Medawar Revisited: Unresolved Issues in Research on Ageing

Bruce A. Carnes, University of Oklahoma Health Sciences Center

Yuri R. Nakasato, University of Oklahoma Health Sciences Center and

S. Jay Olshansky, University of Illinois at Chicago

Abstract

Ageing is a subject that can be and has been studied from an almost endless number of perspectives. For example, theories on the causes of ageing exist at levels of biological organization ranging from the molecular to the population, and the scientific literature is replete with debates on the relative validity and merits of these theories. The breadth of biological involvement described by these competing theories shows that ageing affects almost every aspect of living matter. As a result, ageing is easy to observe but almost impossible to define precisely or measure operationally. Although much has been learned about ageing since Medawar referred to it as 'an unsolved problem in biology,' many important issues and questions remain unresolved.

The divergence of opinion caused by incomplete knowledge is especially evident in the field of ageing because it is informed by numerous and diverse disciplines. A lack of consensus on fundamental issues creates an environment of unavoidable uncertainty. For example, scientists disagree over whether there is a distinction between ageing and disease (Holliday, 1995; Hayflick, 2000; Evans, 2002; Blumenthal, 2003), whether ageing is an underlying cause of death (Kohn, 1982; John & Koelmeyer, 2001; Hayflick, 2003), and even when ageing begins (Hayflick, 1994; Carnes and Olshansky, 1997; Dolejs, 1997). These issues are not new, they remain unresolved, and they have important implications. For example, if disease and ageing are unrelated processes, then the medical treatment of disease (and its complications) will have no impact on the processes responsible for ageing. As such, disease interventions (e.g., dialysis, by-pass surgery, chemotherapy) may eventually augment the burden of age-determined morbidity by converting lethal diseases to chronic diseases. Further, by delaying death, these interventions provide more time for additional age-related pathologies to emerge (Olshansky *et al*, 1998; Wilson, 2004). This likely consequence of successful disease management raises another important and unresolved issue. Namely, has the success of the medical approach to health care produced longer life at the expense of worsening health (Olshansky *et al*, 1991)?

There is a clear divergence of opinion on whether people are achieving both longer and healthier lives. Although not universally accepted (Olshansky et al, 1991; Wilson, 2004), the compression of morbidity hypothesis (Fries, 1980) remains a popular conceptual goal (Robine and Michel, 2004). Despite concerns (Strawbridge *et al*, 2002), the concepts of successful ageing (Rowe and Kahn, 1987; Kahn 2002) or healthy ageing have become standard components of medical training, thinking and practice. Analyses of more recent U.S. trends in disability suggest that longer life has been accompanied by an expanded period of health (Manton, 1997; Crimmins *et al*, 1997; Schoeni *et al*, 2001). These trends, however, can be deceptive. For example, better medical care can improve longevity and diminish the severity of disease conditions at the same time that the prevalence of these diseases is increasing (Manton, 1982). In other words, morbidity can expand in a global sense (overall morbidity) while appearing to compress in a specific sense (e.g., prevalence of severe disability), and there are studies that suggest this may be happening in low mortality populations (van de Water *et al*, 1995; Robine and Michel, 2004; Albert, 2004).

Further, disability is not the same as frailty and trends for one of these health states need not be predictive of the other (Fried *et al*, 2001, 2004). Frailty should have linkages to pathology and it is known that the pathology burden increases with age and is distributed across all organ systems (Carnes *et al*, 2003). Linkages should also exist between prescriptions for medications and the underlying conditions that contribute to morbidity (frailty, disability and comorbidity). For example, 20% of Medicare beneficiaries are reported to have 5 or more chronic conditions, and 50% of these beneficiaries are taking 5 or more medications (Tinetti & Fried, 2004). A typical 75 year old takes 15 medications per day (Tinetti *et al*, 2004), presumably to alleviate symptoms for 3 to 5 of the most common chronic conditions observed in older individuals (arthritis, hypertension, hearing impairment, cataracts, chronic sinusitis, COPD, ischemic heart disease, varicose veins, orthopedic impairments of back, diabetes, arteriosclerosis and visual impairments – Albert, 2004). Despite being the epitome of successful survival, the majority of centenarians are also coping with multiple conditions that produce severe disability and frailty (Forette, 1997). Thus, for every Kozo Haraguchi, the 95 year old Japanese man who recently set a world record in the 100 meter dash for his age group (22.04 seconds), the majority of the aged will experience significant declines in both health and physical

function (Dovenmuehle, *et al*, 1970). Successful ageing may have more to do with successfully coping with the age-determined decrements of health and function than avoiding them (Gillick, 2001).

Population level analyses of ageing and disease are a two-edged sword. Statistics cannot be calculated for a sample size of one. However, it is only through the study of populations that it becomes possible to identify the major causes of mortality and morbidity and estimate the age-specific risks of experiencing them. Statistics are typically expressed as average values and individuals rarely exhibit the attributes implied by these population averages (Carnes and Olshansky, 2001). Consequently, the health reality of individuals is sacrificed for the probabilistic clarity of statistics, and pronounced differences of interpretation can arise from these two perspectives. Nowhere is this more evident than the debates over how long humans can live and how high the life expectancy of human populations can climb (Carnes *et al*, 2003).

There is no debate about whether life expectancy has increased and how the increase was achieved in the past. Life expectancy at birth in the United States (U.S.) was around 20 years at the time of the Declaration of Independence. By 1900, it had climbed to 48 years for females and 46 years for males, and according to the Centers for Disease Control (CDC) these figures have now reached 80.1 for women and 74.8 for men. Other developed countries have experienced similar increases in life expectancy over this same brief span of time. Invariably, the longevity gains can be attributed to saving children from infectious disease deaths and reducing maternal mortality (Olshansky *et al*, 1993).

As life expectancy has climbed there has also been a dramatic shift in cause of death from infectious diseases that are imposed on individuals to degenerative diseases that are linked to the fundamental biology of individuals (Carnes *et al*, 1996). Even the latter source of mortality appears to be yielding to advances of modern medicine. For example, although heart disease and cancer accounted for 51% of U.S. deaths in 2003, the CDC reports that the number of deaths attributed to these causes declined from their 2002 levels by 3.6% and 2.2%, respectively. Some demographers predict the impressive decline in death rates at virtually every age that has occurred over the last century will continue throughout the 21st century (Wilmoth, 2000). For example, life expectancy at birth in the U.S. and other developed nations is predicted to reach 100 years by the year 2060 (Oeppen and Vaupel, 2002). A still impressive but more cautious timeline has been offered by the United Nations; it predicts a 100 year life expectancy will be attained by both sexes in most countries by the year 2300 (UN, 2004). Life expectancy gains of this magnitude require reductions in death rates of at least 80% at every age, or to express it differently, mortality reductions greater than those needed for the hypothetical elimination of all deaths from cardiovascular disease, diabetes and cancer (Olshansky *et al*, 1990). Although these predictions represent the prevailing view of some actuarial modelers, there seems to be a disconnect between these mathematical predictions and biological expectations.

Neither the present nor the recent past provides an appropriate temporal window for thinking about the biology of ageing and longevity for humans or any other species (Carnes, 2004). If the evolutionary biologists (e.g., Kirkwood and Holliday, 1979) are correct, then we must go back to the time of the origin of species in order to develop expectations for the biological phenomena that influence ageing and duration of life. Recent research has placed the origin of anatomically modern humans at approximately 195,000 years ago (McDougall *et al*, 2005). A common theme runs through the evolutionary theories of ageing (see Carnes *et al*, 1993 for an overview). In condensed form, the logic goes like this. The hostile environments of the natural world made (and continue to make) indefinite survival impossible for organisms, and life's solution to the inevitability of death was to make genetic information immortal rather than the bodies that carry it (Dawkins, 1976). This, in turn, created a race between reproduction and death because delayed reproduction increases the risk of no reproduction, and no reproduction is the ultimate evolutionary failure. The legacy of the strategies that evolved to run this reproductive race can be seen in the species-specific rates that exist for the carefully orchestrated processes of growth and development that were needed to attain sexual maturity in the hostile (high mortality) environments of the past. Once sexual maturity is attained, the duration of the reproductive period is determined by the temporal dynamics of a reproductive biology that was also calibrated to the mortality risks of historical environments, as well as the mortality risks imposed by the contemporary environment. The various theories of ageing (e.g., mutation accumulation, antagonist pleiotropy, disposable soma) then arise from the hypothesized biological consequences of natural selection as its age-specific effectiveness progressively diminishes to insignificance. For humans, this evolutionary scenario has resulted in the attainment of sexual maturity by around 13-15 years, the effective end of reproduction somewhere between 35 to 40, and menopause (or its equivalent for the usual situation of males bonded to females of similar age) around 50 years (Carnes *et al*, 2003). Thus, our human ancestors could have been grandparents many times over by the age of 50.

This timeline for the human life course raises some conceptually troublesome issues. According to the species concept, we are, despite the acquired polymorphisms, the same *Homo sapiens* as our ancient ancestors. Further, if the disposable soma theory is correct (Kirkwood and Holliday, 1979), organisms will invest in reproduction rather than longevity enhancing processes in environments where extended longevity is an improbable outcome. Hamilton's (1966) seminal work on inclusive fitness and the subsequent validation of that concept might push the age for human grandparenting out to the 60s. Evolutionary

fitness, however (whether direct or inclusive), diminishes as the number of individuals attaining progressively higher ages diminishes because their cumulative contribution to the gene pool will be small. Thus, it is difficult to make credible evolutionary arguments about the benefit of great-great grand parenting and beyond. So, while it was biologically possible for our ancestors to survive to the ages we see today, it was not probable. From this perspective and coupled with the earlier discussions of age-related disability, frailty and pathology burden, it is hard to understand why humans are surviving in large numbers to age 80. It is even harder to fathom why human bodies would be designed to permit life expectancies greater than 100 to be achievable.

Of course, like off-road vehicles, humans may have had to be built tough to function 50 or 60 years in hostile environments without the benefit of anything more than rudimentary technology. The many redundancies that we see throughout the human body are consistent with this 'build them tough for wear and tear' view of longevity. If bodies are like appliances and other man-made products, then the built-in redundancy of biological systems is part of what defines an expected operation time or warranty period. From an evolutionary perspective, this warranty period ought to be calibrated to aspects of reproduction like the onset, duration and/or effective end of reproduction.

In the real world, organisms die from extrinsic causes that terminate life abruptly and have little or nothing to do with the physiological/biological state of the organism shortly prior to the lethal encounter. As such, observed life spans are shorter than potential life spans (Olshansky *et al*, 2002a). A better estimate of potential life span can be achieved by 'censoring' out (in the statistical sense) the 'extrinsic' deaths. When that is done, the quantitative relationship (i.e., regression) between a typical life span (median age of intrinsic death) and the effective end of reproduction for humans adheres to the same equation that describes this relationship for laboratory mice (Carnes *et al*, 2003). This implies that humans are not unusual in regards to their relative longevity. The predicted value for a median age of survival for humans comes out to be somewhere between 85 and 90 years (Carnes *et al*, 2003). This is the median age that could be attained if all accidental (extrinsic) deaths could be eliminated. Further, the laboratory animals used in our research were well taken care of but they received no special medical attention. Thus, the predicted value for humans is predicated on the absence of medical intervention. These findings, therefore, suggest that further improvement in human survival (i.e., reductions in death rates, increases in life expectancy) is possible even in places like Okinawa that hold the record for the highest life expectancies (Todoriki *et al*, 2004).

Achieving life expectancies (or median survival times) of 85 to 90 requires the creation of a perfect world (whatever that is) for virtually everyone in a population. Achieving the predictions made by the forecasters of extreme longevity (Oeppen & Vaupel, 2002) requires more than this. In order for 100 years to become the average survival age, the majority of people in the population will have to survive beyond their inherent life span potential (biological warranty period). This extended survival already occurs when biomedical interventions manufacture survival time for people who would otherwise have died at a younger age from a health crisis linked to their intrinsic biology (Olshansky *et al*, 1998).

It is conceptually useful to distinguish manufactured survival time and interventions for ageing from the survival benefits of behavior and lifestyle modifications (Paffenbarger *et al*, 1993). Poor health decisions (excessive use of alcohol, taking drugs and smoking) clearly cause people to die before they achieve their life span potential, and good health decisions (e.g., eating right, eating less and exercising more) are required to increase the odds of achieving their potential. However, achieving your potential life span is not the same as surpassing it. Medical interventions can help overcome the life-shortening consequences of poor health decisions, and by suppressing intrinsic disease processes they manufacture survival time that may take some people beyond their life span potential. The goal of ageing interventions is to manipulate biology in order to take people into the uncharted waters that lie beyond their life span potentials, hopefully in good health.

Most of the survival time manufactured today is the result of managing the symptoms of disease rather than curing the disease. Clearly, interventions that eliminate the underlying pathogenesis of a previously lethal disease process would improve the quality of life for the afflicted individuals by removing an obstacle to better health. The effect on measures of health for a population (i.e., healthy life expectancy, prevalence of disability and frailty, compression of mortality and morbidity), however, depends on the forms of mortality and/or morbidity that replace the eliminated diseases (van de Water *et al*, 1995). Similar arguments and conclusions could be made for interventions that slow or delay disease processes. The weakest intervention scenario is the current one where most interventions suppress the symptoms of disease without affecting their underlying cause. This observation should not be viewed as a criticism. Learning how to suppress the symptoms of disease is a likely, if not necessary, step toward learning how to delay the pathogenesis or eliminate the disease entirely. This scenario, however, creates difficult to interpret outcomes that give rise to the differences of opinion that have been discussed throughout this paper.

The prior discussion focused on the medical treatment and/or prevention of disease. As such, it was a 'clinical' perspective and a lively debate has arisen over whether a 'clinical' approach to the study of ageing has retarded progress on understanding ageing (see Binstock, 2003 for an overview). The distinction between disease and ageing

lies at the core of the debates (Blumenthal, 2003). Despite disputes over how it happens, there is broad agreement among biologists that ageing involves the degradation and/or failure of processes that are responsible for maintaining and repairing the molecular machinery of cells. As such, ageing is an inadvertent byproduct of processes that evolved for other purposes, and this indirect nature of ageing is what has made and continues to make an understanding of ageing so elusive.

From this biological perspective, the 'loss of molecular fidelity' (Hayflick, 2000) is what causes ageing, and this molecular entropy is not inextricably linked to any specific disease. Thus, there is no disease (e.g., Alzheimer's) whose successful treatment (or elimination) would have any impact on the processes responsible for ageing. While there may be no deterministic links between ageing and specific diseases, there are certainly probabilistic ones that create a middle ground between the opposing poles of the ageing/disease debate. Namely, while disease does not cause ageing, ageing does give rise to disease. This continuum of ageing-determined phenomena offers countless opportunities for contributions to the field of ageing from the laboratory bench to the patient bedside and every discipline in between.

It is almost inevitable that the biggest divergence of opinion occurs over predictions about the future. This is especially true when it comes to the issue of human life extension. The public is already inundated with schemes that purport to slow, stop or reverse ageing (so called anti-ageing interventions). An entire issue of the *Journal of Gerontology: Biological Sciences* (Olshansky *et al*, 2004) has been devoted to discussing the hype and reality of anti-ageing medicine. Although there is nearly universal agreement in the scientific community that no current methods exist to stop or reverse ageing, there are disagreements among respected scientists over whether ageing can be slowed (Olshansky *et al*, 2002b, 2002c).

One of the most intensively examined interventions linked to the modulation (slowing) of ageing is caloric restriction (CR) (Masoro, 1993; Anson *et al*, 2005). By reducing the amount of glucose available to cells, CR reduces the number of free radicals generated during the conversion of glucose to the energy used by cells. In fact, CR produces a range of desirable 'anti-ageing' effects at the biochemical level that are consistent with the widely accepted free radical hypothesis of ageing (Lane *et al*, 2002). Assessing the magnitude of the anti-ageing effect, however, is difficult because part of the life extension attributed to CR is due to a reduction of obesity rather than a slowing of ageing. Unfortunately, the levels of CR needed to produce the presumed anti-ageing affects can cause infertility – a highly non-adaptive outcome from a Darwinian perspective. More extreme caloric reductions would presumably produce the detrimental physiological effects observed in people with anorexia. Finally, the levels of CR needed to achieve an optimum effect are so austere that most people

will not adhere to them, especially over the long term needed to affect ageing. These difficulties have led scientists to actively search for pharmaceuticals that mimic the beneficial biochemical effects of CR without actually undergoing CR (Lane *et al*, 2002). Although it is impossible to predict the magnitude of the health and longevity effects of these yet to be discovered CR mimetics, this area of research is based on sound scientific principles and holds a great deal of promise.

Most of the interventions proposed for the ageing phenotype are targeted at causes or mechanisms at the molecular and biochemical level (Rattan, 2004; Wadhwa *et al*, 2005; Warner, 2005). Many, like CR, have conceptual ties to the free radical theory of ageing (Beckman & Ames, 1998; Kenyon, 2001; Van Voorhies, 2003). However, even the venerated free radical theory has its detractors who argue that the accumulation of cellular garbage from such processes as non-enzymatic glycation, carbonyl stress and protein crosslinking provide a more compelling explanation for ageing (Yen & Chen, 2005; Stroikin *et al*, 2005).

The modern era of molecular biology, genomics and proteomics has expanded our awareness of ageing-related phenomena that occur within the cells of a wide range of organisms. There has been a similar proliferation of theories to explain these phenomena, and as we have seen, scientists challenge both the theories and their implications. These disputes frequently involve extrapolation, whether it is from molecular to cellular effects or from individual to population consequences of those effects. The problem is that very little is known about how an effect observed at the molecular level is integrated across levels of biological organization (cells, tissues, organs) in order to produce an effect at the level of the individual. For example, attempts to use information on the behavior of genes and proteins in order to develop predictive models for cell, tissue and organ function (the so-called physiome project) are in their infancy (Hunter and Borg, 2003). The uncertainties created by this lack of knowledge are propagated when extrapolations are made from the individual to the population level, and they are magnified even further when the extrapolations involve predictions about the future course of human longevity and health.

Despite remarkable scientific progress, Medawar's (1952) description of ageing as an unsolved problem in biology remains a fair description of the current state of knowledge. The balance between what is and what is not known about ageing at this time has put human societies in a precarious position. Death rates that have declined at every age over the last century for many human diseases reveal the impact of new and improved medical treatments that have emerged from a research focus on disease. However, countries around the globe are now experiencing the consequences (frailty, disability, comorbidity, poly-pharmacy, population ageing) of Darwinian (biological) bodies living in a Lamarkian (technological) world that knows how to extend old age but has not yet learned how to extend the health

and vigor of youth (Carnes, 2004). The societal costs of population ageing (e.g., insolvency of age-based entitlement programs, escalating costs for health insurance, health care and malpractice insurance) will continue to rise until solutions are found to Medawar's unsolved problem in biology. Fortunately, there is a dedicated community of physicians and scientists actively trying to define the challenges and find the solutions.

References

Albert, S.M. (2004) *Public Health and Aging: An introduction to maximizing function and well-being*. New York: Springer Publishing Company.

Anson, R.M., Jones, B., & de Cabo, R. (2005) The diet restriction paradigm: A brief review of the effects of every-other-day feeding. In: *Age,* 27, pp. 17–25.

Beckman, K.B. & Ames, B.N. (1998) The free radical theory of aging matures. In: *Physiological Reviews,* 78, pp.547–581.

Binstock, R.H. (2003) The war on 'anti-aging medicine'. In: *The Gerontologist,* 43, pp. 4–14.

Blumenthal, H.T. (2003) The aging-disease dichotomy: True or false? In: *Journal of Gerontology: Medical Sciences,* 58A, pp. 138–145.

Carnes, B.A. & Olshansky, S.J. (1993) Evolutionary perspectives on human senescence. In: *Population and Development Review,* 19, pp. 793–806.

Carnes, B.A., Olshansky, S.J., & Grahn, D. (1996) Continuing the search for a law of mortality. In: *Population and Development Review,* 22, pp. 231–264.

Carnes, B.A. & Olshansky, S.J. (1997) A biologically motivated partitioning of mortality. In: *Experimental Gerontology,* 32, pp. 615–631.

Carnes, B.A. & Olshansky, S.J. (2001) Heterogeneity and its biodemographic implications for longevity and mortality. In: *Experimental Gerontology,* 36, pp. 419–430.

Carnes, B.A., Olshansky, S.J., & Grahn, D. (2003) Biological evidence for limits to the duration of life. In: *Biogerontology,* 4, pp.31–45.

Carnes, B.A. (2004) Darwinian bodies in a Lamarkian world. In: *The Gerontologist,* 44, pp. 274–279.

Crimmins, E., Saito, Y., & Ingegneri, D. (1997) Trends in disability-free life expectancy in the United States, 1970–90. In: *Population and Development Review,* 23, pp. 555–572.

Dawkins, R. (1976) *The Selfish Gene*. Oxford: Oxford University Press.

United Nations, Department of Economic and Social Affairs (2004) *World Population to 2300*. New York: United Nations (ST/ESA/SER.A/236).

Dolejs, J. (1997) The extension of Gompertz law's validity. In: *Mechanisms of Ageing and Development,* 99, pp. 233–244.

Dovenmuehle, R.H., Busse, E.W. & Newman, G. (1970) Physical problems of older people. In E. Palmore (ed.) *Normal Aging: Reports from the Duke Longitudinal Study, 1955–1969*. Durham, NC: Duke University Press.

Evans, J.G. (2002) The gifts reserved for age. In: *International Journal of Epidemiology,* 31, pp. 792–795.

Forette, F. (1997) Centenarians: Health and frailty. In J.M. Robine, J.W. Vaupel, B. Jeune, & M. Allard (eds.), Longevity: *To the limits and beyond*. Berlin: Springer-Verlag.

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. In: *Journal of Gerontology: Medical Sciences,* 56A, pp. M146–M156.

Fried, L.P., Ferrucci, L., Darer, J., Williamson, J.D., & Anderson, G. (2004) Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. In: *Journal of Gerontology: Medical Sciences,* 59, pp. 255–263.

Fries, J.F. (1980) Aging, natural death, and the compression of morbidity. In: *New England Journal of Medicine,* 303, pp. 130–135.

Gillick, M.R. (2001) Lifelines: *Living longer, growing frail, taking heart*. New York: W.W. Norton & Company.

Hamilton, W.D. (1966) The moulding of senescence by natural selection. In: *Journal of Theoretical Biology,* 12, pp. 12–45.

Hayflick, L. (1994) *How and Why We Age*. New York: Ballantine Books.

Hayflick, L. (2000) The future of ageing. In: *Nature,* 408, pp. 267–269.

Hayflick, L. (2003) *Has Anyone Ever Died of Old Age*? New York: International Longevity Center Occasional Paper.

Holliday R. (1995) *Understanding Aging*. Cambridge, Cambridge: University Press.

Hunter, P.J. & Borg, T.K. (2003) Integration from proteins to organs: The Physiome project. In: *Nature Reviews: Molecular Cell Biology,* 4, pp. 237–243.

John, S.M. & Koelmeyer, T.D. (2001) The forensic pathology of nonagenarians and centenarians: Do they die of old age? (The Auckland Experience). In: *American Journal of Forensic Medicine and Pathology,* 22, pp. 150–154.

Kahn, R.L. (2002) Guest Editorial: On 'Successful aging and well-being: self-rated compared with Rowe and Kahn'. In: *The Gerontologist,* 42, pp. 725–726.

Kenyon, C. (2001) A conserved regulatory system for aging. In: *Cell,* 105, pp. 165–168.

Kirkwood, T.B.L. & Holliday, R. (1979) The evolution of longevity and longevity. In: *Proceedings of the Royal Society,* B 205, pp. 532–546.

Kohn, R.R. (1982) Cause of death in very old people. In: *Journal of the American Medical Association,* 247, pp. 2793–2797.

Lane, M.A., Ingram, D.K., & Roth, G.S. (2002) The serious search for an anti-aging pill. In: *Scientific American,* 287, pp. 36–41.

Manton, K.G. (1982) Changing concepts of morbidity and mortality in the elderly population. In: *The Milbank Quarterly,* 60, pp. 183–244.

Manton, K. (1997) Chronic disability trends in elderly United States populations: 1982–1994. In: *Proceedings of the National Academy of Science,* 94, pp. 2593–2598.

Masoro, E.J. (1993) Dietary restriction. In: *Journal of the American Geriatrics Society,* 41, pp. 994–999.

Medawar, P.B. (1952) *An Unsolved Problem in Biology*. London: Lewis.

McDougall, I., Brown, F.H., & Fleagle, J.G. (2005) Stratigraphic placement and age of modern humans from Kibish, Ethiopia. In: *Nature,* 433, pp. 733–736.

Oeppen, J. & Vaupel, J. (2002) Broken limits to life expectancy. In: *Science,* 296, pp. 1029–1031.

Olshansky, S.J., Carnes, B.A., & Cassel, C.K. (1990) In search of Methuselah: Estimating the upper limits to human longevity. In: *Science* 250, pp. 634–640.

Olshansky, S,J., Rudberg, M.A., Carnes, B.A., Cassel, C.K., & Brody, J.A. (1991) Trading off longer life for worsening health. In: *Journal of Aging and Health,* 3(2), pp. 194–216.

Olshansky, S.J., Carnes, B.A., & Cassel, C.K. (1993) The aging of the human species. In: *Scientific American,* 268, pp. 46–52.

Olshansky, S.J., Carnes, B.A., & Grahn, D. (1998) Confronting the boundaries of human longevity. In: *American Scientist* 86, pp. 52–61.

Olshansky, S.J., Carnes, B.A., & Brody, J. (2002a) A biodemographic interpretation of life span. In: *Population and Development Review* 28, pp. 501–513.

Olshansky, S.J., Hayflick, L., & Carnes, B.A. (2002b) No truth to the fountain of youth. In: *Scientific American,* 286(6), pp. 78–81.

Olshansky, S.J., Hayflick, L., & Carnes, B.A.. (2002c) Position statement on human aging. In: *Scientific American* (www.sciam.com/explorations/2002/051302aging/html); also *Journal of Gerontology: Biological Sciences,* 57A(8), pp. B1–B6.

Olshansky, S.J., Hayflick, L., & Perls, T.T. (guest editors) (2004) Anti-Aging Medicine: the Hype and the Reality – Part 1. In: *Journal of Gerontology: Biological Sciences,* 59A.

Paffenbarger, R.S., Hyde, R.T., Wing, A.L., Lee, I.M., Jung, D.L., & Kampert, J.B. (1993) The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. In: *New England Journal of Medicine,* 328, pp. 538–545.

Rattan, S.I.S. (2004) Aging, anti-aging, and hormesis. In: *Mechanisms of Ageing and Development,* 125, pp. 285–289.

Robine, J.M. & Michel, J.P. (2004) Looking forward to a general theory on population aging. In: *Journal of Gerontology: Medical Sciences,* 59A, pp. 590–597.

Rowe, J.W. & Kahn, R.L. (1987) Human aging: Usual and successful. In: *Science,* 237, pp. 143–149.

Schoeni, R.F., Freedman, V.A., & Wallace, R.B. (2001) Persistent, consistent, widespread, and robust? Another look at recent trends in old-age disability. In: *Journal of Gerontology: Social Sciences,* 56B, pp. S206–S218.

Strawbridge, W.J., Wallhagen, M.I., & Cohen, R.D. (2002) Successful aging and well-being: Self-rated compared with Rowe and Kahn. In: *The Gerontologist,* 42, pp. 727–733.

Stroikin, Y., Dalen, H., Brunk, U.T., & Terman, A. (2005) Testing the 'garbage' accumulation theory of ageing: Mitotic activity protects cells from death induced by inhibition of autophagy. In: *Biogerontology,* 6, pp. 39–47.

Todoriki, H., Willcox, D.C., & Willcox, B.J. (2004) The effects of post-war dietary change on longevity and health in Okinawa. In: *The Okinawan Journal of American Studies,* 1, pp. 52–61.

Tinetti, M.E., Bogardus, S.T. Jr., & Agostini, J.V. (2004) Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *New England Journal of Medicine,* 351, pp. 2870–2874.

Tinetti, M.E. & Fried, T. (2004) The end of the disease era. In: *American Journal of Medicine,* 116, pp. 179–185.

van de Water, H.P.A., van Vliet, H.A. & Boshuizen, H.C. (1995) *The Impact of 'Substitute Morbidity and Mortality' on Public Health Policy*. TNO Prevention and Health, TNO Report 95.059, Leiden: The Netherlands.

Van Voorhies, W.A. (2003) Is life span extension in single gene long-lived *Caenorhabditis elegans* mutants due to hypometabolism? In: *Experimental Gerontology,* 38, pp. 615–618.

Yen D. & Chen, K. (2005) The essential mechanisms of aging: Irreparable damage accumulation of biochemical side-reactions. In: *Experimental Gerontology,* 40, pp. 455–465.

Wadhwa, R., Deocaris, C.C., Widodo, N., Taira, K., & Kaul, S.C. (2005) Imminent approaches towards molecular interventions in ageing. In: *Mechanisms of Ageing and Development,* 126, pp. 481–490.

Warner, H.R. (2005) Longevity genes: From primitive organisms to humans. In: *Mechanisms of Ageing and Development,* 126, pp. 235–242.

Wilmoth, J.R. (2000) Demography of longevity: Past, present, and future trends. In: *Experimental Gerontology,* 35, pp. 1111–1129.

Wilson, M-M. G. (2004) Clash of the Titans: Death, old age, and the devil's advocate. In: *Journal of Gerontology: Medical Sciences,* 59A(6), pp. 612–614.

Correspondence:

Dr Bruce A. Carnes
The University of Oklahoma Health Sciences Center
Reynolds Department of Geriatric Medicine
921 N.E. 13th Street (11G)
Oklahoma City, OK 73104
E-mail: Bruce-Carnes@ouhsc.edu