ISSN 1070-3632, Russian Journal of General Chemistry, 2010, Vol. 80, No. 7, pp. 1507–1513. © Pleiades Publishing, Ltd., 2010.
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Does Aging Need an Own Program or the Existing Development Program is More Than Enough?

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Received June 10, 2009

Abstract—According to author's concept, the aging process is caused by cell proliferation restriction-induced accumulation of various macromolecular defects (mainly DNA damage) in cells of an organism or cell population. In case of cell cultures, this proliferation restriction is related to either so-called contact inhibition or Hayflick's limit, and in case of multicellular organisms, to the appearance, in the process of differentiation, of organs and tissues consisting of postmitotic or very slowly dividing cells. Cell proliferation is absolutely incompatible with normal functioning of a macroorganism. Thus, the development program automatically leads to a situation inducing the aging process (martaliry rates increase with age). Therefore, any special program of aging simply becomes senseless. This, however, does not reject for some organisms the reasonability of programmed death, which makes possible the elimination of harmful, from the species's point of view, individuals. It is also very important to understand that increase or decrease of organism's life span under the action of various factors are not necessarily related to a modification of the aging process, even though the experimental results in this field are interpreted just in this way.

DOI: 10.1134/S1070363210070479

IMMORTALITY

A toy which people cry for,
And on their knees apply for,
Dispute, contend and lie for,
And if allowed
Would be right proud
Eternally to die for
Ambrose Bierce

When Acad. V.P. Skulachev, who is an initiator of the preparation of this issue of the "Russian Chemical Journal" devoted to problem of programmed aging, suggested to me to write the present paper, I immediately realized that should appear here as a rabid "antiprogrammist," which is indeed the case. This is just this role that I already played in 2007 when gave the corresponding lecture at the conference "From *Homo sapiens to Homo sapiens discatenatus*" held in Lomonosov Moscow State University. The present paper is, in fact, an extended and updated version of the mentioned lecture.

Like in that case, I will start with definitions. Unfortunately, most problems in gerontology are associated just with the absence of uniform definitions, and, in particular, of the terms "aging" and "program." Actually, if we, when debating, speak about different issues, our debate simply makes no sense.

Thus, I define aging as ***a complex of age-related changes in an organism, increasing the probability of its death***. Consequently, if the process of population extinction follows an exponential law, i.e. at an invariable death rate, then we can consider these organisms unaging irrespective of how long is their lifespan. Age resistance does not mean a long life (and vice versa). In other words, aging and lifespan are far not always interrelated. Even if a human would never aged, he all the same would has not lived forever like Koschei the Immortal. People would simply die for

accidental reasons, and the average lifespan would has increased to as little as 700–800 years.

As to the term "program," then one can find in dictionaries a multitude of definitions for this word. In particular, my most respective Webster's Dictionary [1] contains nine such definitions. Only one of them is suitable for biology: "A sequence of coded instructions (as genes or behavioral responses) that is part of an organism." Surely, it sounds slightly abstructely, but in essence it seemingly means the following: A program (in biology) is implemented in time, and whether it occurs in a normal way depends exclusively on time. A classical example is provided by the developmental program. This program is not so difficult to disturb, but in the absence of any unfavorable factors it is implemented completely "per se" and again in time.

In view of the aforesaid, we can note that, in terms of this definition, apoptosis can correctly be called a programmed cell death only if it reveals itself in the process of embryonic development, when there occurs a programmed elimination of cells already unnecessary for specific tissues and organs.

There is one more important circumstance. Regretfully, correlations between death probability and age are presently possible at a population level by constructing survivorship curves (a graphs of the survival rate of a cohort of organisms). Therewith, of importance is not only the shift of the curve (fitted by the Gompertz–Mannheim equation in the case of aging organisms and by an exponential equation in the case of unaging organisms) to the right or to the left, but also the shape of this curve. By the way, it is not at all necessary that such changes are determined by a modification of the aging process. Steven Austad reasonably mentioned in his excellent book [2]: "The theoretical limit of our lifespan depends on the behavior of people, rather than on their physiology. If teenagers would not run around in cars like mad, this would has increased the mean life expectancy than the victory over cancer"[1].

Thus, shifting the exponential survivorship curve to the right or to the left without changing its shape, while affecting the lifespan (both average and maximum), but has nothing in common with an effect on the aging process. Unfortunately, even in experiments on cohorts of animals extincting "by Gompertz," it is quite difficult to decide whether the applied experimental exposures affect the basic mechanisms of aging. In the present paper I cannot dwell in detail of the methodology of gerontological research, but would like to only mention that it is only a significant increase of the maximum (or at least 90%) lifespan can be interpreted as a real retardation of aging. There are millions ways to shorten life (infections, starvation, traumas, etc.), but even at least one of them can pretend to the title of a real geropromoter (except for, may be, ionizing radiation which can shift the survivorship curve of aging animals to the left, not affecting its asymmetry and excess).

In the last few years, a vigorous renewal of a nearly decayed interest in the free-radical theory of aging and, as a consequence, antioxidants of different nature as potential geroprotectors has taken place [3–6]. Followers of this theory, including the group headed by Acad. Skulachev [3, 4, 7–12], obtained a lot of seemingly encouraging results. However, almost always antioxidants only improved the quality of life of experimental animals (like adequate nutrition and normal physical activity) and had no effect on the species-specific (maximum) lifespan: Nothing but rectangularization of the survivorship curve was observed in view of the fact that more and more animals reached an age close to the maximum lifespan). However, even if antioxidants would allow to raise the maximum lifespan, this would has brought grist to the mill of gerontologists opposing the theory of programmed aging, since I can hardly imagine how such geroprotectors can modify the genetic program of aging.

It is also important to understand that aging may proceed very slowly and is undetectable by presently available methods. As far back as 20 years ago, Caleb Finch [13] introduced the term "negligible aging" and formulated its criteria: (1) lack of appreciable changes in mortality rates with age, (2) lack of changes in reproduction rates after maturation, (3) lack of appreciable decay of physiological functions with age, and (4) deterioration of resistance to diseases.

The biological species with "negligible aging" include Greenland whale, giant tortoise, flatfish, sturgeon, lobster, etc. One of my favorite papers [14], devoted to such organisms, was witty titled by the author "Senescence and the genome or, change and decay in all except lobsters I see." It is necessary to say that almost all organisms with "negligible aging" have

[1] Here and hereinafter, free citation (Translator).

one important common property: They possess an unlimited growth. Therewith, as a rule, the larger the size of species memberes, the longer the recorded species-specific lifespan. The expression "as a rule" is not accidental here: Like with each rule, there are certain exceptions. A well-known example is ocean perch (*Sebastes marinus*) [13, 15]. This family comprises about 50 species whose lifespan varies from 12 to 205 years. However, the record holders (especially among mammals) still remain species with unlimited growth and, consequently, having a very large size. For example, Greenland whale reaches 20 m in legth and more than 90 tons in weghvol. According to the most recent data, the maximum lifesapn of this animal is no less than 211 years.

It is also interesting to mention that (again, as a rule) one more regulatiry takes place: The larger the body weight, the lower fecundity of species members.

The concept that growth restriction of organisms is the main reason of their aging was formulated as back as the first third of the XX century [16–18] by Minot, Bidder, and Shmal'gausen. According to their ideas, the implementation of the development program forms populations of postmitotic cells incapable of growth and reproduction, which makes impossible their full-scale regeneration.

In 1908s, I, trying to modernize the above concept, formulated a theory of aging, which is based on the following postulates [19–26]. It is known that highly developed organisms are simply unable to fulfill their physiological functions without populations of highly differentiated cells with a zero or very low proliferative activity. An example is provided by neurons and cardiomyocytes. Their function is incompatible with mitotic divisions which can immediately disorder the complex system of intercellular interactions, but just this interactions determine the functional possibilities of corresponding organs. At the same time, such cells, like all other body cells, face DNA damage which, unfortunately, are impossible to repare completely [19, 27]. If dividing cells simly "dilute" the damaged cells (on the whole population basis) by division, i.e. due to the appearance of new, "undamaged" cells, then postmitotic or slowly diving cells are unable to do that (in the second case, only if the rate of cellular proliferation is not high enough to keep damages at a safe level). Thus, the number of DNA defects per cell steadily increases with age, enhancing the probability of disturbance in functioning organs or tissues, and, as a result, vulnerability to age-related diseases. Eventually this process increases the probability of organism death, i.e. to aging.

One circumstance following from this concept predetermined the strategy of our experimental research for many years. I assumed that the restriction of proliferation of cultured cells would result in accumulation in the culture of various macromolecular changes similar to those arising in age-related cellular changes in an aging organism. Our numerous experiments [28–33] showed that the contact inhibition of cell proliferation induces the above-mentioned changes, specifically single-strand DNA breakage, DNA–protein cross-linking, DNA demethylation; furthermore, spontaneous sister chromatide exchange slows down; structural changes in cell nuclei occur; defects in plasmatic membranes develop; cellular response to mitogens (factors stimulating cell division) and the ability of cells to form colonies decay; the content of the known aging biomarker 8-oxo-2'-deoxyguanosine in DNA increases; and poly(ADP ribose) polymerase (PARP 1) inhibition occurs. The most important among them is the damage of DNA, since all other macromolecules can, in principle, be synthesized *de novo*, if an undamaged template, i.e. DNA, is present.

The obtained evidence showed that the idea that the inhibition of cell proliferation as the principal triggering mechanism of aging, indeed, has a right to exist. As a result, an opinion arose that the development program along can explain the reasons of aging of a macroorganism.

In those cases when cell proliferation inhibition is delayed for an indefinite term (species with unlimited body growth) or does not occur at all (freshwater hydra), the aging process either slows down considerably or is even arrested. Hydra is an ideal illustration of this conclusion [19, 34]. At certain temperature conditions the so-called *i*-cells of hydra ceaseless divide, renewing the organism, whereas oil cells desquamate either from tentacle ends or from the side of the aboral pore. Therewith, the size and individual features of the polyp remain unchanged, and this individual does not age at all.

One more example of "immortality" (here and hereinafter, in the sence of the absence of aging) is provided by the finite lines of transformed animal and human cells [35]. In this case, too, no signs of aging of

the cell population capable of infinitely dividing over an almost unlimited time. Therewith, certain cells may "impair" and die, but they are almost immediately replaced by new cells formed by ceaseless divisions. As soon as we make normal fibroblasts infinitely dividing [36] by introducing in them a telomerase gene, they immediately lose the ability to age "by Hayflick."

Analogous conclusions can also be drawn from an analysis of mechanisms underlaying the virtual "immortality" of clonal plants. Say, saffron crocus clonally reproduce for over more that 2500 years, while aspen forests in the Rocky Mountains gave no seeds from the Ice Age. Another matter that we can hardly speak here about the "immortality" of a concrete plant. The embryonic cell line in humans is, in principle, also "immortal," but this relates not to separate individuals, but to the whole chain of organisms transferring the genetic material from ancestors to descendants. As reasonably noted the German botanist of the XIX century Alexander Brown: "Already internal sensation suggests that an extremely branched plant is not a single entity or a single being compared with an animal or a human, no, it is more likely a whole universe of inividuals which grow one from another in a chain of generations."

At the same time, many plants have quite a clear leaf's aging program which manifests itself every autumn in the appearance of a red and yellow color.

Thus, there is a fairly great number of organisms in the nature, which do not experience aging. Certain advocates of programmed aging (we call them "programmists") suggest that such species, unlike others, simply do not have any aging program.

I think that the necessity to preserve individuality (animals and plants) or personality (humans and, possibly, animals) is the main barrier on the way to the "immortality."

The list of arguments in favor of programmed aging is fairly standard [12, 37–39]. In my opinion, the most common of them are the following:

(1) different species-specific lifespans;

(2) similar lifespans of parents and children;

(3) existence of progeroid diseases;

(4) increase of the lifespan of certain experimental animals due to switching-off certain genes;

(5) existence of the phenomenon of programmed death in certain organisms.

All arguments "against," too, are well-documented [5, 40, 41], and, as a matter fact, this issue has many times been debated (see, for example, the publications of Bredesen and Austad in the *Aging Cell* journal [37, 41, 42]). Therefore, I will only briefly dwell on some arguments of "antiprogrammists," which deserve the most attention.

Thus, in succession. As already mentioned above, there is no strict correlation between lifespan and aging. Therefore, the differences in species-specific lifespans may be determined not different programs of aging but different programs of development, which create organisms with different reliabilities of functioning. As a result, children inheritate from parents a genetically programmed reliability pre-determinng their life expectancy, rather than a program of aging. The developmental program brings up an organism to a certain stage to ensure successful reproduction and then, as a rule, turns it adrift. It is known that cars, too, tend to age (i.e. the probability of their irreversible impairment increases with age); however, nobody provides them with a special aging program. More expensive cars work longer simply because they are more reliable than cheap. The same reasons may underlay faster aging of organisms with progeroid diseases. At the same time, it should be noted that such diseases are quite rare, which makes impossible measuring survivorship curves for cohorts of sick individuals and, therefore, correctly dfferentiate such cases from increased rates of death from other diseases (not progeroid).

I am inclined to the view on the problem of programmed aging, belonging to the prominent gerontologist Robin Holiday. In 2007 in his book "Aging: the Paradox of Life" with a subtitle quite common in books on this subject "Why we age" he writes: "Some people beleive that aging is genetically programmed or, even more emphatically, that aging is simply bound to have the corresponing program. However, this point of view may well oversimplify the situation, and I many times described the situation with tooth aging, which is a simple illustration of my approach to the problem. The size and structure of teeth are genetically programmed, but teeth tear and destroy completely because of their use. Thus, teeth are actially programmed to service to the organism over its life, but, hypothetically, were they not used, they would exist much longer that the individual lifespan. Body architectonics is determined by genes,

but this "design," as we can see, is fully incompatible with endless life" [43].

Quite similar ideas underlay the Suresh Rattan's [44] concept of gerontogenes, i.e. genes whose functioning maintains functioning cellular molecular systems and protect an organism from age-related changes.

The known facts of the extension of lifespan of experimental animals (the most illustrative examples of such results were obtained on nematodes) by switching-off certain genes (for a detailed review, see [45]), too, are not an undeniable evidence in favor of programmed aging. Steven Austad reasonably notes [41] that certain *daf-2 Caenorhabditis elegans* mutants die 10 days old, whereas others, 50 days old. These data are indicative a large lifespan dispersion in this population. Moreover, it was found that under conditions of stiff competition with wild-type species, *age-1* and *daf-2 C. elegans* mutants turn to be far behind them in terms of vitality [46–48].

And, finally, about programmed death. This phenomenon actually is widely distributed in the nature (plants, octopus, salmon, marsupials, etc.), but it has nothing in common with aging. Programmed death generally occurs quite differently from death in a deep senility [41], and, which is the most important, its probability doesn't grow steadily with age, wherease just such a growth, as mentioned above, is prerequisite for aging. I consider the very this phenomenon, i.e. programmed death, as further evidence for the existence of a program of death, rather than aging. This is just a tool that the nature uses to get rid of useless individuals, not resorting to an extremely complicated and scarcely realized, by means of evolutionary mechanisms, method for eliminating organisms by ***a program increasing the probability of their death with time*** (a real aging program should operate just in this way).

The main feature of any program is that it allows violation. Malfunctions in the development program are quite common. However, to my knowledge, there are no mutations, i.e. malfunctions in the aging program, leading to the appearance of "immortal" individuals. Even if an organism does not have a specific aging program, it will all the same age, since this is intrinsic of the organism, and aging, to all appearances, is a usual "by-product" of the aging program.

The discussion of the possible existence of a program of aging was initiated by the great genetic scientist August Weismann, and what is important, he first of all debated with himself (cf. an excellent review of Kirkwood and Kremer, devoted to Weissman's concepts [49]). If in his early works he admitted the adaptivity of aging, i.e expediency of this phenomenon from the evolutionary viewpoint, but then he completely rejected this idea and came to a conclusion that the program of aging (which would have develop over the course of evolution, if existed in principle) is absent.

By the way, it is Weismann who was the first to set primordial germ cells (Keimplasma) whose population is immortal in principle against somatic cells which age and die. Then, already in the XX century, after Carrel's experiments [50] on culturing isolated animal cells, gerontologists suggested for over almost 50 years that such cells can divide indefinitely. It is only in 1950–60s that the experiments of Swim and Parker [51] and later Hayflick [52–54] gave evidence to show that the results of Carrel are likely to be an artifact. It turned out that all normal animal cells possess a limited proliferative capacity and can divide in the culture no more than 100–120 times (which corresponds to about 50 doublings of the cell population). A multitude of concepts were formulated in the attempt to explain the Hayflick's phenomenon and correlate it with aging in vivo. However, later these concepts all were ruled out after the discovery of the telomere "counter" [55] reponsible for the limited capacity of normal cells for division. This gave rise to a new wave of aging theories explaining this phenomenon specifically by telomere shortening in dividing cells. Therewith, as strange it might seem, the overwhelming majority of researches ignored that fact that the key organs of highly developed animals consist of postmitotic or slowly dividing cells, and, therefore, the very term "proliferative potential" no longer makes sense. As to cells capable of dividing, then over an organism's life, they almost never exhaust their potential. Convincing evidence for the latter statement was obtained from a comparison of these parameters for fibroblasts from children and almost healthy long-livers [56]. In view of the aforesaid, the attemps of certain gerontologists to present the mechanism of telomere shortening as a tool for the implementation of the aging program no longer seem unreasonable.

And, finally. We can, in principle, suggest existence of a certain external program controlling the aging process from the outside and having some effect

on certain body structures. Fairly recently Olovnikov, the author of the known marginotomy theory [55], has formulated one more concept, the so-called concept of lunar sensors, according to which gravitational changes due to the lunar cycle induce changes in epiphyseal cells. However, these changes are not "bad" for cells themselves and have no effect on their vitality. They only induce release of neuromediators which enter the hypotalamus and already there trigger processes later leading to aging of the whole organism [57, 58]. This idea may seem fantastic, but it allows one to solve many problems of the classical gerontology, since it does not require searching for fine mechanisms of aging directly in the organism itself. Unfortunately, this theory leaves open such question as how the process of aging will occur in space pilots far from the Earth or Moon and why this program is triggered in adult people only and differently works in species with different lifespans. Moreover, it does not explain the aging of plants, mushrooms, and primitive or more developed organisms which have no epiphysis and hypothalamus. And, of course, the key question always remains: ciu bono, or, in any words, what is the origin of organisms whose aging is controlled in such an exotic way?. I am afraid that not resorting to ideas of Supreme Mind, which have gained popularity in the last few years, we will never find an answer to this question.

REFERENCES

1. *Merriam-Webster Online Dictionary and Thesaurus, http://www.merriam-webster.com.*
2. Austad, S.N., *Why we Age: What Science is Discovering About the Body's Journey Through Life*, New York: Wiley, 1999.
3. Skulachev, V.P., *IUBMB Life*, 2005, vol. 57, pp. 305–310.
4. Skulachev, V.P., *Exp. Gerontol*., 2001, vol. 36, pp. 995–1024.
5. de Grey, A.D.N.J., *The Mitochondrial Free Radical Theory of Aging* (Molecular Biology Intelligence Unit 9), Austin, Tex: Landes Bioscience, 1999.
6. Kol'tover, V.K., *Usp. Gerontol*., 2000, vol. 3, no. 4, pp. 38–41.
7. Skulachev, V.P., *Biokhimiya,* 2007, vol. 72, no. 12, pp. 1700–1714.
8. Skulachev, V.P., *IUBMB Life,* 2000, vol. 49, pp. 177–180.
9. Skulachev, V.P., *Ibid.*, 2000, vol. 49, pp. 365–373.
10. Skulachev, V.P., *Quart. Rev. Biophys*., 1996, vol. 29, pp. 169–202.
11. Skulachev, V.P. and Longo, V.D., *Ann. NY Acad. Sci*., 2005, vol. 1057, pp. 145–164.
12. Longo, V.D., Mitteldorf, J., and Skulachev, V.P., *Nat. Rev. Genet*., 2005, vol. 6, pp. 866–872.
13. Finch, C.E., *Longevity, Senescence, and the Genome*, Chicago: Univ. of Chicago Press, 1990.
14. Downes, C.S., *BioEssays*, 1993, vol.15, pp. 359–362.
15. Finch, C.E., *Between Zeus and the Salmon. The Biodemography of Longevity*, Wachter, K.W. and Finch, C.E., Eds., Washington, D.C.: National Academy Press, 1997, pp. 245–268.
16. Bidder, G.P., *Brit. Med. J*., 1932, vol. 2, pp. 583–585.
17. Minot, C.S., *The Problem of Age, Growth, and Death; a Study of Cytomorphosis, Based on the Lectures at the Lowell Institute*, March 1907, New York: Patnam's Sons, 1908.
18. Shmal'gauzen, I.I., *Problema smerti i bessmertiya* (Problem of Death and Immortality), Moscow: Gosizdat, 1926.
19. Khokhlov, A.N., *Itogi Nauki Tekh., Ser. Obshchie Probl. Fiz.-Khim. Biol*., 1988, vol. 9.
20. Khokhlov, A.N., *Tsitologiya,* 2002, vol. 44, no. 12, pp. 1143–1148.
21. Khokhlov, A.N., *Ontogenez*, 2003, vol . 34, no. 5, pp. 382–389.
22. Khokhlov, A.N., *Probl. Star. Dolgol.*, 2008, vol. 17, no. 4, pp. 451–456.
23. Khokhlov, A.N., *Ibid*., 2009, vol. 18, no. 1, pp. 32–36.
24. Khokhlov, A.N., *Ann. NY Acad. Sci*., 1992, vol. 663, pp. 475–476.
25. Khokhlov, A.N., *Biomarkers of Aging: Expression and Regulation*, Licastro, F. and Caldarera, C.M., Bologna: CLUEB, 1992, pp. 209–216.
26. Khokhlov, A.N., *Ann. NY Acad. Sci*., 1998, vol. 854, p. 519.
27. Vilenchik, M.M., Khokhlov, A.N., and Grinberg, K.N., *Stud. Biophys*., 1981, vol. 85, pp. 53–54.
28. Khokhlov, A.N., Chirkova, E.Yu., and Nadzharyan, T.L., *Tsitologiya*, 1984, vol. 26, no. 8, pp. 965–968.
29. Khokhlov, A.N., Chirkova E.Yu., and Gorin, A.I., *Byull. Eksperim. Biol. Med*., 1986, vol. 101, no.4, pp. 416–418.
30. Khokhlov, A.N., Chirkova, E.Yu., and Chebotarev, A.N., *Tsitol. Genet*., 1987, vol. 21, no. 3, pp. 186–190.
31. Khokhlov, A.N., Kirnos, M.D., and Vanyushin, B.F., *Izv. Akad. Nauk SSSR, Ser. Biol*., 1988, no. 3, pp. 476–478.
32. Shram, S.I., Shilovskii, G.A., and Khokhlov, A.N., *Byull. Eksp. Biol. Med*., 2006, vol. 141, no. 5, pp. 567–571.

33. Esipov, D.S., Gorbacheva, T.A., Khairullina, G.A., et al., *Usp. Gerontol.,* 2008, vol. 21, no.3, pp. 485–487.
34. Brian, P., *Proikhozhdenie i razvitie polovykh kletok v ontogeneze pozvonochnykh i nekotorykh grupp bespozvonochnykh* (Origin and Development of Sex Cells in the Ontogenesis of Vertebrates and Certain Groups of Invertebrates), Svetlov, P., Ed., Leningrad: Meditsina, 1968, pp. 17–74.
35. *Cell Immortalization (Progress in Molecular and Subcellular Biology, vol. 24),* Macieira-Coelho, V., Ed., Berlin: Springer, 2000.
36. Bodnar, A.G., Ouelette, M., Frolkis, M., et al., *Science*, 1998, vol. 279, pp. 349–352.
37. Bredesen, D.E., *Aging Cell,* 2004, vol. 3, pp. 255–259.
38. Lewis, K., *Mech. Ageing Dev.,* 1999, vol. 109, pp. 43–51.
39. Goddio, A.-S., *Eur. J. Plast. Surg*., 1991, vol. 14, pp. 261–264.
40. Kirkwood, T.B.L., *Mech. Ageing Dev*., 2002, vol. 123, pp. 737–745.
41. Austad, S.N., *Aging Cell*, 2004, vol. 3, pp. 253–254.
42. Bredesen, D.E., *Ibid*., 2004, vol. 3, pp. 261–262.
43. Holliday, R., *Aging: the Paradox of Life. Why we Age,* Dordrecht: Springer, 2007.
44. Rattan, S.I.S., *FASEB J*., 1995, vol. 9, pp. 284–286.
45. Vanfleteren, J.R. and Braeckman, B.P., *Neurobiol. Aging*, 1999, vol. 20, pp. 487–502.
46. McColl, G., Jenkins, N.L., Walker, D.W., and Lithgow, G.J., *Ann. NY Acad. Sci*., 2000, vol. 908, pp. 319–320.
47. Walker, D.W., McColl, G., Jenkins, N.L., et al., *Nature*, 2000, vol. 405, pp. 296–297.
48. Jenkins, N.L., McColl, G., and Lithgow, G.J., *Proc. Biol. Sci*., 2004, vol. 271, pp. 2523–2526.
49. Kirkwood, T.B.L. and Cremer, T., *Hum. Genet*., 1982, vol. 60, pp. 101–121.
50. Carrel, A., *J. Exp. Med*., 1912, vol. 17, pp. 14–19.
51. Swim, H.E. and Parker, R.F., *Am. J. Hyg*., 1957, vol. 66, pp. 235–243.
52. Hayflick, L., *Exp. Cell Res*., 1965, vol. 37, pp. 614–636.
53. Hayflick, L., *Mech. Ageing Dev.,* 1979, vol. 9, pp. 393–408.
54. Rattan, S.I.S., *Biogerontology*, 2000, vol. 1, pp. 79–87.
55. Olovnikov, A.M., *Dokl. Akad. Nauk SSSR*, 1971, vol. 201, no.6, pp. 1496–1499.
56. Cristofalo, V.J., Allen, R.G., Pignolo, R.J., et al., *Proc. Natl. Acad. Sci*., 1998, vol. 95, pp. 10614–10619.
57. Olovnikov, A., *Ann. NY Acad. Sci*., 2005, vol. 1057, pp. 112–132.
58. Olovnikov, A. J., *Alzheimer's Dis.,* 2007, vol. 11, pp. 241–252.