PEGGY
27/12/04

19

Anti-aging Medicine and the Quest for Immortality

S. Jay Olshansky and Bruce A. Carnes
University of Illinois at Chicago, and University of Oklahoma, USA.
Emails: sjayo@uic.edu; bruce-carnes@ouhsc.edu

Introduction

In recent years, there has been an abundance of scientific articles, letters, and editorials published in prominent journals devoted to issues associated with the modern rise of an old concept known as anti-aging medicine.[1–7] The history of efforts to intervene in the aging process dates back thousands of years — an account that has been well chronicled in the scientific literature.[8,9] In fact, it appears that a belief and interest in anti-aging interventions coincides with advances in the medical sciences that embolden those who believe that such interventions are possible.[8] This was the case in the early 20th century as progress was made against infectious diseases, and it is therefore not surprising that entrepreneurs selling anti-aging products have surfaced once again given the combination of recent advances in the biomedical sciences and rapid population aging.

The notion of anti-aging medicine as it is currently promoted and sold at what have come to be known as anti-aging or longevity clinics include a combination of traditional preventive medicine, a battery of tests intended to measure biological age, dietary modification, exercise,

and the introduction of hormones and nutritional supplements. Added to this combination of sound advice and substances thought to have anti-aging properties is a heavy dose of exaggerated claims based on the idea that aging is little more than a disease that is already amenable to modification. The underlying premise is that if physiological parameters that are believed to measure biological age in individuals can be modified through interventions so that they resemble levels present at younger ages, then it is suggested that aging has been reversed and length and quality of life extended.

In spite of numerous claims to the contrary, there is no empirical evidence to support the claim that aging in humans has ever been modified by any means,[6,10] nor is there evidence that it is possible to measure biological age[11] or that so-called anti-aging products extend the duration of life. The General Accounting Office (GAO) concluded that the modern anti-aging industry is not only making false claims to the public about the products they sell and the promises they make, but there are also serious risks of physical and financial harm associated with this industry.[10]

The irony is that in recent years, researchers from a broad range of scientific disciplines have begun to piece together important elements of the puzzle of aging, leading many to argue that it is only a matter of time before interventions are developed that modulate the rate of aging in humans.[12–17] Some scientists contend that the inevitable demographics of a rapidly aging population, combined with an increased life expectancy, warrants a significant increase of financial resources and acceleration of scientific efforts to develop aging interventions.[13,14,16,18] Others suggest that if successful, interventions that modify the biological rate of aging in humans would change the fabric of human society — leading to questions about whether such interventions should be pursued.[19–21]

What is evident now is that the public is being exposed to two competing messages. From the anti-aging industry, they are being led to believe that the secret to the fountain of youth already exists, and that it is currently available through clinicians that have been trained in anti-aging medicine. From scientists who work in the various fields that inform the study of aging, the public is being told that anti-aging medicines do not currently exist, but that researchers are closing in on an understanding of the biological processes that contribute to aging — perhaps leading in the future to an intervention that may slow down the

process.[6]

We contend that one of the best ways for clinicians interested in the health and quality of life of their patients to address these inquiries about anti-aging medicine is to understand the science of aging. In this chapter we provide an overview of the science that underlies current theoretical and empirical developments in the field of aging. Once the science of aging is understood, it will be self-evident why the claims being made by those currently involved in the anti-aging industry are exaggerated or false, and why both clinicians and the general public should be extremely cautious about so-called anti-aging products.

Why do Species Live as Long as They Do?

Why is the average duration of life 1000 days for most strains of mice, 5000 days for beagle dogs, and 29,000 days for humans? Why is the risk of death extraordinarily high at birth for most forms of life, followed by a notable decline in age-specific mortality until puberty, and then an exponential increase from sexual maturity throughout most of the remaining lifespan?

Why are the bodies that carry the immortal genetic instructions — DNA — not themselves immortal? These and other related questions about life, death and the duration of life have not only occupied the minds of the greatest thinkers of every era, but they have led to countless failed efforts to combat aging and forestall death.[8]

One of the more interesting developments in the study of aging and mortality that formed the core of a heated debate among numerous scientists for nearly two centuries was a discovery in 1825 by the British actuary Benjamin Gompertz. He noted that human deaths tend to occur in a predictable age pattern[22] — a seemingly innocuous and now obvious finding that has done nothing less than shape the mathematics of death ever since. Gompertz believed he had discovered a law about the timing of death that was akin to Newton's law of gravity. Gompertz called his equation the "law of mortality." So much attention was paid to Gompertz's law for more than a century that many scientists from a wide range of disciplines devoted their entire research careers attempting to understand why common age patterns of death should exist. Indeed, scientists were so convinced by the biological arguments for a law of mor-

tality that they extended its applicability to all living things — suggesting that just as Newton's law was universal, so too was the law of mortality. Thus began an intensive era of biological and demographic research to understand and quantify the temporal kinetics of senescence.

Ironically, antecedents to a biological understanding of the timing of death and Gompertz's law of mortality existed well before Gompertz was born. Although there is certainly a literature on aging and death that extends as far back as Egyptian times,[8] one of the earliest related ideas was the belief based on the Old Testament that the lifespans of humans and other species are fixed by a supernatural power or by biological laws that apply to all living things. "My spirit will not contend [remain in] man forever, for he is mortal; his days will be a hundred and twenty years" (Genesis 6:3). The famous Italian noble and health "expert" of the 17th century, Luigi Cornaro, in a now classic statement on this topic, suggested that "even the weakest people had enough 'vital principle' to live for 100 years, and those endowed with a stronger constitution could live to the biblical maximum of 120 years".[23]

One of the more interesting theories about the timing of death was devised by the influential 18th century zoologist, Georges Buffon.[24] Buffon suggested that every person has the same allotment of time from birth to death, and that the duration of life depends not on our habits, customs, or quality of food, but rather on **physical laws** [our emphasis] that regulate the number of our years. This belief was based on his observation that species possessed a suite of fixed biological attributes (e.g. gestation period, age patterns of growth, constant physical form). If all biological phenomenon conform to fixed laws like those governing the timing of gestation and sexual maturity, Buffon reasoned, then duration of life must also be fixed. Buffon's interest in lifespan was based on an extensive database of life history characteristics that he collected for a variety of species (e.g. dogs, cats, rabbits, humans, etc.). Based on these data, Buffon reasoned that a species' lifespan was a product of interconnected chains of functional relationships between biological attributes. He envisioned a fixed duration of gestation giving rise to a fixed duration of growth, which in turn, leads to a fixed duration of life. These data supported his hypothesis that the average lifespan of individuals within a population (i.e. life expectancy) should be proportional to the amount of time that is allocated to growth and development. Specifically, Buffon

discovered that life expectancy was consistently six to seven times greater than the time required to reach puberty. As you will see from the evolutionary theory of senescence discussed below, Buffon's observation was prophetic, although he made the common mistake of his time in assuming, much like Luigi Cornaro, that everyone had the potential to live the same length of time. In other words, the early thinkers in this area predicted that a fixed biologically-based limit to life existed and applied equally to everyone, while Gompertz discovered, to the contrary, that there is an age pattern of death suggesting that not everyone shares the same chance of living to older ages.

The Evolutionary Model of Senescence

In order to understand why species live as long as they do, it is important to recognize and appreciate the evolutionary theory of senescence. At the heart of this theory is a fundamental biological link between the timing of reproduction and death. According to evolution theory, the force of natural selection begins to decline rapidly once reproduction commences at puberty, approaching negligible levels at the end of the reproductive window (at menopause).[25] What is meant by "the force of natural selection" is the ability of selection to influence the distribution and frequency of alleles in subsequent generations.

According to Medawar,[26] natural selection operates not just on individuals, but also on all of the genes in our bodies. As the force of selection wanes following the onset of puberty, it then becomes possible for harmful alleles to accumulate in the gene pool because under normal living conditions, there is no penalty for detriments to health occurring in older regions of the lifespan where only a few members of the species normally survive.[26–29] Thus, genes that prove to be harmful and which may be associated with aging are figuratively "pushed" by natural selection to later and later ages, where they have less of an effect on reproduction. Over many generations, harmful alleles will tend to have their age of expression accumulate at or near the end of the reproductive window and beyond. Williams[29] later extended this theory by suggesting that natural selection would favor the accumulation of genes that do beneficial things early in life, even if they are known to be harmful later in life. This concept, known as antagonistic pleiotropy, operates under the same premise that

there would normally be no penalty for favoring genes with harmful effects expressed later in life, as long as they enhance reproductive fitness.

Why does aging or senescence occur then? Using the poetic words of Medawar, aging is revealed "only by the most unnatural experiment of prolonging an animal's life by sheltering it from the hazards of its ordinary existence". In other words, aging becomes evident only when survival is extended into the post-reproductive region of the lifespan — as is now the case for most people living in low mortality populations.

Empirical tests of these hypotheses have shown that the age trajectory of death is, in fact, a species-specific phenomenon that, as predicted from evolution theory, is calibrated to the onset and length of a species' reproductive window.[30,31] This means that sea turtles, whales, elephants and humans — species that experience an extended period of growth and development, a significant delay in puberty, and a longer time window within which reproduction can occur — live longer than species that reproduce early and for shorter time periods.

It is important to remember that the reproductive window is a genetically determined and fixed attribute that is established as part of every species' life history strategy that was molded by the environment within which species evolved. Thus, all modern evolutionary theories of senescence rely on the premise that selection is blind to the consequences of gene expression in the post-reproductive period of the lifespan. This premise has numerous implications for aging, health, and longevity. First among these is that aging and death genes or programs cannot arise from the direct action of natural selection. Instead, senescent-related diseases and disorders arise from the unintended degradation of processes that are essential to achieving reproductive success (e.g. growth, development, maturation, maintenance, and repair), but whose continued fidelity of function could not be maintained by an evolutionary process indifferent to post-reproductive survival. The good news in this message is that in the absence of a genetic program for aging, its manifestations (e.g. many of the physiological parameters that change with the passage of time and which cause both frailty and death) are inherently modifiable. This is why exercise, diet and some pharmaceuticals have been used successfully to modulate both physical and physiological attributes of our bodies.

The evolutionary view of senescence also implies that aging is not an unnatural disease. This is in direct contrast to the proponents of

anti-aging medicine who claim that aging is itself a disease, and that returning physiological parameters of the body back to levels present at younger ages implies that aging has been reversed and that people can actually grow younger.[32] The biological reality is that aging is a natural and inevitable byproduct of survival extended into the post-reproductive period of the lifespan. This also implies that bodies are not designed for indefinite survival.[33] The biological warranty period implied by the certitude of death has important implications for limits on the lifespan of individuals and the life expectancy of populations.[34]

The reality of what is being demonstrated at anti-aging clinics is a fact about human physiology that has been known for thousands of years. It has always been possible to modify and improve human physiology and physical well-being at any age through diet, exercise, and more recently by pharmaceuticals. The proponents of anti-aging medicine confuse the plasticity of physiology with the manifestations of aging. Further, the tenets of evolutionary biology suggest that it is not possible to influence or measure an aging process that does not exist. Thus, while the mainstays of the anti-aging industry (exercise, diet, hormones and antioxidants) cannot make anyone grow younger, there is abundant scientific evidence showing that physical fitness can be improved at any age with dramatic improvements in quality of life as a beneficial byproduct.

Projecting Life Expectancy Using Mathematical Models

Although demographers study populations, the results of their work are often used to make inferences about limits on the lifespan of individuals. The basic logic is that if there is a limit to the life expectancy of a population, then limits must also exist for the lifespans of the individuals who make up that population. Some researchers have argued that if low mortality populations are approaching a limit to life expectancy as claimed by some biodemographers,[30,35,36] then the approach to these limits should be reflected in the behavior of vital statistics. For example, populations approaching a limit should be characterized by a stagnation in the age trend of the oldest prevalent individual.[37] Critics of limit hypotheses also argue that limits imply that there must be an age beyond which there can be no survivors. Documented violations of both of these conditions have

led some demographers to conclude that limits on human life expectancy either do not exist or are not yet in sight.[37,38]

Critics of a purely mathematical approach to the study of human lifespan suggest that the validity of limit hypotheses cannot be ascertained without considering biological evidence on senescence.[34] Duration of life is an outcome variable for scientists in the demographic/actuarial sciences. However, from a biological perspective, duration of life is the product of a multidimensional process involving biological, behavioral, environmental, and random forces.[39,40] As such, there is no defensible basis for the claim, based on purely mathematical models of mortality, that there are no biological or demographic reasons why death rates cannot decline to zero[41] and that life expectancy at birth can rise to 100 years or more.[38]

The regularity of the rise in human life expectancy during the 20th century perceived by the advocates of mathematical extrapolation has led them to predict dramatic increases in life expectancy in this century.[38] However, the unprecedented life expectancy gains achieved during the 20th century occurred primarily because of dramatic reductions in death rates among the young. Duplicating these gains in low mortality populations by the same means is no longer possible because the lives of children can only be saved once. The advocates of mathematical extrapolation also ignore the biomedical significance of the profound shift that has occurred in underlying causes of death (Olshansky SJ, Carnes BA and Siegel JS, manuscript under review). Historically, infectious and parasitic diseases (extrinsic mortality) caused the vast majority of deaths in humans. Heart disease, cancer, stroke and diabetes (intrinsic mortality) dominate the mortality schedule today. Biologically, there is no reason to expect that these two fundamentally different categories of death should or would adhere to the same mortality trend.

Contrary to the perception of those advocating extrapolation methods for projecting life expectancy, the time-frame from the past that has been used to predict the future is anything but representative of the historical mortality experience of humans. The quantum leap in life expectancy achieved over the last 100 years is an unprecedented anomaly in a human history better characterized by fluctuating,[42] stagnating, or slowly rising life expectancy.[43] Because the future course of mortality cannot possibly mimic such an episodic anomaly (characterized by

declining early age mortality), this unusual time frame should not be used as the basis for predicting the future course of human life expectancy. The public policy implications and practical importance of this recommendation are evident: 1) it is essential that government agencies responsible for assessing the future solvency of their age-based programs incorporate biological reasoning into their long-term forecasts; and 2) claims made by advocates of anti-aging medicine that the duration of human life can now be extended dramatically based on existing technology, are false.

Death is a biological phenomenon of individuals, not a mathematical property of populations, and the biological evidence is undeniable. The pathology burden within individuals clearly exhibits an age dependence.[34] Cancer and cardiovascular disease are symptoms of a complex underlying age-related pathogenesis that causes cells to lose functionality; a functionality that is necessary for the health and well-being of the individual. The molecular repair processes that maintain the functional integrity of cells also degrade over time. Managing the symptoms of age-related disease (geriatric medicine) is not the same as intervening in the underlying processes (biogerontology) that give rise to these manifestations.[20] Although evolution does not and cannot produce genetic programs for aging or death, forces of deterioration that exist at virtually all levels of biological organization (e.g. molecules, cells, tissues, organs) lead to the undeniable conclusion that there is a limit (expiration date) to how long (warranty period) an individual can live. Since every member of a population is operating under their own unique warranty period, then it is equally impossible to deny that limits also exist for the life expectancy of populations.

Aging and death are predictable byproducts of stable reproductive biologies that evolved under environments far less conducive to survival than those experienced today. Although it is likely that anticipated advances in biomedical technology and lifestyle modification will permit life expectancy to continue its slow rise over the short-term, a repetition of the large and rapid gains in life expectancy observed during the 20th century is extremely unlikely. Such gains would require an ability to slow the rate of aging[3,16] — a technological capability that does not exist today, and even if it did, would require implementation on a broad scale in order to have a measurable impact on the vital statistics of a population.[6]

As such, mathematical models that assume the future course of life expectancy over the long-term will continue the trend observed during the 20th century are likely to fail because they ignore the underlying biology that influences duration of life. Further, the predictions of extreme longevity (life expectancy of 100 years or more) produced by these models are not supported by the biological evidence.

The image of a biological warranty period for the duration of life has been used here to capture a universal and undeniable biological reality — indefinite survival is not possible, and the duration of life would remain limited by biological constraints even if every cause of premature death could be eliminated.

Conclusions

At its core, the fundamental biological explanation for why individuals senesce — the basic question asked by Gompertz in 1825 about the age pattern of death he observed for humans — is predicated on the importance of natural selection and its declining effectiveness relative to the timing and distribution of reproduction (including a period of grandparenting) within the lifespan of organisms. Applying these principles of evolutionary biology in order to explain age patterns of death among and between sexually reproducing species has come to be known as the biodemography of aging — a concept with historical roots in the search for a law of mortality,[45–50] and contemporary interdisciplinary research on aging.[30,51–53] Although a vast number of genetically-based biological processes that exist within organisms to sustain life and maintain functional integrity have been identified and characterized, senescence is not among them. A genetic program for aging is not required for animals to age, just as there is no program for aging required for man-made machines to experience degradation with time.[16,20]

Although unknown to Buffon in the 18th century and Gompertz in the 19th century, it is the underlying and invisible action of genes that control and establish the predictability and temporal regularity of growth, development, reproduction, and physical form that led to their speculations on a fixed lifespan. After all, it does appear on the surface that lifespan is genetically programmed because species tend to live for prescribed durations of time. As it turns out, natural selection favored

these life history traits and biological clocks as ways to ensure that genes are passed on through time.[55] These biological phenomena were molded by the environments in which they arose. Their specific forms and functions were not actively designed in the same way that an engineer would draw the plans for creating a machine and then constructing it. Instead, the biological attributes of individuals that influence duration of life are the product of a directionless and ongoing competition among preexisting genetic variants (alleles) whose "victors" are determined by their ability to propagate themselves.

Most of the rise in human life expectancy has come from saving children from infectious and parasitic diseases, and by reducing mortality in women during childbirth. These gains in life expectancy cannot be repeated in developed countries today because the reservoir of potential person-years associated with further declines in these causes of death has been nearly exhausted. Future gains in life expectancy will have to come from saving the lives of older people through the development and use of interventions that alter the fundamental processes of aging. Although not impossible, there are no interventions in existence today that have been demonstrated to modulate the rate of aging.[6] As such, if another quantum leap in human life expectancy is going to occur among today's population, future trends in mortality will have to be fundamentally different from those observed in the past.

Although Buffon and Gompertz lacked access to knowledge about evolution, Buffon's intuition that senescence and species-specific duration of life is related to a fixed period of growth and development, and Gompertz's prediction of a biological basis for a law of mortality, can now both be supported by evolutionary theory and biological evidence.[34] This, in turn, establishes effective constraints on how long individuals can live and how high life expectancy and maximum lifespan can practically rise. Today, aging and death are viewed as the inadvertent but inevitable byproduct of the degradation of biological structures and processes that evolved for growth, development and reproduction rather than extended operation. These structural and functional constraints exist at every level of biological organization (cells, tissues, organs and organ systems) within an individual, and it is their existence that imposes practical (i.e. probabilistic) limits on the lifespan of individuals and the life expectancy of populations.

Given what is known about the biology of aging, the evolutionary theory of senescence, consistent age patterns of death observed across species, and biodemographic and biomechanical constraints on the duration of life, what messages can clinicians convey to their patients when they come calling for therapies to forestall aging? The answer is simple. The biological process of aging cannot as yet be measured; there is no scientific evidence to support the claim that aging can be modified by any means; it is not currently possible to grow younger; there is no known intervention that has been demonstrated to extend the duration of life of humans; nutritional supplements (in particular antioxidants) may in some cases reduce the risk of disease, but they have no demonstrated affect on aging; and hormone supplements should not be administered except in unusual cases of demonstrated clinical hormonal deficiency. The best approaches available for dealing with the manifestations of aging include a dietary regimen based on moderation, lower caloric intake to reduce body fat, regular exercise, and the avoidance of behaviors that increase the risk of diseases and disorders — such as smoking, excessive alcohol consumption, excessive exposure to sun, and obesity. Although scientists are optimistic that interventions will someday be developed to forestall the aging process, such interventions do not currently exist.

Acknowledgments

Funding for this work was provided by the National Institute on Aging (Grant Nos. AG-00894-01 and AG13698-01). Elements of this manuscript have been published in Olshansky SJ (2003) From Michelangelo to Darwin: The Evolution of Human Longevity. *Israel Medical Association Journal* **52**: 316–316; and Carnes BA, Olshansky SJ, Grahn D (2003) Biological Evidence for Limits to the Duration of Life. *Biogerontology* **4**: 31–45.

References

1. Butler RN, Fossel M, Harman SM *et al.* (2002) Is there an antiaging medicine? *J Gerontol A Biol Sci Med Sci* **57**: B333–338.
2. Binstock R (2003) The War on Anti-Aging Medicine. *The Gerontologist* **43**: 4–14.

Serene: Pls check style for these references cap here OK or set lower case? Pls check thruout Refs 1-55

3. de Grey AD, Gavrilov L, Olshansky SJ, Coles LS, Cutler RG, Fossel M, Harman SM (2002a) Antiaging technology and pseudoscience. *Science* **296**: 656.
4. Fisher A, Morley JE (2002) Editorial: Antiaging medicine: the good, the bad, and the ugly. *J Gerontol Med Sci* **57**: M636–639.
5. International Longevity Center. (2002) *Workshop Report, Is There an Antiaging Medicine?* Canyon Ranch Series; New York.
6. Olshansky SJ, Hayflick L, Carnes BA, *et al.* (2002) Position Statement on Human Aging. Scientific American (June), http://www.sciam.com/explorations/2002/051302aging/html. Also published in *J Gerontol Biol Sci* **57A**: B1–B6.
7. Wick G (2002) 'Anti-aging' medicine: does it exist? A critical discussion of 'anti-aging health products'. *Exp Gerontol* **37**: 1137–1140.
8. Gruman GJ (1966) A history of ideas about the prolongation of life. *Transactions of the American Philosophical Society* **56**: 1–102.
9. Olshansky SJ, Carnes BA (2001) *The Quest for Immortality: Science at the Frontiers of Aging.* Norton Press, New York.
10. General Accounting Office. (2001) *Antiaging Products Pose Potential for Physical and Economic Harm.* Special Committee on Aging, GAO-01-1129.
11. Butler R, Sprott R, Warner H, *et al* (2004) Biomarkers of Aging: From Primitive Organisms to Man. *J Gerontol Biol Sci* (in press).
12. Arking R (2004) Extending Human Longevity: A Biological Probability. In: Post SG, Binstock R (eds.) *The Fountain of Youth* pp. 177–200. Oxford University Press.
13. de Grey ADNJ, Baynes JW, Berd D, Heward CB, Pawelec G, Stock G (2002b) Is human aging still mysterious enough to be left only to scientists? *Bioessays* **24**: 667–676.
14. de Grey ADNJ, Ames BN, Andersen JK, Bartke A, Campisi J, Heward CB, McCarter RJM, Stock G (2002c) Time to talk SENS: critiquing the immutability of human aging. *Annals NY Acad Sci* **959**: 452–462.
15. Guarente L (2003) *Ageless Quest.* Cold Spring Harbor Laboratory Press.
16. Miller R (2002) Extending Life: Scientific Prospects and Political Obstacles. *Milbank Quart* **80**: 155–174.
17. Rattan S (2004) Aging intervention, prevention and therapy through hormesis. *J Gerontol Biol Sci* (in press).
18. Butler RN, Warner HR, Williams TF, *et al.* (2004) The aging factor in health and disease: The promise of basic research on aging. *Aging Clin Exp Res* **16**: 104–112.
19. Kass L (2001) L'Chaim and its limits: why not immortality? *First Things* **113**: 17–24.
20. Hayflick L (2000). The Future of Ageing. *Nature* **408**: 267–270.
21. Stock G, Callahan D (2004) Would doubling the human lifespan be a net positive or negative for us either as individuals or as a society? *J Gerontol Biol Sci* (in press).
22. Gompertz B (1825) On the Nature of the Function Expressive of the Law of Human Mortality and on a New Mode of Determining Life Contingencies. *Philosophical Transactions of the Royal Society of London* **115**: 513–85.
23. Cornaro L (1634) Discourses on the Temperate Life. In: Butler W (ed.) *The Art of Living Long.*
24. Buffon GLL (1747) *Histoire Naturelle Générale et Particuli* 're.
25. Charlesworth B (1994) *Evolution in Age-Structured Populations*, 2nd Edition. Cambridge University Press, New York.

26. Medawar PB (1952) *An Unsolved Problem of Biology*. Lewis, London.
27. Hamilton WD (1966) The Moulding of Senescence by Natural Selection. *J Theor Biol* **12**: 12–45.
28. Kirkwood TBL (1977) Evolution of Aging. *Nature* **270**: 301–304.
29. Williams GC (1957) Pleiotropy, Natural Selection, and the Evolution of Senescence. *Evolution* **11**: 298–311.
30. Carnes BA, Olshansky SJ, Grahn D (1996) Continuing the Search for a Law of Mortality. *Popul Dev Rev* **22**: 231–264.
31. Rose MR (1984) Laboratory evolution of postponed senescence in *Drosophila melanogaster*. *Evolution* **38**: 1004–1010.
32. Roizen M (1999) *RealAge: Are you as young as you can be?* Cliff Street Books New York.
33. Olshansky SJ, Carnes BA, Butler R (2003) If Humans Were Built to Last. *Scientific American* Special Issue on Evolution, May.
34. Carnes BA, Olshansky SJ, Grahn D (2003) Biological evidence for limits to the duration of life. *Biogerontology* **4**: 31–45.
35. Olshansky SJ, Carnes BA, Cassel C (1990) In Search of Methuselah: Estimating the Upper Limits to Human Longevity. *Science* **250**:634–640.
36. Olshansky SJ, Carnes BA, Désesquelles A (2001) Prospects for Human Longevity. *Science* **291**: 1491–1492.
37. Wilmoth JR (1997) In Search of Limits. In: *Between Zeus and the Salmon: The Biodemography of Longevity*, pp. 38–64. National Academy Press, Washington, D.C.
38. Oeppen J, Vaupel J (2002) Broken limits to life expectancy. *Science* **296**: 1029–1031.
39. Carnes BA, Olshansky SJ (2001) Heterogeneity and its Biodemographic Implications for Longevity and Mortality. *Exp Gerontol* **36**: 419–430.
40. Finch CE, Kirkwood TBL (2000) *Chance, Development, and Aging*. Oxford University Press Oxford.
41. Wilmoth J (2001) How long can we live? Science dEbate 2001; http://www.sciencemag.org/cgi/eletters/291/5508/1491.
42. Olshansky SJ, Carnes BA (1996) Prospects for Extended Survival: A Critical Review of the Biological Evidence. In Caselli G, Lopez A (eds.) *Health and Mortality Among Elderly Populations* pp. 39–58 Oxford, Clarendon Press.
43. McNeill WH (1976) *Plagues and Peoples*. Anchor, Garden City.
44. Brody S (1924). The Kinetics of Senescence. *J General Physiol* **6**: 245–257.
45. Brownlee J (1919) Notes on the Biology of a Life-Table. *Royal Statistical Soc* **82**: 34–77.
46. Deevey ES Jr (1947) Life Tables for Natural Populations of Animals. *Q Rev Biol* **22**: 283–314.
47. Greenwood M (1928) Laws of Mortality from the Biological Point of View. *J Hyg* **28**: 267–294.
48. Loeb J, Northrop JH (1916) Is There a Temperature Coefficient for the Duration of Life? *Proc Natl Acad Sci USA* **2**: 456–57.
49. Pearl R, Miner JR (1935) Experimental studies on the duration of life. XIV. The comparative mortality of certain lower organisms. *Q Rev Biol* **10**: 60–79.
50. Pearl R 1921.

51. Carnes BA, Olshansky SJ (1993) Evolutionary Perspectives on Human Senescence. *Pop Dev Rev* **19**: 793–806.
52. Olshansky SJ, Carnes BA (1994) Demographic Perspectives on Human Senescence. *Pop Dev Rev* **20**: 57–80.
53. Olshansky SJ, Carnes BA, Grahn D (1998) Confronting the boundaries of human longevity. *Am Sci* **86**: 52–61.
54. Wachter KW, Finch CE (eds.) (1997) *Between Zeus and the Salmon: The Biodemography of Longevity*. National Academy Press, Washington, D.C.
55. Dawkins R (1992) *The Blind Watchmaker: Why the Evidence of Evolution Reveals a Universe Without Design*, W.W. Norton, New York.