INTRODUCTION

The postulate of the existence of a genetic program of organism self-destruction (phenoptosis) [4, 31] is a revolutionary breakthrough in theoretical gerontology. However, the mechanism of this program’s realization has yet to be found, and thus the conception of phenoptosis has a declarative character that most gerontologists do not accept. Its appearance did not influence the vectors of applied research aimed at finding ways of prolongation of a maximum specific lifespan (the main aim of gerontology). They continue mainly in the direction indicated by the free radical theory. The application of new, effective antioxidants allowed recently obtaining impressive results in this area [5]. However, neutralization of disturbing factors provides a considerable effect only in the struggle with senile diseases. Improving health longevity can be increased, but only within a specific maximum lifespan. However, this area has no prospects for solving the main task of gerontology: oxidants are only one of many aging factors and not the most important of them.

Obviously, achievement of the primary goal lies in the path of development of the real mechanism of phenoptosis.

Species-specific maximum lifespan and intraspecific heritability of longevity from generation to generation, as well as the existence of numerous genes mutations in which influence lifespan indisputably testify in support of programmed aging [1, 2]. On the other hand, as Anisimov said, “even the presence of numerous genes the modifications of which indeed can increase or decrease lifespan allows doubting the existence of a universal aging program” [3]. The confusing abundance of aging theories [2, 21], most of which are built on real factors able to influence longevity, can be added here. This background brings most researchers to the conclusion that aging is a multiple-factor process and a single genetic phenoptosis program does not exist.

However, the nigh-chaotic set of empirical factors that gerontology uses now can be reduced to a common denominator and a single theory of programmed...
aging can be created. For this purpose a function the programmed change of which is able to influence all varieties of phenomena accompanying aging should be used as a starting mechanism. Bioenergetics is the only such function [9]. Indeed, generally, life is a variety of interrelated physical and chemical processes propelled by bioenergetics. Termination of bioenergy synthesis via, for example, oxygen cutoff to mitochondria (respiratory arrest) leads to immediate termination of vital processes. Gradual programmed decrease of the bioenergetics level will inevitably cause “slow and coordinated weakening of all organism functions with age” [5] until a level incompatible with life is reached. For convincing substantiation of such a universal aging mechanism, it is necessary to show that bioenergetics decrease causes the main harmful processes accompanying aging. It has been shown earlier that species-specific lifespan is under severe control by natural selection, i.e., the phenoptosis program is necessary for species survival [7], and age-dependent increase of active oxygen production by mitochondria is a result of programmed decrease of the bioenergetics level [6, 9]. Therefore, age-related increase of damage to an organism’s structures by active oxygen is not an initial cause of aging, as is stated by the free radical theory; but only one of the consequences of phenoptosis program realization via the programmed bioenergetics decrease. The latter causes decrease of the total level of protein synthesis [8], which induces multiple second degenerative changes [24]. In this paper it is shown that limitation of cell proliferation (the Hayflick limit) causing age tissue senility is also a consequence of the programmed decrease of the bioenergetics level.

MODERN VIEWS ON THE CAUSE OF CELL PROLIFERATION LIMITATION

Tissue senility is the most visible phenomenon and one of the most harmful phenomena of organism aging. Its cause was determined half a century ago [14]: higher eukaryotic cells do not divide infinitely, and, after a certain number of doublings, they enter a nondividing but viable state. Human fibroblasts, for example, are able to divide 53 ± 6 times over 302 ± 27 days and be in a stationary state for 305 ± 41 more days [10]. This limitation of division, the Hayflick limit, underlies the replicative aging theory, which is recognized to be one of the most striking modern aging theories [2]. The main postulate of this theory is that, due to accumulation of old nondividing cells, tissue-renewing homeostasis is violated, which causes their degradation [1, 16, 17, 33]. A convincing mechanism of termination of old cells division was predicted theoretically by Olovnikov and then confirmed experimentally [13]. Vertebrates’ chromosome ends from the DNA 3’-end have repeating nucleotide sequences—telomeres. They prevent fusion of chromosome ends, protect DNA from nuclease digestion, and participate in doubled chromosome disjunction in mitosis. In embryonic cells telomeres are synthesized by a special enzyme telomerase, which most somatic cells do not have. Because of the necessity of RNA-primer during DNA reduplication initiation, the telomere ends of somatic cells chromosomes are shortened during every cycle. As a result, after a certain number of doublings, the telomere end is depleted and divisions are terminated due to chromosome erosion [17]. This mechanism was confirmed by numerous empirical factors: 90–95% of potentially immortal cancer cells possess telomerase activity and the telomere end of their chromosomes is not shortened; suppression of telomerase activity in these cells causes shortening of the telomere end and division termination, i.e., aging; and restoration of telomerase activity makes them potentially immortal again. Therewith, facts contradictory to this conception were accumulated. The most convincing of them were obtained by a research group led by Blasco [11]. They obtained mice zygotes lacking a telomerase gene but with full-sized initial chromosome telomere ends. Mice developed from these zygotes were not only viable, but also fertile. This initial telomere length is sufficient to maintain normal viability of six mouse generations. In the first generation, for example, mice passed through youth and maturity successfully and died in old age having 80% of telomeres in reserve. Only in the fifth and sixth generations did anomalies caused by chromosome telomere end depletion appear. These data were confirmed by another group of authors led by Herrera [15]. They obtained an analogous mouse line, but with a shortened initial telomere end, and repeated the experiments of Blasco et al. These mice were viable for only four generations, and anomalies in late generations were related with depletion of telomeres in cells of tissues with the most intensive proliferation [19]. By the present time, researchers of the telomere mechanism incline to the conclusion that loss of the telomere end indeed leads to chromosome erosion and cell death, but cell proliferation termination during normal physiological cell aging happens earlier than this critical moment and a cell that has expended all its proliferative potential still contains a significant telomere reserve. The telomere mechanism serves as an additional barrier on the road to reproduction of malignant cells [17]. The conclusion that there is non-participation of the telomere apparatus in the mechanism of termination of old cells’ division could have been drawn from the very beginning. It followed from the results of the initial Hayflick experiments that, after a certain number of doublings, a cell enters a nondividing, but viable, state, and there is no sense in discussing viability if division termination due to chromosome erosion is accepted. Therefore, the question of the Hayflick limit’s nature is without answer. Apparently, an alternative reason for this phenomenon should be looked for in the mechanism of cell division.