The Concept of Phenoptosis and its Usefulness for Controlling Aging

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Abstract: Aging is generally interpreted according to two opposing paradigms: 1) as a non-adaptive phenomenon, caused by the age-related failure of homeostatic mechanisms; 2) as a specific function, favored by natural selection, which determines the self-destruction of the organism, namely explaining aging as phenoptosis. This interpretation requires genetically determined and regulated age-specific mechanisms, now well documented by an impressive and growing scientific evidence. It follows that, in principle, aging is modifiable even up to the condition, already existing for many species, of "negligible senescence", alias unlimited longevity.

Keywords: Aging, apoptosis, evolutionary gerontology, phenoptosis, cell turnover, telomere.

INTRODUCTION

When Darwin published his theory of evolution by natural selection [1], the main criticism was the contrast between the astonishing power attributed to natural selection, capable of shaping the eye, the brain and numberless very sophisticated characters, and its apparent incapacity to avoid senescence decay. This question was terrible, a possible deadly blow for the new theory, and Darwin knew its great danger. He had two possible answers: 1) (*Non-adaptive hypothesis*) The first was to postulate that natural selection could shape the infinite marvels of the living beings but not to preserve a body from the damages caused by time. This was a postulate without any proof and had the flavor of an *ad hoc* hypothesis. Moreover, among the species there were enormous differences in aging rates. It was necessary to also assume that the limits in the powers of natural selection were different from species to species: another postulate without any proof and with the flavor of an *ad hoc* hypothesis. 2) (*Adaptive hypothesis*) The second possible answer, chosen by Darwin, was to propose that the age-related progressive decline of all functions had some supra-individual advantage. Darwin hypothesized that aging was advantageous for the species [1], but he knew very well that this explanation was not proved and therefore was weak and easily disputable. Likely, he preferred it because it did not, as the first answer did, undermine the roots of evolutionism, but the explanation was a temporary setback that needed a careful reassessment.

Weissmann, following the path indicated by Darwin, hinted that the decay of the individuals was useful to the species because this caused a faster generation turnover and therefore a faster evolution [2]. However, he did not expand on his hypothesis and later disavowed it [3]. For about 70 years, the question was practically ignored by the biologists: aging as a natural phenomenon which did not need an explanation was (and is) a common assumption both for the general public and for scientists. Even the opponents of evolutionism did not appreciate that this problem could jeopardize the whole evolutionary notion. The concept that prevailed - and still prevails - was that "aging" was only a useful word to indicate the effects of a number of distinct causes of wear and deterioration. These were uncontrollable in their action as demonstrated by the fact that natural selection could not influence them (wear and tear hypotheses [4]): "Ageing is a stochastic process that ... results from the diminishing energy available to maintain molecular fidelity. This disorder has multiple aetiologies including damage by reactive oxygen species" [5]. The denial of aging as a distinct phenomenon was formalized in the international classifications of diseases (ICD) ([6]), where no separate code to indicate aging was available. For health official statistics, nobody dies from old age and even a centenarian can die from heart failure, kidney failure, cancer, or for many other reasons but not from old age [7], although it is well known that about two thirds of the deaths in the world may be attributed to age-related diseases [8].

In the fifties and later, some biologists began to revive the problem of how to explain aging in the context of evolutionism, but the answers were sought strictly within the logic of aging as the result of defects of natural selection. An early theory (mutation accumulation hypothesis [9, 10]) observed that there is an age-related decline of surviving individuals, thereby weakening the effectiveness of natural selection at older ages and so this could explain aging as due to genes with harmful effects at older ages. A variant of this theory (antagonistic pleiotropy hypothesis [11, 12]) postulated that there exist genes which were advantageous in youth but harmful at older ages. Aging was the result of conflicting selective actions in respect of such genes, which did not allow the elimination of their harmful effects. Another variation of the theory (disposable soma hypothesis [13, 14]) postulated the existence of limited metabolic resources. For the best subdivision of these undefined resources between reproduction and soma necessities, natural selection preferred reproduction, and aging was caused by imperfect maintenance of the soma.

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In fact, all the above-mentioned hypotheses were based on a pivotal concept of evolutionism which is apparently unavoidable but actually an inappropriate simplification. In the original definition of evolution, selection favors the individuals best suited to survive and reproduce [1]. But, even in the simple case of asexual reproduction, it is already necessary to consider two or more individuals (the parent and one or more young) and, in the case of sexual reproduction, we must consider three or more individuals (two parents and one or more young). Moreover, if we consider the non-sexual relationships among individuals, the so-called social relations, it is clear that very often it is essential to consider the selection in supra-individual terms. All this became very clear and agreed with the emergence of the concepts of kin selection [15-17] and of selection in spatially structured species [18], an indirect form of meaning group selection, which was a taboo explanation for many years [19, 20]. Meanwhile, the above-mentioned interpretations of aging were the subject of strong criticism [21-27] and theories for which aging was explained in terms of supra-individual selection were proposed [21, 24, 28-36]. Moreover, strong evidence indicating that the phenomenon was genetically determined and regulated was emerging (see below). In parallel, a growing evidence documented species whose individuals, under certain circumstances, and/or optionally, died without any benefit for the same individuals but with some advantage for other individuals [37]. Clearly, these individual sacrifices could not be explained in terms of individual selection but required some form of supra-individual selection.

There was no single term to define this whole category of phenomena. In fairly recent times, the proposal of an authoritative biochemist, Vladimir Skulachev, who was not an evolutionist, was necessary to define the unifying concept of "phenoptosis" as the programmed death of an organism [28].

DISCUSSION

Phenoptosis is an extraordinary notion because it also embraces the "gradual senescence with defined lifespan" [37], *e.g.* mammal aging, and indeed to such type of phenoptosis was dedicated to the sub-definition "slow phenoptosis" [38]. The concept of phenoptosis implies a paradigm shift, namely a scientific revolution [39]. A century and a half after the birth of evolutionism, for the first time, aging is not classified among the effects of insufficient selection against harmful genes but, on the contrary, among many individual-damaging phenomena favored by natural selection, obviously in terms of supra-individual selection, and therefore determined and regulated by specific genes. The shift from the paradigm of aging caused by selection deficiency ("old paradigm") to the paradigm of aging conceived as a function ("new paradigm ") has some fundamental implications. The old paradigm implies that aging, being caused by multiple and inevitable factors, in principle, may be slowed down - with efforts that are less and less effective with increasing age - but never completely canceled [40]. The new paradigm implies that aging, being a function, may be controlled in principle with relative ease and even annulled [41].While this may seem an abstract theory, on the contrary it is reflected in a series of discoveries that it is now necessary to discuss briefly (a more detailed exposition was proposed elsewhere [42]).

- (*Telomere – Telomerase – Limits in cell duplication capacities*) In 1961, Hayflick demonstrated that cells divide only a finite number of times [43]. Olovnikov proposed that, as each replication shortens DNA sequence, this could explain the finite number of duplications observed by Hayflick [44]. The end of DNA molecule (telomere), was demonstrated to be, in a protozoon, a repetitive sequence of nucleotides [45]. The discovery of an enzyme (telomerase) which added other sequences of the nucleotides was a necessary explanation of why some cells, such as germ line cells, are capable of numberless divisions [46]. Some proteins were shown to have a regulatory repressive action on telomerase [47].

- (*Apoptosis – Cell turnover*) The genetically regulated cell death by apoptosis was first described in 1972 [48] and then was documented for many tissues and organs [42]. Cell deaths by apoptosis, a sophisticated and highly regulated cell function, and other types of programmed cell death, in our species kill every year "a mass of cells equal to almost our entire body weight" [49], balanced, in young subjects, by the duplication of stem cells, a phenomenon controlled by telomere-telomerase system [42]. Cells, such as neurons, which have in general no turnover, have metabolic dependence on other cells (gliocytes) that exhibit turnover [50].

- (*Cell senescence and its reversibility*) The passage from a state in which a cell is capable of duplication (cycling state) to the non-cycling state is a random event inversely proportional in its frequency to telomere length [51]. This passage, defined as "cell senescence", is characterized by stereotyped and predictable changes and has been defined a "fundamental cellular program" [52]. Senescent cells show complex alterations of gene expressions and produce harmful substances in the cell matrix [53]. Cell senescence is a reversible program: telomerase introduction in somatic cells reverts manifestations of cell senescence and makes them able to divide indefinitely [54-57]. The compatibility of this evidence with the two paradigms is illustrated in Fig. (**1**).

- (*Atrophic syndrome - Aging*) The progressive age-related insufficiency of cell turnover to compensate cell loss by programmed cell deaths and the increase of the fraction of cells in senescent state cause aging of all tissues and organs [50], and is described as "atrophic syndrome". It is characterized by [42]:

a) reduced mean capacity of cell replication (replicative senescence of a fraction of the cells);

b) reduced cellularity (atrophy);

c) reduced rate of cell turnover;

d) replacement of the died cells with different nonspecific cells;

e) hypertrophy of the surviving cells;

f) reduced efficiency of the cells with shorter telomeres or in the state of cell senescence, and of the other cells, by alterations of the milieu caused by the secretions of senescent cells;

g) vulnerability to cancer as a consequence of dysfunctional telomere-induced instability [58].

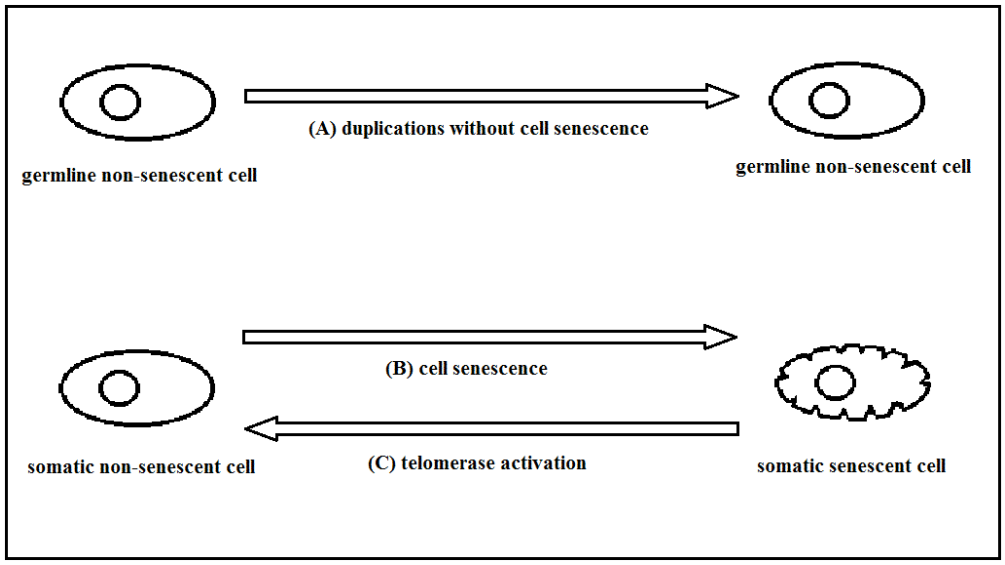

Fig. (1). Compatibility of some empirical data with the two paradigms. The phenomena **A, B** and **C** are perfectly compatible with the new paradigm: in **B**, cells senesce by the action of a program, which is not activated in **A** and is totally reversible (see **C**). For the old paradigm, cells senesce by actions of damaging factors but this does not explain the existence of cell senescence program (see **B**), its reversibility (see **C**) and the non-senescence in **A**.

- (*Aging reversibility or delay*) Telomerase reactivation in aged mice with artificially blocked telomerase determines a marked reversal of degenerative manifestations, even for neurons [59]. In adult or old normal mice, telomerase expression, induced by modified adenoviruses, delays aging and increases longevity without increasing cancer risk [60]. These data indicate that both cell senescence and aging of the whole organism are under genetic control and that both are potentially reversible by telomerase activation. This is perfectly compatible with the concept of aging as a phenoptotic phenomenon, since this idea necessarily requires the presence of specific aging causing mechanisms, which are genetically determined and regulated. On the contrary, the existence of such mechanisms is not compatible with the paradigm of aging as a consequence of heterogeneous events not genetically determined and regulated. Therefore, for the old paradigm it is essential that these mechanisms have an adaptive meaning different from aging [25, 42, 61].

The current explanation, maintained by some eminent authors, is that they constitute a general defense against cancer [62, 63], in fact trading off a greater resistance to malignant tumors with a more precocious aging [64]. This explanation is strongly contrasted by empirical data [25, 42]. In particular: a) species which show no aging ("animals with negligible senescence" [37]) show the same telomerase activity at any age [65, 66] and have no cancer problem, as demonstrated by their constant mortality rate at any age; b) in our species, studied in wild conditions, the increase in age-related mortality is precedent to cancer-related deaths cases and it is impossible that defenses against cancer kill before cancer can develop [67]; c) shortened telomeres, as a result of telomerase inactivity, cause dysfunctional telomere-induced instability and so the likelihood of cancer increases [58]; d) in normal mice, telomerase expression delays aging but does not increase cancer risk [60].

Telomerase activation is documented in many cases of cancer, but this is a consequence of the malignant proliferative mechanisms and not a cause of them [50]. However, the persistence of concepts derived from the old paradigm of aging as non-adaptive phenomenon maintains the fear of increased oncogenic risk by telomerase activation. On the contrary, for the new paradigm that defines aging as a type of phenoptosis, this fear appears unmotivated from a theoretical point of view and empirical data contrasting it are accepted without hesitation. Therefore, the controlled activation of the enzyme telomerase appears the main way to increase longevity, even to the point of indefinite longevity, *i.e.* mortality only by reasons other than aging.

A specific feasible project to examine this has been proposed [61]. In this project, intermediate steps of great importance, both for the project in general and in themselves, refer to the control of two diseases, Alzheimer's disease (AD) and age-related retina macular degeneration (ARMD), which are in fact two characteristics of the aging process [68, 69]. As mentioned before, nervous cells, with some exceptions, are not subject to cell turnover but depend on other cells which are subjected to cell turnover. For the photoreceptor cells (cones and rods), these cells are retina pigmented cells (RPC). Each day, every RPC, by phagocytosis, removes from roughly 50 photoreceptor cells, approximately 10% of the membranes having photopsin or rodhopsin molecules on them. These cells, which have a very high metabolic activity, show cell turnover and, when this turnover slows down, damaging substances such as A2E (a vitamin A-derived breakdown product) accumulate [70], cells of RPC layer rarefy and leave holes in the RPC layer. This results in the death of the photoreceptors served and the onset of symptoms of ARMD, beginning from the macula, which is the part of the retina with the greatest density of photoreceptors [71].

Just like photoreceptor cells (particular neurons without turnover) are dependent on other cells (particular gliocytes showing cell turnover), other neurons - as those of the Central Nervous System - depend on another type of gliocytes

(microglia cells). As explanation for Alzheimer Disease (AD), the decline of turnover and functionality of microglia cells has been hypothesized [50, 61, 72, 73]. Microglia cells remove β-amyloid protein [74, 75] and it is proved that, in AD, there is inadequate removal and harmful accumulation of this protein [76]. Patients likely affected by AD show telomeres that are significantly shorter than in apparently normal subjects [77]. An age-related dysfunction of endothelial cells could be, at least in part, an explanation for AD [50], but "a cell senescence model might explain Alzheimer dementia without primary vascular involvement" [50]. There is an association between Alzheimer disease or ARMD and unhealthy lifestyle [78-80], which reduces the number of endothelial progenitor cells as a likely consequence of a quicker cell turnover of endothelial cells [81]. "Protective drugs" like statins, ACE-inhibitors and sartans, which contrast excessive cell turnover, are effective against AD [78, 82].

Cures in accordance with the view that ARMD and AD are caused by the accumulation of damaging substances have been a big very expensive failure for pharmaceutical companies [83]. Although "the retina, with its high oxygen content and constant exposure to light, is particularly susceptible to oxidative damage" [84], the meta-analysis of 12 studies "did not show that antioxidant supplements prevented early [ARMD]" [84]. Drugs or vaccines against the formation of β-amyloid peptide have proven unsuccessful against AD [69]. "Post-mortem analyses showed that almost all the patients had stripped-down amyloid plaques, despite most of them having progressed to severe dementia before they died" [69]. Cures that treat the cognitive alterations of AD have been another big failure [81, 85]. Rational therapies for ARMD and AD, consistent with the concept of aging as a phenoptotic phenomenon and with the mechanisms described above, would be to avoid the decline of cell turnover of the aforesaid trophic cells. This would be possible with telomerase reactivation in these cells, which should block the progress of the two above-mentioned diseases. This could demonstrate that the theoretical foundations are correct, and therefore the control of aging is a feasible goal. For ARMD, by an extraordinary coincidence, the first experiment where telomerase activation was tried on senescent cells was conducted precisely on RPC and showed that cells transfected with vectors which encoded the human telomerase catalytic subunit "had elongated telomeres, divided vigorously, and showed reduced staining for beta-galactosidase, a biomarker for senescence. ..." [54]. All this suggests that the control of diseases such as AD and ARMD is possible with methods based on the modulated activation of the enzyme telomerase.

CONCLUSION

Apart from the huge importance of the control of these diseases that alter the brain function or the vision of a growing number of people, these methods would pave the way for a general control of the telomere-telomerase system with the pursuit of the complete taming of aging according to the program already proposed elsewhere [61]. However, it is absolutely necessary to distinguish between: A) the control of aging, B) the effects of improved prevention and treatment of the diseases caused by unhealthy lifestyles. Often, the improvements in life expectancy resulting from B, are presented as progress in the control of aging but this interpretation is misleading and should be avoided [42].

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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PATIENT'S CONSENT

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REFERENCES

[1] Darwin C. The origin of species by means of natural selection. 6th ed., Murray, London 1872.
[2] Weismann A. Essays upon heredity and kindred biological problems. 2nd ed., Oxford, Clarendon Press, UK 1889, 1891: Vol. I.
[3] Weismann A. Essays upon heredity and kindred biological problems. Oxford, Clarendon Press, UK 1892: Vol. II.
[4] Comfort A. The biology of senescence. 3rd ed., Churchill Livingstone, Edinburgh and London 1979.
[5] Hayflick L. The future of ageing. Nature 2000; 408: 267-9.
[6] http://www.who.int/classifications/icd/en/.
[7] World Health Organization, Annex Table 2: Deaths by cause, sex and mortality stratum in WHO regions, estimates for 2002. The world health report 2004 - changing history.
[8] Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006; 367(9524):1747-57.
[9] Medawar PB. An unsolved problem in biology. H.K. Lewis & Co., London 1952. Reprinted in: Medawar PB. The uniqueness of the individual. Methuen, London 1957.
[10] Hamilton WD. The moulding of senescence by natural selection. J Theor Biol 1966; 12: 12-45.
[11] Williams GC. Pleiotropy, natural selection and the evolution of senescence. Evolution 1957; 11: 398-411.
[12] Rose MR. Evolutionary biology of aging. Oxford University Press, New York 1991.
[13] Kirkwood TBL. Evolution of ageing. Nature 1977; 270: 301-4.
[14] Kirkwood TBL, Holliday R. The evolution of ageing and longevity. Proc R Soc Lond B Biol Sci 1979; 205: 531-46.
[15] Hamilton WD. The genetical evolution of social behaviour. J Theor Biol 1964; 7: 1-52.
[16] Hamilton WD. Selfish and spiteful behaviour in an evolutionary model. Nature 1970; 228: 1218-20.
[17] Trivers RL. The evolution of reciprocal altruism. Quart Rev Biol 1971; 46: 35-57.
[18] Nowak AM, Tarnita CE, Wilson EO. The evolution of eusociality. Nature, 2010; 466: 1057-62.
[19] Maynard Smith J. Group selection and kin selection. Nature 1964; 201: 1145-7.
[20] Maynard Smith J. Group selection. Quart Rev Biol 1976; 51: 277-83.
[21] Libertini G. An adaptive theory of the increasing mortality with increasing chronological age in populations in the wild. J Theor Biol 1988; 132: 145-62.
[22] Mitteldorf J. Can experiments on caloric restriction be reconciled with the disposable soma theory for the evolution of senescence? Evolution 2001; 55(9): 1902-5.
[23] Goldsmith TC. Aging as an evolved characteristic - Weismann's theory reconsidered. Med Hypotheses. 2004; 62(2): 304-8.
[24] Libertini G. Evolutionary explanations of the "actuarial senescence in the wild" and of the "state of senility". ScientificWorldJournal 2006; 6: 1086-108.
[25] Libertini G. Empirical evidence for various evolutionary hypotheses on species demonstrating increasing mortality with increasing

chronological age in the wild. ScientificWorldJournal 2008; 8: 182-93.
[26] Mitteldorf J. Aging is not a process of wear and tear. Rejuvenation Res 2010; 13(2-3): 322-6.
[27] Goldsmith TC. Arguments against non-programmed aging theories. Biochem (Mosc) 2013; 78(9): 971-8.
[28] Skulachev VP. Aging is a specific biological function rather than the result of a disorder in complex living systems: biochemical evidence in support of Weismann's hypothesis. Biochem (Mosc) 1997; 62(11): 1191-5.
[29] Skulachev VP. The programmed death phenomena, aging, and the Samurai law of biology. Exp Gerontol 2001; 36(7): 995-1024.
[30] Mitteldorf J. Ageing selected for its own sake. Evol Ecol Res 2004; 6: 1-17.
[31] Travis JM. The evolution of programmed death in a spatially structured population. J Gerontol A Biol Sci Med Sci 2004; 59(4): 301-5.
[32] Zhmylev PY. [The evolution of plant life span: facts and hypotheses] [Article in Russian]. Zh Obshch Biol 2006; 67(2): 107-19.
[33] Goldsmith TC. Aging, evolvability, and the individual benefit requirement; medical implications of aging theory controversies. J Theor Biol 2008; 252(4): 764-8.
[34] Mitteldorf J, Pepper J. Senescence as an adaptation to limit the spread of disease. J Theor Biol. 2009; 260(2): 186-95.
[35] Martins AC. Change and aging senescence as an adaptation. PLoS One 2011; 6(9): e24328.
[36] Goldsmith TC. On the programmed/non-programmed aging controversy. Biochem (Mosc) 2012; 77(7): 729-32.
[37] Finch CE. Longevity, senescence, and the genome. The University of Chicago Press, Chicago and London 1990.
[38] Skulachev VP. Programmed death phenomena: from organelle to organism. Ann N Y Acad Sci 2002; 959: 214-37.
[39] Libertini G. Phenoptosis, another specialized neologism, or the mark of a widespread revolution? Biochem (Mosc) 2012; 77(7): 795-798.
[40] Gladyshev VN. On the cause of aging and control of lifespan: heterogeneity leads to inevitable damage accumulation, causing aging; control of damage composition and rate of accumulation define lifespan. Bioessays 2012; 34(11): 925-9.
[41] Libertini G. Classification of phenoptotic phenomena. Biochem (Mosc) 2012; 77(7): 707-15.
[42] Libertini G. The role of telomere-telomerase system in age-related fitness decline, a tameable process, in telomeres: function, shortening and lengthening. Nova Science Publishers Inc., New York 2009.
[43] Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res 1961; 25: 585-621.
[44] Olovnikov AM. A theory of marginotomy: The incomplete copying of template margin in enzyme synthesis of polynucleotides and biological significance of the problem. J Theor Biol 1973; 41: 181-90.
[45] Blackburn EH, Gall JG. A tandemly repeated sequence at the termini of the extrachromosomal ribosomal RNA genes in Tetrahymena. J Mol Biol 1978; 120: 33-53.
[46] Greider CW, Blackburn EH. Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. Cell 1985; 51: 405-13.
[47] van Steensel B, de Lange T. Control of telomere length by the human telomeric protein TRF1. Nature 1997; 385: 740-3.
[48] Kerr JFR, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972; 26: 239-57.
[49] Reed JC. Dysregulation of Apoptosis in Cancer. J Clin Oncol 1999; 17: 2941-53.
[50] Fossel MB. Cells, Aging and Human Disease. Oxford University Press, New York, USA, 2004.
[51] Blackburn EH. Telomere states and cell fates. Nature 2000; 408: 53-6.
[52] Ben-Porath I, Weinberg R. The signals and pathways activating cellular senescence. Int J Biochem Cell Biol 2005; 37: 961-76.
[53] Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol 2007; 8: 729-40.
[54] Bodnar AG, Ouellette M, Frolkis M, *et al*. Extension of life-span by introduction of telomerase into normal human cells. Science 1998; 279: 349-52.
[55] Counter CM, Hahn WC, Wei W, *et al*. Dissociation among *in vitro* telomerase activity, telomere maintenance, and cellular immortalization. Proc Natl Acad Sci USA 1998; 95: 14723-8.
[56] Vaziri H. Extension of life span in normal human cells by telomerase activation: a revolution in cultural senescence. J Anti-Aging Med 1998; 1: 125-30.
[57] Vaziri H, Benchimol S. Reconstitution of telomerase activity in normal cells leads to elongation of telomeres and extended replicative life span. Cur Biol 1998; 8: 279-82.
[58] DePinho RA. The age of cancer. Nature 2000; 408: 248-54.
[59] Jaskelioff M, Muller FL, Paik JH, *et al*. Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. Nature 2011; 469(7328):102-6.
[60] de Jesus BB, Vera E, Schneeberger K, *et al*. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. EMBO Mol Med 2012; 4: 1-14.
[61] Libertini G. Prospects of a longer life span beyond the beneficial effects of a healthy lifestyle, in handbook on longevity: genetics, diet & disease. Nova Science Publishers Inc., New York 2009.
[62] Campisi J. The biology of replicative senescence. Eur J Cancer 1997; 33(5): 703-9.
[63] Wright WE, Shay JW. Telomere biology in aging and cancer. J Am Geriatr Soc 2005; 53(9 Suppl): S292-4.
[64] Campisi J. Cancer, aging and cellular senescence. In Vivo 2000; 14(1): 183-8.
[65] Klapper W, Heidorn K, Kühne K, Parwaresch R, Krupp G. Telomerase activity in 'immortal' fish. FEBS Lett 1998; 434: 409-12.
[66] Klapper W, Kühne K, Singh KK, Heidorn K, Parwaresch R, Krupp G. Longevity of lobsters is linked to ubiquitous telomerase expression. FEBS Lett 1998; 439: 143-6.
[67] Libertini G. Evidence for aging theories from the study of a hunter-gatherer people (ache of paraguay). Biochem (Mosc) 2013; 78(9): 1023-32.
[68] Berger JW, Fine SL, Maguir MG. Age-related macular degeneration. Mosby, USA 2009.
[69] Gorelick PB. Risk factors for vascular dementia and Alzheimer disease. Stroke 2004; 35: 2620-2.
[70] Sparrow JR. Therapy for macular degeneration: Insights from acne. Proc Natl Acad Sci USA 2003; 100: 4353-4.
[71] Fine SL, Berger JW, Maguire MG, Ho AC. Age-related macular degeneration. N Engl J Med 2000; 342: 483-92.
[72] Fossel MB. Reversing human aging. William Morrow and Company, New York 1996.
[73] Flanary B. Telomeres: function, shortening, and lengthening, in telomeres: function, shortening and lengthening. Nova Science Publishers Inc., New York 2009.
[74] Qiu WQ, Walsh DM, Ye Z, *et al*. Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. J Biol Chem 1998; 273(49): 32730-8.
[75] Vekrellis K, Ye Z, Qiu WQ, *et al*. Neurons regulate extracellular levels of amyloid beta-protein *via* proteolysis by insulin-degrading enzyme. J Neurosci 2000; 20(5): 1657-65.
[76] Bertram L, Blacker D, Mullin K, *et al*. Evidence for genetic linkage of Alzheimer's disease to chromosome 10q. Science 2000; 290(5500): 2302-3.
[77] von Zglinicki T, Serra V, Lorenz M, *et al*. Short telomeres in patients with vascular dementia: an indicator of low antioxidative capacity and a possible risk factor? Lab Invest 2000; 80(11): 1739-47.
[78] Vogel T, Benetos A, Verreault R, Kaltenbach G, Kiesmann M, Berthel M. [Risk factors for Alzheimer: towards prevention?] [Article in French] Presse Med 2006; 35(9 Pt 2): 1309-16.
[79] Rosendorff C, Beeri MS, Silverman JM. Cardiovascular risk factors for Alzheimer's disease. Am J Geriatr Cardiol 2007; 16(3): 143-9.
[80] Mares JA, Voland R, Sondel SA, *et al*. Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. Arch Ophthalmol 2011; 129(4): 470-80.
[81] Hill JM, Zalos G, Halcox JP, *et al*. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med 2003; 348: 593-600.
[82] Ellul J, Archer N, Foy CM, *et al*. The effects of commonly prescribed drugs in patients with Alzheimer's disease on the rate of deterioration. J Neurol Neurosurg Psychiatry 2007; 78(3): 233-9.
[83] Abbott A. The plaque plan. Nature 2008; 456: 161-4.

[84] Chong EW, Wong TY, Kreis AJ, Simpson JA, Guymer RH. Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. BMJ 2007; 335(7623); 755.

[85] Ballard C, Hanney ML, Theodoulou M, *et al*. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol 2009; 8: 151-7.

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