in humans only where, primarily due to our mental and social capacities, this survival instinct has been translated into efforts to achieve longevity. The quest for longevity has thus become an integral part of our civilization; it has permeated the way we think and the way we act. Magic, medicine and religion have all played a role in this quest.

Medical history has thought us that if we truly want to be effective we must act preventively, although at these times treating symptoms is the best we can do. Detrimental manifestations of old age should be seen as something, if not completely preventable, then surely possible to postpone significantly.

At present, unfortunately, the way medicine has approached this issue is to deal with various symptoms. Cancer, stroke, and heart attack are still the number one cause of the death and of the low quality of life. Obviously, we need to change the way we look at longevity and old age in general. As long as humans have been around, we attempted to find a "cure" for old age, some kind of fountain of youth, and although we have made certain steps forward, our most meaningful accomplishments did not came from treating symptoms but rather from preventing the disease. Introduction of vaccines has prolonged human life by 28 years on average. So, would it not be possible to invent a "vaccine" for prevention of old age [29, 30]?

We should seriously consider the hypothesis that on the population level, apart from majority with unstable genome, there is a subgroup of individuals whose genes are more stable and less susceptible to mutations and accordingly also to manifestations of aging [10,30,31]. Accurate identification of these two groups would allow us to apply the "vaccine" on unstable genes only. By doing so we would be able to prevent or postpone the development of cancer, which given enough chances for mutation (and operating on stochastic principles), will surely develop. If we are able to prevent or at least delay the onset of malignant developments and possibly of the cardio-vascular diseases, we would clearly prolong human life in a rather significant manner.

Current state of knowledge in this area, tells us that both regular physical activity and healthy foods are crucial for a healthy life. How many people, however actually follows this prescription? The result of these preventive measures is therefore minimal today. The effect of prospective "vaccine", however, would be much broader and would cut across the population boundaries. The whole human population could benefit from such an approach.

This attempt to prolong life should imply that old age could become truly beautiful and meaningful period of life. Such longer life span can allow humans to accomplish more and at least approach their dream of longevity.

The critics might argue that by prolonging life we interfere with the course of nature in an unacceptable manner. To some extent, this is a reasonable concern. The concept of "longevity vaccine" however should be seen as a tool for improving the quality of life and not merely as a tool for its alteration. Although, at present, as we still do not have such a tool, it is

legitimate to already think about its ethical implications. On the other hand, we also need to consider ethical implications of not developing something that could improve the life of so many people without any discrimination.

Further criticism might be directed to far-reaching effects behind such an endeavor, the ones leading to significant and profound population growth. It is obvious that there are already problems with over population of the planet, but in no way can we morally allow ourselves to attempt to deal with this issue by not offering the best medical care available. We should therefore ask ourselves one ultimate question: how would this world look like if we…..lived longer.

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