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What is an anti-aging treatment?

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ABSTRACT

Key objectives of biogerontology are to understand the biology of aging and to translate scientific insight into interventions that improve late-life health — or *anti-aging treatments*. In this context, when considering the problem of how to effect translational research, it is useful to have a clear, consensus view on what exactly constitutes an anti-aging treatment. This essay critically assesses the understanding of this concept common among biogerontologists, and proposes a new definition. A current conception of anti-aging treatment imagines a primary cause of aging that is causally upstream of, and the cause of, all age-related pathology. Intervening in this aging process thus protects against the totality of age-related diseases. However, this underlying aging process remains an abstraction. By contrast, what is demonstrable is that interventions in model organisms can improve late-life health and extend lifespan. Furthermore, a safe deduction is that treatments that extend lifespan do so by reducing age-related pathology, both florid and subtle. What is currently identifiable about aging (i.e. senescence) is that it is a very complex disease syndrome, likely involving a number of biological mechanisms. Treatments that substantially extend lifespan must suppress multiple pathologies that otherwise limit lifespan, but whether they suppress the entire aging process remains undemonstrated. A more pragmatic and realistic definition of anti-aging treatment is any preventative approach to reduce late-life pathology, based on the understanding that senescence is a disease syndrome. This definition would encompass preventative approaches aimed at both broad and narrow spectra of age-related pathologies. Its adoption would facilitate translation, since it would shift the emphasis to medical practice, particularly the introduction of preventative approaches. Narrow spectrum anti-aging treatments (e.g. the cardiovascular polypill) could establish a practice that eventually extends to broader spectrum anti-aging treatments (e.g. dietary restriction mimetics).

1. Introduction

Pathologies of aging underlie much of the disease burden worldwide. Work on animal models has revealed interventions that lead to an increase in healthy lifespan (Kenyon, 2010). Such studies suggest that by slowing the underlying process of aging one can achieve broad spectrum protection against diseases of aging (Butler et al., 2008). Understandably, there is a strong desire among biogerontologists to shift from pure to translational research, and to identify paths that would lead to clinical trials of anti-aging therapies. This aspiration underpinned the recent conference *Interventions to Slow Aging in Humans: Are we Ready?* held in October 8–13th 2013 in Erice, Sicily (organized by Valter Longo, Luigi Fontana and Donald Ingram).

In order to promote translational research the meeting was oriented to two main objectives. First, to survey the (now) many different approaches in the laboratory that have been to extend lifespan in animal models, and seek a consensus about which approaches would be most promising to test first in humans. Second, to develop a consensus on the most appropriate biomarkers of aging to use as a readout of treatment efficacy.

Arguably, fulfillment of these two objectives, while necessary for translation, is far from being sufficient. This is because relative to conventional views about the nature of aging, the approach of anti-aging therapies is a radical one. Such conventions affect both public and political attitudes towards aging and medical practice. Adoption by the medical establishment of an anti-aging approach to improve late-life health would involve radical, even revolutionary change. It would, for example, involve a re-conceptualization of the nature of aging and the relationship between aging and disease, the introduction of a preventative approach to age-related disease, a more active role of the patient in managing their own late-life health — and even teaching medical students about the biology of aging (currently medical students are taught little about the biological basis of the most prevalent cause of disease).

One impediment to translation, noted by one speaker at the conference, Brian Kennedy, Director of the Buck Institute for Research on Aging, is the lack of clarity and consensus about the definition of *anti-aging treatment*. One might mistake this for a minor issue of semantics, but here I will argue the opposite: that a good definition of anti-aging treatment is important not only to clearly define the goals of biogerontology, but also to enable them to be fulfilled. In this essay, I will first give a brief account of the standard biogerontological conception of anti-aging medicine (at least, as I have understood it), and then

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make a critical assessment of this definition. I will then propose an alternative definition, one that is, arguably, more realistic and pragmatic.

2. Anti-aging treatments: a standard view from biogerontology

A common conception among biogerontologists of *anti-aging treatment* is based on a straightforward premise: that a biological process, aging, gives rise in later life to a broad spectrum of diseases. This being so, any intervention that inhibits aging itself will reduce incidence of a broad spectrum of late-life diseases (Butler et al., 2008). Consistent with this premise, a variety of interventions improve late-life health and extend lifespan in a range of animal models. For example, dietary restriction (caloric restriction) has long been known to slow aging and improve late-life health in rodents, and may be effective in rhesus monkeys (Bodkin et al., 2003; Colman et al., 2009; Mattison et al., 2012) and possibly humans (Berrington de Gonzalez et al., 2010; Fontana et al., 2004). There seems no reason in principle why some form of anti-aging treatment should not be efficacious in humans, and lead to great improvements in late-life health in times to come. Even so, closer scrutiny of the concept of anti-aging treatment reveals some weaknesses in this standard view, involving the following questions.

i) Is there a real distinction between age-related disease and aging?
ii) Where should one draw the line between anti-aging treatment and conventional treatments for late-life diseases?
iii) To what extent do treatments that extend lifespan in animal models slow aging?
iv) Which is a better defining characteristic of anti-aging treatments: that they inhibit the central process of aging, or that they prevent age-related diseases?

In the next section, I will start by attempting to clarify the relationship between aging and age-related pathology.

3. The myth of "pure aging"

Conceptually, the idea of protecting against age-related diseases by retarding aging remains somewhat fuzzy due to the lack of a clear understanding of what aging actually is. Most obviously, the word "aging" itself can cause confusion because of its multiple meanings. First, it denotes an increase in calendar age, regardless of changes in any other properties of the entity affected. Second, it can refer to any alterations in properties of the things whose calendar age is increasing, whether positive, neutral or negative. Third, it can refer to the deteriorative changes seen in living organisms with increasing age — or *senescence*. Thus, *anti-aging treatments* are, specifically, *anti-senescence treatments*.

A traditional view, and one that predominates in contemporary medicine (including geriatrics) is that while aging (senescence) increases the risk of late-life disease, aging itself is not a disease. Aging is regularly portrayed as a wholesome part of the human life cycle that gives meaning and dignity to the human condition (Kass, 1983), and this view of aging as a good, termed *apologism*, has a long historical tradition (Gruman, 1966). The concern is expressed that calling aging a pathology will stigmatize and degrade the elderly, while treating aging would lead to catastrophic over-population and exhaustion of natural resources. To assuage such concerns, the goal of research on aging is sometimes defined as not to intervene in aging itself, but rather to reduce the incidence of age-related diseases.

The question of whether aging should be viewed as a disease or a non-pathological process accompanying disease has been argued over since classical times (Blumenthal, 2003). However, the fact is that from the perspective of modern biogerontology, i.e. in terms of biological phenomenology, there is really no clear reason to distinguish aging from pathology (Caplan, 2005; Gems, 2011). Aging is a process characterized by a broad spectrum of pathologies the sum of which leads inevitably to death (Blagosklonny, 2009). Arguably, the idea that elderly people die without pathology is absurd: in biological terms, by definition, endogenous factors harmful enough to cause death must entail severe pathology. Put simply: "No one dies from healthy senescence" (Blagosklonny, 2006). The notion of death from "pure aging" (i.e. aging without pathology) is surely a myth. One source of this myth may well be that some aspects of aging are more identifiable as pathologies than others. As examples, one cannot fail to identify cancer and macular degeneration as pathologies, but this is less the case for sarcopenia and osteoporosis.

Human health has been defined in terms not only of the absence of disease, but also of the presence of a level of function that is typical of human beings of a given age and gender (Boorse, 1977). By this view, given that all old people experience it, aging is a normal process and therefore distinct from disease — despite the fact that it is accompanied by a broad spectrum of diseases. Clues to a resolution of this paradox may be found in the evolutionary theory of aging, which provides a biological perspective upon the purpose and meaning of the aging process (Caplan, 2005). According to the evolutionary theory, aging is a consequence of a reduction in the force of selection against mutations with deleterious effects later in life (Medawar, 1952; Partridge and Barton, 1993). This leads to accumulation within populations of alleles with deleterious effects later in life — particularly alleles that also have beneficial effects on reproductive fitness early in life (Williams, 1957). The evolutionary theory provides the bleak insight that aging serves no purpose in terms of fitness, but instead is a lethal genetic disease that afflicts all human beings. Arguably, the significance of the universality of human aging is not that aging is not a disease, but rather that it is a special form of disease. To argue that aging is not a disease by virtue of its universality is as unhelpful as it is to argue that the Basenji is not a dog because it does not bark.

In short, senescence is an inherently pathological process. Thus, "healthy aging" in the sense of "healthy senescence" is an oxymoron. However, in terms of calendar aging or age-related change, healthy aging is a desirable goal. One reading of the history of ideas on aging is that apologism has generated not only the standard (and nonsensical) medical view of aging as distinct from pathology ("healthy senescence"), but also the conception by biogerontologists of pathology-free theories of aging.

4. Insights into aging viewed as a disease

If aging is a disease syndrome, then it is likely that the etiology of aging will share general characteristics with other diseases that lead to gross pathology. To put this another way, if aging is a disease, then proposals of properties or mechanisms of aging that are clearly different from those of pathologies in general fall under suspicion of being incorrect. One possible example of this kind of error involves the oxidative damage theory of aging. Senescence, whether in nematodes, fruitflies or mammals, is associated with an increase in levels of molecular damage, which rise markedly from mid-life onwards (Halliwell and Gutteridge, 2007). This fact contributed to an influential theory of aging: that it is caused by the accumulation of molecular damage (e.g. oxidative damage), and that processes of somatic maintenance contribute to longevity (Harman, 1956; Kirkwood, 1977). However, severe pathologies often cause dyshomeostasis and increased levels of molecular damage (Halliwell and Gutteridge, 2007). Thus, given that aging is accompanied by severe and inevitably lethal pathologies, one would expect that, whatever its primary cause, it would be accompanied by increased molecular damage. In fact, in recent years the role of molecular damage as the major driver of aging has been challenged (Blagosklonny, 2008; Gems and Partridge, 2013; Perez et al., 2009; Van Raamsdonk and Hekimi, 2010).

Many diseases, particularly those caused by pathogens, involve the following basic pattern. Within a healthy organism a cumulative biological process occurs which over a period of time leads to disease symptoms. Its initial cause may be exogenous (e.g. a virus, such as HIV), or

endogenous (e.g. hyperplasia of prostatic cells). In its early, pre-pathological stages, it has little effect on health and function (as in an asymptomatic patient with HIV viremia). Then as it progresses, it begins to disrupt biological function, leading to gradual loss of homeostasis, and increases in molecular damage and frailty. It then leads to debilitation, the experience of illness and, perhaps, death. Aging, considered as a disease syndrome, is likely to conform to these basic properties.

This suggests that, like molecular damage as a cause of aging, other common properties of diseases that have been identified as special causes or properties of aging are unlikely to be such. For example, aging is sometimes portrayed as being caused by a gradual loss of homeostasis, e.g. as in a shrinkage of homeodynamic space (Demirovic and Rattan, 2013), leading to a loss of physiologic reserves that give rise to organismal frailty (Campbell and Buchner, 1997; Fried et al., 2001). In terms of disease generally, dyshomeostasis, molecular damage and frailty result from the action of specific primary pathogenic causes, e.g. in AIDS, infection with the HIV virus. By contrast, a correct account of the pathogenesis of aging should involve explicit reference to primary causes. A potential example of such an account is inherited overactivity of mammalian target of rapamycin kinase (Tor) signaling, which promotes fitness in early life but generates pathology later (Blagosklonny, 2006, 2008).

5. Defining anti-aging treatment without reference to aging

Given that the nature of the primary mechanisms of aging remains unclear, conceptualizing anti-aging treatments inevitably requires some sort of hypothetical picture. From listening to discussions between biogerontologists, my impression is that the predominant view is as follows. There exist a limited set of mechanisms fundamental to the entire aging process, mechanisms that lie upstream and apart from the causal cascade of events leading to the bewildering pathological cascade of old age disease. One instance of this way of thinking is that aging reflects inadequate somatic maintenance, causing molecular damage to accumulate which leads to pathology (e.g. Alzheimer's disease). Thus, intervening in aging can protect against the entire spectrum of age-related pathologies (Fig. 1), and improving somatic maintenance sufficiently could stop aging altogether (Kirkwood, 1977).

However, limiting our discussion of anti-aging treatments to what has been demonstrated: the critical observation is that treatments exist which extend lifespan in laboratory animals. In some cases, mainly where increases in lifespan are substantial, it really appears as if aging is slowed down. Striking examples here are effects of dietary restriction on rodents, and the enormous increases in lifespan in the worm *Caenorhabditis elegans*: these clearly involve an increase in youthspan. This strongly implies some sort of retardation of aging. However, in many published studies, increases in lifespan are small, such that it is far from clear that intervention in any central mechanism of aging has been achieved, as opposed e.g. to suppression of a single life limiting pathology.

Arguably, a high priority of translational biogerontology should be to remove the barriers between geroscience and established medical practice. I would argue that central to this is the removal of the distinction between aging and age-related disease. To this end, I will attempt to define *anti-aging treatment* without reference to aging in the sense of Fig. 1 (though I realize this may sound slightly odd, as in John Huston's film *Wise Blood* [1979] where a man founds a ministry called *The Holy Church of Christ Without Christ*). To be precise, aging (i.e. senescence) is here defined as the set of endogenously generated pathologies that increase in later life, some of which contribute to mortality. The following model draws to some extent on Mikhail Blagosklonny's ideas about the origins of age-related disease.

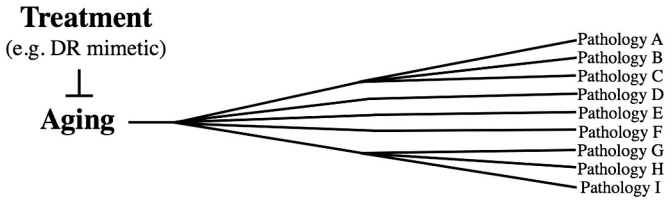

Fig. 1. Schematic representation of a standard conception of how anti-aging treatments operate. Aging, an undefined, non-pathological process gives rise to a wide spectrum of age-related pathologies.

The model: aging is a disease syndrome that gives rise to a wide range of different pathologies. The relationship between these pathologies and lifespan is complex, and involves the following considerations.

i) There is much variation between individuals in terms of which pathologies limit life. One person may die of a stroke in their 50s while otherwise in good health. A second person may die of congestive heart disease in their 80s, who is also suffering from rheumatoid arthritis, breast cancer and dementia. A third person in their 90s who has no gross pathology may die as the result of the lethal combination of effects of numerous subtle pathologies (and not of "pure aging").

ii) Within an aging individual, the pathologies exist in a rank order with respect to which is likely to cause death. Treatment of a life-limiting pathology results in its replacement by a new life-limiting pathology, that which is next in the rank order (Fig. 2A). For example, over the course of the last century, success in treating infectious diseases not only contributed to increased lifespan, but also increased numbers of people suffering from age-related diseases. More recently, drugs to reduce risk of cardiovascular disease are increasingly in use, but the frequency of Alzheimer's disease is increasing, by 38.7% between 2000 and 2010 in the United States (Tejada-Vera, 2013).

iii) In model organisms with extended lifespan, e.g. those with inhibition of growth control pathways, e.g. growth hormone, insulin/IGF-1 signaling (IIS) and target of rapamycin (Tor) signaling, increased lifespan and youthspan represent suppression of a number of life-limiting pathologies. However, these organisms still exhibit aging, just at a later time. This could imply that the entirety of age-related pathologies has been mildly retarded. An alternative explanation is that life-limiting pathologies, high in the rank order with respect to life limitation, have been suppressed and replaced by pathologies of lower rank (Fig. 2B).

iv) The existence of interventions that extend lifespan and youthspan does not necessarily imply the presence of a single underlying mechanism of aging. The role of nutrient-sensitive pathways, such as IIS/Tor, in effecting organism-wide coordination of phenotypic plasticity, potentially explains how a single gene (e.g. Tor) (Tsang et al., 2007) can affect a wide range of different age-related pathologies, and thereby affect lifespan. But this does not in any way mean that the pathologies affected by Tor represent the entirety of the aging process, only those age-related pathologies that limit lifespan.

v) One recent hypothesis about the origins of age-related pathology is that they result from the non-adaptive run-on of developmental and reproductive programs in later life, with cumulative, pathogenic effects (Blagosklonny, 2006). While such run-on (or "quasi-programs") involving growth-promoting mechanisms may limit lifespan, it is very likely that other types of run-on also contribute to aging pathology. Also, of course, other cumulative mechanisms may also contribute to aging, such as accumulation of stochastic molecular damage (Blagosklonny, 2008).

6. What is an anti-aging treatment?

The model proposed here suggests a new meaning of *anti-aging treatment*. This may be illustrated by means of a question that I posed to participants of the Erice meeting. Of the following three types of

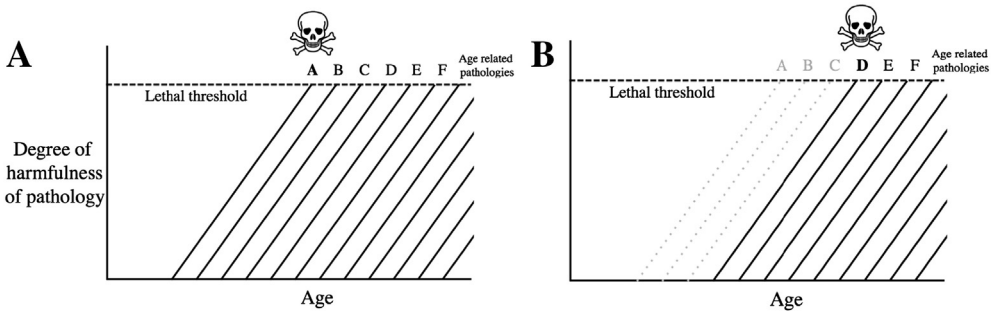

Fig. 2. Hypothetical scheme. Lifespan is limited by pathologies existing in a rank order in terms of which are limiting in terms of lifespan. Each pathology develops with time and the first one reaching a lethal threshold causes death. A) Pathology A limits lifespan. B) A life-extending treatment suppresses pathologies A–C, and extends lifespan. This results in a new life-limiting pathology, D.

intervention aimed at prevention of age-related disease, which constitutes an anti-aging treatment? First, a drug that mimics the effect of dietary restriction, and inhibits aging itself and, thereby, all age-related disease (treatment A in Fig. 3). Second, a treatment that blocks a subset of age-related pathology (treatment B in Fig. 3). Here an example could be the cardiovascular polypill. A decade ago it was estimated that administration to everyone from the age of 55 years of a combination of treatments for cardiovascular disease (or *polypill*) would reduce mortality due to heart disease and strokes by as much 80% (Wald and Law, 2003). Third, a drug that protects against a single age-related disease (treatment C in Fig. 3). For example, prophylactic use of the estrogen receptor inhibitor tamoxifen can reduce the risk of invasive breast cancer by almost 50% (Fisher et al., 1998). (In reality, this is not a practical approach because of side effects of tamoxifen, such as increased risk of endometrial cancer, but it is the principle that matters here.) Among meeting participants there was no clear consensus about whether treatment type B represented an anti-aging treatment, though most agreed that treatment type C was not. However, I will now argue that it would be helpful to view all three types of treatment as anti-aging treatments.

One problem with the claim that only type A treatments are anti-aging is that existing regimens that increase lifespan may well be of type B, or even type C. If it is true that age-related disease results from a wide range of cumulative processes, including diverse quasi-programs, then it is more likely that interventions like dietary restriction and reduced IIS/Tor are of type B. By this view, excess activity of IIS/Tor generates a set of life-limiting pathologies. Upon reduction of IIS/Tor, these pathologies are suppressed and replaced by other lower ranking pathologies (Fig. 2). It also implies a view of aging as a syndrome of syndromes (or multi-syndrome), in which lifespan is commonly limited by an IIS/Tor hyperactivity syndrome.

While the biological basis of aging remains unclear, what is evident is that it manifests as a diverse spectrum of pathologies. Moreover, a particular goal of research on aging is to try to protect against such pathologies. Among biogerontologists there is a clear consensus that what is needed is to introduce into medical practice a preventative approach to protect against late-life disease. Treatment types A, B and C have in common the application of a preventative approach to late-life disease, something which sets them apart from contemporary geriatric medical practice. Other kinds of preventative approaches to medicine have been accepted, e.g. to protect against infection by immunization, and against tooth decay by water fluoridation. However, the use of pharmacological interventions to protect against aging in asymptomatic older people still lies largely beyond the pale. This is illustrated by the marked lack of interest in seemingly such a good idea as the cardiovascular polypill (Boseley, 2008); similarities have been noted previously between difficulties in accepting anti-aging treatments and another type of preventative intervention, the oral contraceptive pill (Lucke et al., 2009).

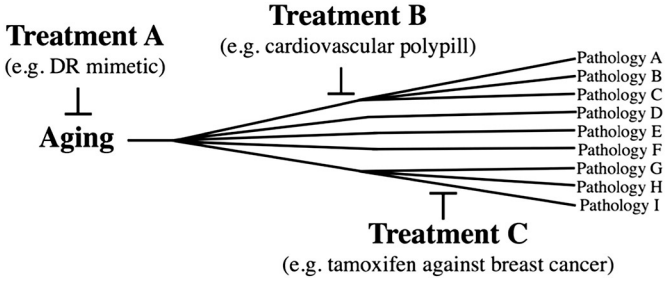

Fig. 3. Treatment A represents the conventional view of an anti-aging treatment. If anti-aging treatments are defined as those involving a preventative approach to age-related disease, then types A, B and C are all anti-aging treatments.

Arguably, a major objective of translational biogerontology should be to establish as medical practice *any* form of preventative approach to age-related disease, however narrow the range of target pathologies. A good definition of *anti-aging treatment* is one that is not only realistic and logical, but also useful, and should therefore include the application of a preventative approach to late-life disease as a defining criterion. Thus, it should encompass treatments of types A, B and C.

In terms of the broader strategy for translation, type C and narrower type B strategies (e.g. the cardiovascular polypill) could represent the thin end of a wedge, helping to establish and then broaden the preventative approach. As discussed informally at the Erice meeting, even the development of preventative approaches to improve late-life health in household pets (Hill, 2009) could help to establish such a practice.

7. Conclusions

The arguments in this essay do not pretend to refute the standard definition of *anti-aging treatment*. However, they do identify weaknesses in it, and the alternative definition proposed is more defensible, in so far as it derives from a more skeptical interpretation of the existing evidence. The central idea presented here is a simple one: that aging is the set of endogenously generated pathologies that increase in later life, and that anti-aging treatments are best defined as those that prevent one or more pathologies of aging. I have argued that this is a more pragmatic definition: one that will help to remove the conceptual barriers between biogerontology and conventional medical practice, and promote the practice of preventative approaches to age-related disease.

Of course, other valid definitions of anti-aging treatment are possible. For example, it could be argued that if aging is just a pathology, then treatment of any age-related pathology, whether preventative or otherwise, is an anti-aging treatment. By this definition, hip-replacement or coronary artery bypass operations are anti-aging treatments. Yet, arguably, the definition proposed here, where “anti” connotes prevention, is a more useful one.

The definition of anti-aging treatment presented here was developed in the context of a symposium about the translation of progress

in biogerontology into human benefits. But the conception of aging which underpins it also defines priorities in biogerontological research itself. If aging is a set of pathologies, some of which cause mortality, the key to understanding aging is to better characterize these pathologies and identify their original causes. A lack of knowledge in this area is a particular problem in invertebrate models such as *C. elegans* and *Drosophila* where even the pathologies that cause death are unknown.

Conflict of interest

The authors have no conflicts of interests.

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References

Berrington de Gonzalez, A., Hartge, P., Cerhan, J.R., Flint, A.J., Hannan, L., MacInnis, R.J., Moore, S.C., Tobias, G.S., Anton-Culver, H., Freeman, L.B., Beeson, W.L., Clipp, S.L., English, D.R., Folsom, A.R., Freedman, D.M., Giles, G., Hakansson, N., Henderson, K.D., Hoffman-Bolton, J., Hoppin, J.A., Koenig, K.L., Lee, I.M., Linet, M.S., Park, Y., Pocobelli, G., Schatzkin, A., Sesso, H.D., Weiderpass, E., Willcox, B.J., Wolk, A., Zeleniuch-Jacquotte, A., Willett, W.C., Thun, M.J., 2010. Body-mass index and mortality among 1.46 million white adults. N. Engl. J. Med. 363, 2211–2219.

Blagosklonny, M.V., 2006. Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition. Cell Cycle 5, 2087–2102.

Blagosklonny, M.V., 2008. Aging: ROS or TOR. Cell Cycle 7, 3344–3354.

Blagosklonny, M.V., 2009. Validation of anti-aging drugs by treating age-related diseases. Aging 1, 281–288.

Blumenthal, H.T., 2003. The aging-disease dichotomy: true or false? J. Gerontol. A Biol. Sci. Med. Sci. 58, 138–145.

Bodkin, N.L., Alexander, T.M., Ortmeyer, H.K., Johnson, E., Hansen, B.C., 2003. Mortality and morbidity in laboratory-maintained rhesus monkeys and effects of long-term dietary restriction. J. Gerontol. A Biol. Sci. Med. Sci. 58, 212–219.

Boorse, C., 1977. Health as a theoretical concept. Philos. Sci. 44, 542–573.

Boseley, S., 2008. Tests start on pill that could lengthen millions of lives. The Guardian.

Butler, R.N., Miller, R.A., Perry, D., Carnes, B.A., Williams, T.F., Cassel, C., Brody, J., Bernard, M.A., Partridge, L., Kirkwood, T., Martin, G.M., Olshansky, S.J., 2008. New model of health promotion and disease prevention for the 21st century. BMJ 337, a399.

Campbell, A.J., Buchner, D.M., 1997. Unstable disability and the fluctuations of frailty. Age Ageing 26, 315–318.

Caplan, A.L., 2005. Death as an unnatural process. Why is it wrong to seek a cure for aging? EMBO Rep. 6, S72–S75 (Spec No).

Colman, R.J., Anderson, R.M., Johnson, S.C., Kastman, E.K., Kosmatka, K.J., Beasley, T.M., Allison, D.B., Cruzen, C., Simmons, H.A., Kemnitz, J.W., Weindruch, R., 2009. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 325, 201–204.

Demirovic, D., Rattan, S.I., 2013. Establishing cellular stress response profiles as biomarkers of homeodynamics, health and hormesis. Exp. Gerontol. 48, 94–98.

Fisher, B., Costantino, J.P., Wickerham, D.L., Redmond, C.K., Kavanah, M., Cronin, W.M., Vogel, V., Robidoux, A., Dimitrov, N., Atkins, J., Daly, M., Wieand, S., Tan-Chiu, E., Ford, L., Wolmark, N., 1998. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J. Natl. Cancer Inst. 90, 1371–1388.

Fontana, L., Meyer, T., Klein, S., Holloszy, J., 2004. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc. Natl. Acad. Sci. U. S. A. 101, 6659–6663.

Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 56, M146–M156.

Gems, D., 2011. Tragedy and delight: the ethics of decelerated ageing. Philos. Trans. R. Soc. 366, 108–112.

Gems, D., Partridge, L., 2013. Genetics of longevity in model organisms: debates and paradigm shifts. Annu. Rev. Physiol. 75, 621–644.

Gruman, G.J., 1966. A history of ideas about the prolongation of life. Trans. Am. Philos. Soc. 56, 1–97.

Halliwell, B., Gutteridge, J.M.C., 2007. Free Radicals in Biology and Medicine, Fourth edition. Oxford University Press, Oxford.

Harman, D., 1956. Aging: a theory based on free radical and radiation chemistry. J. Gerontol. 11, 298–300.

Hill, R.C., 2009. Conference on "Multidisciplinary approaches to nutritional problems". Symposium on "Nutrition and health". Nutritional therapies to improve health: lessons from companion animals. Proc. Nutr. Soc. 68, 98–102.

Kass, L., 1983. The case for mortality. Am. Sch. 52, 173–191.

Kenyon, C., 2010. The genetics of ageing. Nature 464, 504–512.

Kirkwood, T.B.L., 1977. Evolution of ageing. Nature 270, 301–304.

Lucke, J.C., Diedrichs, P.C., Partridge, B., Hall, W.D., 2009. Anticipating the anti-ageing pill. Lessons from the history of the oral contraceptive pill and hormone replacement therapy. EMBO Rep. 10, 108–113.

Mattison, J.A., Roth, G.S., Beasley, T.M., Tilmont, E.M., Handy, A.M., Herbert, R.L., Longo, D.L., Allison, D.B., Young, J.E., Bryant, M., Barnard, D., Ward, W.F., Qi, W., Ingram, D.K., de Cabo, R., 2012. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. Nature 489, 318–321.

Medawar, P.B., 1952. An Unsolved Problem Of Biology. H.K. Lewis, London.

Partridge, L., Barton, N.H., 1993. Optimality, mutation and the evolution of ageing. Nature 362, 305–311.

Perez, V.I., Bokov, A., Van Remmen, H., Mele, J., Ran, Q., Ikeno, Y., Richardson, A., 2009. Is the oxidative stress theory of aging dead? Biochim. Biophys. Acta 1790, 1005–1014.

Tejada-Vera, B., 2013. Mortality from Alzheimer's disease in the United States: data for 2000 and 2010. NCHS Data Brief 1–8.

Tsang, C.K., Qi, H., Liu, L.F., Zheng, X.F., 2007. Targeting mammalian target of rapamycin (mTOR) for health and diseases. Drug Discov. Today 12, 112–124.

Van Raamsdonk, J.M., Hekimi, S., 2010. Reactive oxygen species and aging in *Caenorhabditis elegans*: causal or casual relationship? Antioxid. Redox Signal. 13, 1911–1953.

Wald, N.J., Law, M.R., 2003. A strategy to reduce cardiovascular disease by more than 80%. BMJ 326, 1419.

Williams, G.C., 1957. Pleiotropy, natural selection and the evolution of senescence. Evolution 11, 398–411.