Chapter 33
The Future of Human Longevity

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Introduction

The modern rise in life expectancy is one of humanity's crowning achievements. After more than 200,000 years of slow but steady increases in life expectancy for anatomically modern people like us (McNeill 1976), a new chapter in the book of human longevity began in the middle of the 19th century when a quantum leap in duration of life began (Omran 1971). The external forces of mortality (e.g., infectious diseases, predation and accidents) that precluded survival beyond the first few years of life for most people were significantly relaxed as modern humans learned how to insulate themselves from the major hazards of the outside world. As a result, the biological consequences of aging are now a common occurrence for the first time in the history of our species. This longevity benefit, however, was accompanied by a trade-off involving a rise in such fatal diseases as cancer, heart disease, stroke and Alzheimer's disease, as well as such chronic conditions as sensory impairments, arthritis and dementia.

In today's world we see countries with life expectancies as high as 85 years for women and approaching 80 years for men. It would appear to some that this historic rise in longevity has no end in sight (Oeppen and Vaupel 2002; Wilmoth 1998). Others suggest that while there are no genetic mechanisms that evolved to limit the duration of life, there are nevertheless limits on duration of life imposed by a spectrum of forces (e.g., biochemical, biomechanical, biodemographic and stochastic) that exist at virtually every level of biological organization. Although large increases in life expectancy are still possible, attaining those increases will require a source of mortality decline different from those observed in the past (Olshansky et al. 2001, 2005).

How much further can the envelope of human survival be extended? Is it possible that life expectan cy in developed countries can continue to rise in the future as it did during most of the 20th century? Can the maximum documented lifespan of 122 years for humans (experienced by Madame Jeanne Calment from France; Allard et al. 1998) be broken and if this record was broken would it have any scientific relevance? Is there any reason why humans cannot live to 200 years or more? Is physical immortality possible as some suggest (de Grey et al. 2002; Kurzweil and Grossman 2004)?

Pathways to Longer Life

There are three basic views of the future of human longevity. One view has been developed by those we shall label ***futurists***. The futurists contend that yet-to-be-developed advances in biomedical technology and the anticipated emergence of nanotechnology are going to radically transform the landscape of human aging and longevity – leading us down a pathway toward physical immortality and eternal youth. A second view has been developed by a group we shall label ***optimists***. The optimists believe that the historic rise in life expectancy will continue at its previous pace of about 2.5 years added per decade – leading to a life expectancy at birth of 100 years for some coun-

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tries later in this century. The third view comes from a group we shall label ***realists***. The realists contend that there are identifiable and measurable biological, biodemographic, biomechanical, evolutionary and stochastic reasons why life expectancy at birth is unlikely to rise much beyond about 88 years for women and 82 years for men – a "barrier" that the realists contend can be breached if technology capable of slowing the rate of biological aging can eventually be discovered and broadly disseminated.

The Futurists

The futurists claim that life expectancy is on the verge of being dramatically extended, that physical immortality is on the horizon and that some people alive today will drink from a fountain of youth that science has yet to discover (de Grey 2002; Kurzweil and Grossman 2004). De Grey identifies seven cellular and molecular differences between the young and old that if fixed will eliminate aging and make physical immortality possible (de Grey et al. 2002). He predicted (with 95 per cent confidence) that a massive funding effort could produce the breakthroughs needed to achieve immortality somewhere between 2015 and 2040 (de Grey 2005). According to the futurists, immortality will occur when life-extending treatments reduce age-specific death rates faster than aging can raise them – a point that de Grey calls the "Longevity Escape Velocity" (LEV).

Kurzweil and Grossman (2004) based their claim for immortality on the anticipated and required development of three technological bridges to the future of life extension. "Bridge One" technologies are composed of nutritional supplements, changes in lifestyle and extensive health care screening that when combined will, according to the authors, allow people to live an additional 20 years beyond the life expectancies that prevail today. After 20 years, "Bridge Two" biomedical technologies (e.g. stem cell therapy, genetic engineering and "rejuvenation technologies") are then expected to come on line. Around the middle of the 21st century, the expectation is that the Bridge Two survivors will begin benefiting from the Bridge Three technologies (e.g., nanotechnology) that Kurzweil and Grossman claim will lead to immortality. A fundamental tenet of the futurist reasoning is the premise that technological development will continuously increase at a progressively faster rate (Kurzweil 2005). In both the de Grey and Kurzweil scenarios, physical immortality accompanied by eternal youth will be achieved for all of humanity sometime by the middle of the 21st century. In their future world, the extreme elderly by today's standards (i.e., those aged 85 +) would be indistinguishable (physically and mentally) from people at young and middle ages today. In effect, old age would cease to exist and the world would become populated only by those who are physically healthy and mentally vibrant.

The futurist line of reasoning is totally dependent on something that does not currently exist – life-extending technologies that yield eternal life. Furthermore, there is no evidence to support the initial assertion of Kurzweil and Grossman (2004) that people alive today can survive another 20 years because of Bridge One interventions. Although this picture of the future is painted with a chain of speculations and unsupported assumptions (Warner et al. 2005), the interventions promulgated by futurists serve a useful role by stimulating thinking about novel evidence-based interventions. It must be said, however, that visions of a world filled with immortal and forever young people is a recurring scenario that longevity prophets of every era have been predicting for thousands of years (Gruman 1966). Unfortunately for the futurists, immortality and eternal youth remain wishful pursuits lacking scientific credibility and biological plausibility.

The Optimists

In developed nations over the last century and a half there have been relatively consistent declines in the age-specific risk of death and increases in life expectancy at birth. The historical record documenting these demographic changes is the key source used by optimists for their projections of life expectancy in the future. As such, the optimists are assuming that the future will be a continuation of the past (Oeppen and Vaupel 2002). This approach to forecasting has led to the prediction that life expectancy at birth in the United States will rise to 100 years by the year 2060 (Oeppen and Vaupel 2002). Advocates of this approach have declared that there are no biological or demographic reasons why death rates cannot decline to zero (Wilmoth 2001). Biologically imposed upper limits on the life

span of individuals and the life expectancy of populations are also rejected by the optimists. Data used to support these positions include unabated historical increases in the world record for life expectancy at birth (defined by one country annually; Oeppen and Vaupel 2002), largely unabated increases in the maximum age at death (defined by one person annually in one country – Sweden; Wilmoth et al. 2000), as well as steady declines in old-age mortality observed in G7 nations (Tuljapurkar and Boe 2000).

The validity of the method used by optimists to forecast life expectancy depends on a strong demographic assumption; namely, that future trends in mortality are invariant continuations of those observed in the recent past. This approach to forecasting not only ignores documented biological constraints on duration of life (Austad 1999; Carnes et al. 2003; Hayflick 2000; Holliday 2007; Olshansky and Carnes 2001; Kirkwood 2003), it rejects them. In the absence of limits, optimists rely on biomedical technologies that do not currently exist in order to achieve their predictions of large declines in old age mortality in the future. Further, by ignoring cause of death and relying on past trends in total mortality, their extrapolation models cannot capture the mortality changes that are already occurring as infectious disease deaths at young ages are being progressively replaced by degenerative disease deaths at old ages (Carnes 2004; Carnes et al. 2006). Finally, the optimists' approach ignores emerging cohort effects that are already having a negative impact on life expectancy (e.g. childhood obesity – Olshansky et al. 2005; infectious disease – Olshansky et al. 1997) and observed declines in life expectancy already being observed in the modern era (United Nations 2003).

The Realists

Realists contend that there are an abundance of documented biological and non-biological forces known to influence duration of life for humans and other organisms. One of the most prominent of these is aging itself. The current reality is that aging cannot be stopped or reversed and there is disagreement among respected experts in the field of aging on whether or how much it can be slowed (Olshansky et al. 2002). Even if a means of slowing aging is found, it is unlikely that the intervention could be implemented on a large enough scale in the near term to have a measurable impact on a population statistic like life expectancy. Realists also suggest that aging and duration of life is fundamentally linked to processes (growth, development, maturation, reproduction and nurturing) that are intrinsic to the biology of all living things, including humans (Carnes et al. 1996, 2003). These processes and the biological clocks associated with them have their origins in evolutionary antiquity. Manipulating these intricate and evolutionarily conserved mechanisms in order to extend duration of life will be difficult to achieve without also having unintended negative consequences.

At a population level, biodemographic constraints on duration of life have been discussed extensively in the literature (Carnes et al. 1996; Olshansky et al. 1990; Olshansky et al. 2001). So called entropy in the life table makes the demographic measure of life expectancy less sensitive to declines in death rates as life expectancy rises. For example, it becomes extremely difficult to raise life expectancy further when it approaches 80 years (Olshansky et al. 2001). The likely biological reason for this demographic phenomenon is that adding 80 years to the life of an infant is achievable, whereas, adding 80 years to the life of an 80 year old is not biologically or practically plausible. Biomechanical forces that influence duration of life have been described in the literature at various times in the 20th century (Thompson 1942; Morgan 1994), with a recent presentation of this line of reasoning by Olshansky, Carnes and Butler (2001). Classic examples of the problem of life-limiting body design includes the wearing out of the hip and knee joints and the age-dependent loss of bone, neurons and muscle (especially those of the heart), which makes it extremely difficult to operate our bodies much longer than is already the case.

There is growing evidence that stochastic forces have a significant influence on duration of life (Kirkwood and Finch 2000). As an example, genetically identical mice raised under identical laboratory conditions do not all die on the same day as one might hypothesize. Instead, their distribution of death is indistinguishable from that experienced by genetically heterogeneous mice living under the same conditions (Carnes and Olshansky 2001). Stochastic events, by definition, are random in time, location and effect. They contribute to the systemic age-dependent degradations in functional integrity observed at virtually every level of biological organization (Carnes and Olshansky 1997; Shock

1957). The spatial and temporal unpredictability of stochastic effects make them exceedingly difficult targets for intervention. As such, they pose a formidable challenge to efforts aimed at extending duration of life beyond what has already been achieved in low mortality populations. An aging phenotype (pathology profile and pattern of mortality) that is consistent across many species, including humans, has lead realists to suggest that the body of an organism is subject to a biological warranty period and the expiration date of that warranty establishes a biological "limit" to the duration of life (Carnes et al. 2003).

The evolutionary theory of senescence provides realists with a foundation for understanding why there are biological "limits" to the duration of life (Hamilton 1966; Kirkwood 1977; Medawar 1952; Williams 1957). According to evolution theory, senescence originates from biological factors that evolved for other reasons. Evolution theory suggests that mortality pressures within the environments of earth create a race between reproduction and death. For example, prey animals like mice that are under intense mortality pressures must achieve sexual maturity within a month in order to ensure that their genes are passed onto the next generation. By contrast, a species like humans that is subject to low mortality pressures gives birth to altricial young that take up to 15 years to achieve sexual maturity. From this perspective, genes are all about producing a healthy and vigorous sexually mature individual capable of successful reproduction. Thus, while there are biological clocks, those clocks do not regulate aging – they orchestrate growth, development and maturation. As such, genetic forces that contribute to senescence are an inadvertent by-product of genetic programs that evolved for purposes unrelated to aging. If anything, aging is the result of evolutionary neglect rather than intent because the forces of evolution (natural selection) do not operate in the post-reproductive region of the lifespan. Senescence may best be viewed as a shadow cast by a statue. The only way one can modify the shadow (senescence) is to modify the statue (biology).

The optimists and futurists base their reasoning and forecasts on speculation that rapid projected increases in life expectancy in this century will be the product of 1) a continuous development of progressively more superior biomedical technologies that do not yet exist, 2) improvements in health behaviors that are invariably limited at the population level by non-compliance, 3) extrapolations of historical trends in life expectancy into the future coupled with an assumption that these trends are irreversible and 4) the suggestion that older people alive today (who certainly live longer on average than previous generations) are products of uniquely favorable life experiences among these cohorts when they were younger. The realists suggest that it is possible to speculate on the health of future elderly cohorts by examining them today, when they are young. For example, one recent study suggests that today's younger generation in the U.S. and elsewhere is progressing toward levels of obesity that could lead to declines in life expectancy at birth by the middle of this century – possibly countering the anticipated benefits in longevity expected from advances in biomedical technology (Olshansky et al. 2005).

A potential weakness of the realist's argument is their assumption that behavior modification and existing near-term biomedical technologies will have only a limited beneficial effect on life expectancy. In order to exceed these "limits," the realists require the development and broad scale dissemination of the very technologies that the futurists and optimists believe are forthcoming. No one, however, knows with certainty how much more death rates can decline in the absence of futuristic life-extending biomedical breakthroughs. Similarly, there is no way to predict how much higher life expectancy can rise if interventions that slow the biological processes of aging are discovered and widely implemented.

What will be the Future of Human Longevity?

It should be evident to the reader that the authors of this chapter place themselves within the realist school of thought. Why do we believe that the futurists and optimists are making untenable assumptions that should not be used by government agencies, actuaries, or insurance industries in order to a develop forecasts of life expectancy? What is our opinion on the future of human longevity and why do we think it is correct? In the following sections we provide a more detailed presentation of our line of reasoning.

Intimations of Immortality

In our opinion, the futurists' writings read like a science fiction novel; there is no scientific basis for their claims that humans are on the verge of immortality. Proclamations that dramatic extensions of life are imminent have been made for thousands of years by people who Gerald Gruman (1966), the physician and medical historian, referred to as prolongevists. There is no reason to suspect the fate of the modern prolongevists will be any different than their predecessors. Contrary to their predictions, prolongevists die at ages characteristic of their cohort.

Driving with a Rear View Mirror

The ease of implementing the extrapolation model of the optimists has made it attractive to both actuaries and demographers and there is a history and logic behind this approach that provides it with an intuitive appeal (Bongaarts 2006). Ironically, we believe the flaw in this approach to forecasting is what would appear at first glance to be one of its principal strengths. Namely, a dependence on a long time series of mortality change that has proven to be a reliable barometer of past and recent changes in life expectancy. The problem lies in the assumption that mortality change in the 21st century will be just like that experienced in the 20th century. Most of the rise in life expectancy over the last century was a product of declining early age mortality – saving the lives of children and mothers during childbirth. However, mortality declines of this kind can only occur once in a low mortality population, although indeed it is true that they must be repeated for each generation. Thus, life expectancy gains in the 21st century, if they are to even approach the large gains observed in the last century, will require a source of mortality decline that is fundamentally different from that responsible for past trends. Further, if large increases in life expectancy are to occur in this century, the mathematical realities of the life table will require declines in mortality at old ages that are of a far greater magnitude than the reductions in early age mortality that drove the first longevity revolution.

Another key premise of the optimists approach is that it requires a new source of mortality decline in the 21st century. They assume that an accelerating pace of advances in biomedical technology will become the driving force for dramatically lower death rates among future cohorts of older persons. However, even the proponents of this approach to forecasting acknowledge that this assumption requires new and more effective life-extending technologies that do not currently exist. Three difficult goals must be achieved in order to fulfill the expectations of this assumption. First, these yet-to-be-discovered interventions must yield extremely large reductions in death rates from the major causes of death – heart disease, cancer and stroke. Second, a way to dramatically slow the aging process must also be found – a breakthrough of unprecedented proportions that may be plausible but which has not yet occurred. Finally, not only must these interventions be invented but they must also be distributed to a huge number of people in order to have the dramatic effect on life expectancy that they envision.

The lack of theoretical justification or empirical evidence to support most of these "beliefs" illustrates why we believe this school of thought has made untenable assumptions. Despite an awareness of the scientific literature on the biology of aging and death, the optimists persist in their assumption that there are no demographic or biological reasons why death rates cannot decline to zero (Wilmoth 2001). They also continue to argue that in the absence of evidence, there is no reason to alter their assumption that the future will repeat the past. In both cases, the overwhelming evidence that death is a biological phenomenon and that biology (growth, development, maturation, reproduction, somatic maintenance, homeostasis, disease expression and aging) is largely responsible for the timing of death, are ignored. This biological blind spot is an impediment to the biodemographic thinking that is necessary to understand the mortality consequences of aging and to make plausible forecasts of mortality, especially in low mortality populations where these biological forces are becoming increasingly more important (Carnes 2007).

Proponents of the extrapolation approach also favor incorporating cohort information into their forecasts. For example, recent improvements in some measures of morbidity and disability have been observed for the U.S. population (Manton et al. 1995, 2006) – a phenomenon attributed in part to improvements in education among successive birth cohorts. The implication being that the observed trend toward improved health status at older ages will continue if successive birth

cohorts passing through the age structure are more highly educated than those that precede them. Finch and Crimmins (2004) postulated reasonably that a "cohort morbidity phenotype" exists that is a product of early-life exposures to infectious diseases and chronic inflammatory responses. This cohort phenomenon is postulated as a partial explanation for why successive birth cohorts are experiencing progressively lower old age mortality. Neither of these phenomena could have been envisaged if the researchers had chosen to ignore these unique cohort experiences in favor of a simple extrapolation of health and longevity based exclusively on past trends. If it is reasonable to speculate that improvements in the health and longevity of older people alive today are products of uniquely favorable life experiences when they were younger, then it is equally reasonable to speculate about the health and longevity attributes of future cohorts of older persons based on observations of poor lifestyles and rising levels of obesity among the younger generation(s) of today.

Obesity

After remaining relatively stable in the 1960s and 1970s, the prevalence of obesity among adults in the U.S. increased by approximately fifty per cent per decade throughout the 1980s and 1990s (Flegal et al. 2002). In the latest estimates of overweight and obesity for the United States derived from national survey data (NHANES) that include actual measures of height and body weight (Ogden et al. 2006), 17.1 per cent of children and adolescents were overweight and 32.2 per cent of adults were obese as of 2004. The prevalence of overweight in female children and adolescents rose from 13.8 per cent in 1999–2000 to 16.0 per cent in 2003–2004, while for male children the prevalence of overweight rose during this time period from 14.0 to 18.2 per cent. Among men, the prevalence of obesity increased significantly from 27.5 per cent in 1999–2000 to 31.1 per cent by 2003–2004. Among women, no significant increase in obesity was observed between 1999–2000 and 2003–2004 – but the proportion of obese was already at an extremely high level of just over 33 per cent. The prevalence of extreme obesity (BMI ω40) in 2003–2004 was 2.8 per cent in men and 6.9 per cent in women. In 2003–2004, approximately 30 per cent of non-Hispanic white adults were obese as were 45.0 per cent of non-Hispanic black adults and 36.8 per cent of Mexican Americans. Combining overweight and obese categories, fully two-thirds of adults in the U.S. today are considered to have body weight above healthful levels. The distribution of BMI has shifted in a skewed fashion such that the proportion of individuals with extreme obesity has increased at an especially rapid rate (Freedman et al. 2002). These trends have affected all major racial-ethnic groups, all regions of the country and all socioeconomic strata (Mokdad et al. 2001).

Trends in obesity are especially dramatic in children (Ogden et al. 2002). Since 1960 in the U.S. rates of obesity among boys aged 6–11 years increased to twelve per cent among whites, seventeen per cent in non-Hispanic blacks and twenty-seven per cent in Hispanics. For girls aged 6–11 the respective figures are twelve per cent in whites, twenty-two per cent in non-Hispanic blacks and twenty per cent in Hispanics. Ogden et al. (2006) have documented the recent dramatic increases in the prevalence of obesity among children observed during the latest two NHANES surveys from 1999–2000 to 2003–2004.

Obesity is a multi-system risk factor with known medical consequences. Increasing BMI is associated with an elevated risk of a number of adverse health conditions such as type 2 diabetes (mean prevalence ratios, depending on age and degree of obesity ranging from 2.56 to 18.08 in men and from 2.19 to 12.87 in women), coronary heart disease (1.14 to 2.22 in men and 1.58–2.98 in women), gall bladder disease (4.08–21.11 in men and 2.56–5.20 in women) and a variety of other complications. Adolescent obesity not only raises the risk of adult obesity and leads to a higher risk of cardiovascular and all-cause mortality in middle ages (van Dam et al. 2006), childhood and adolescent obesity also lead to a variety of immediate, sometimes life-threatening complications (Must et al. 1999). Children who are obese with type II diabetes have been shown to have the cardiovascular system of middle aged men (Gungor et al. 2005). Similarly, overweight and obesity in children have been associated with musculoskeletal disorders involving the hip, back, knee, foot and ankle and now there is reason to believe they also negatively influence skeletal alignment, muscular conditioning and soft tissue structures such as tendons, fascia and cartilage (Wearing et al. 2006). Obesity adversely affects quality of life in children, with a severity roughly equal to that of cancer (Schwimmer et al. 2003).

The effect of body weight on mortality rate has been extensively assessed. In a recent study of more than 90 thousand women from the Woman's Health Initiative Observational Study, it was demonstrated that the risk of death rises steadily and significantly with higher levels of BMI above normal and that the subsequent rise in all-cause mortality and cardiovascular mortality and incidence is mediated by the elevated risk of diabetes, hypertension and hyperlipidemia (McTigue et al. 2006). In a study of more than one million adults in the U.S., the lowest death rates were found among men with a BMI of 23.5 to 24.9 and in women with a BMI of from 22.0 to 23.4. Death rates from cardiovascular diseases were substantially elevated among people in the upper ranges of BMI (Calle et al. 1999, McTigue et al. 2006). In a prospective study of more than 1.2 million people from Korea aged 30 to 95, the risk of death from atherosclerotic cardiovascular disease and cancer rose steadily as BMI increased above the level of 24.9 (Jee et al. 2006). A prospective cohort study of 52,029 Japanese men and women from 1995–1998 found that both overweight and obesity were positively correlated with a significantly increased risk of total mortality and cancer deaths (Kuriyama 2006). A prospective study of 6,139 subjects in Germany found the greatest obesity-associated excess mortality to be among the young. The standardized mortality ratio (SMR) for individuals aged 18–29 years with a BMI of 40 or above was 4.2 in men and 3.8 in women (Bender et al. 1999). Using three large national surveys, Fontaine et al. (2003) estimated the effect of obesity on years-of-life-lost (YLL) across the lifespan of adults. For any degree of excessive body weight, young age was associated with greater YLL. Among whites age 20–30 years, YLL due to severe obesity (BMI > 45) was 13 for men and 8 for women. Being overweight in childhood was found to directly increase the risk of all-cause and cardiovascular disease-specific mortality in men and cardiovascular morbidity in both genders in a follow-up of the Harvard Growth Study of 1922–1935 (Must et al. 1992). Finally, a recent study using the National Health Interview Survey linked to the National Death Index found that from 1990 to 1992 through 1995, obese men and women in the U.S. lost 1.9 million and 3.4 million quality-adjusted life years, respectively, per year (Muennig et al. 2006).

The rising prevalence of obesity is likely to lead to an elevated risk of a broad range of fatal and non-fatal conditions for people of all ages in the coming decades. The dramatic increase in obesity among the young is particularly disturbing since such trends have the potential to significantly elevate age-specific death rates among future cohorts of middle aged and older persons. A recent autopsy study of the grade of coronary occlusion among a large number of decedents who died before age 65 from extrinsic causes reveals a reversal in the secular trend toward improving signs of coronary artery disease (CAD) (Nemetz et al. 2007), suggesting that today's middle-aged cohorts in the U.S. could face higher risks of CAD than previous generations (Olshansky and Persky 2007). This observation has been associated with the rise in obesity but this conclusion is speculative. If left unchecked, the rise in obesity has the potential to exert a significant negative influence on life expectancy at middle and older ages in the coming decades (Olshansky et al. 2005).

Several facts suggest that as today's younger cohorts age, obesity and its complications will worsen and obesity-induced death rates will rise: 1) estimates of the impact of eliminating obesity for the population alive today are based on past trends when the prevalence was much lower; 2) obesity prevalence, especially among children, is likely to continue to rise given the trends already observed at very young ages (e.g., under age 10); 3) with obesity occurring at younger ages, the children and young adults of today will carry and express obesity-related health and mortality risks for more of their lifespan than previous generations; 4) there has been a significant shift toward higher ranges of BMI at all ages; 5) death rates from diabetes have risen steadily in the last 20 years and there is reason to suspect this trend will continue as younger cohorts age; and 6) the medical treatment of obesity has been largely unsuccessful (Ebbeling et al. 2002). These trends suggest the relative influence of obesity on the life expectancy of future generations could be markedly worse in the coming decades as the overweight and obese who are now at younger ages carry their elevated risks of death into middle and older ages.

Diabetes

A recent forecast of death rates for diabetes in the U.S. made by the SSA illustrates the problem with forecasts that are based on extrapolation or which invoke hypothetical interventions (Bell and Miller

2002). From 1979 to 1999, death rates from diabetes increased annually by an average of 2.83 per cent for males and 1.78 per cent for females. In 1990, the negative effect of diabetes on life expectancy was 0.22 years and 0.31 years for males and females, respectively. The negative impact of diabetes has risen sharply since then (NCHS 1999) and could be as much as 5–6 times greater than in 1990 (Manuel and Schultz 2004). Given the biomedical realities of a worsening obesity epidemic and its implications for diabetes, an assumption that death rates from diabetes will begin declining in the year 2010 by 1.0–3.2 per cent annually and continue this decline throughout the 21st century cannot be justified. The rationale to support this view is the presumption that diabetes will fall largely within the control of biomedical technology within the next five years and that these interventions will not only be developed but will also be widely available during the next fifty years. Although we share their aspirations for these biomedical advancements, the question remains as to whether forecasts should be based on what is currently observable, or on assumptions that depend not only on the development of interventions but also on their efficacy and their widespread availability.

Infectious Diseases

Between 1980 and 1992 in the U.S., the age-adjusted death rate from infectious diseases rose by 39 per cent; overall infectious disease mortality increased 4.8 per cent annually from 1980 to 1995 (Armstrong et al. 1999); hospital-acquired infections have increased (Diekema et al. 2003; Osmon et al. 2003); and recent decreases in HIV-related mortality have leveled off (Karon et al. 2001). The negative influence of infectious diseases on life expectancy could rise to much higher levels if, as anticipated, pandemic influenza strikes (WHO 1999). Although developing and developed nations are potentially far more vulnerable to a global pandemic of influenza today than in 1918 due to population aging, antibiotic resistance, more rapid transport of microbes, etc. (Olshansky et al. 2000), this heightened risk is balanced, in part, by better global surveillance and interventions already present (Olshansky et al. 1997). Although estimating the negative effects of epidemics on future life expectancy is problematic, we already know from experience that when infectious diseases do re-emerge, as they have in many of today's developing nations; they can wipe out a century's worth of health and longevity gains in less than one generation (United Nations 2003). There is sufficient evidence from developed nations like the U.S. and the U.K. to suggest that even low mortality populations could experience a significant increase in infectious disease mortality in the coming decades (Olshansky et al. 2000). Thus, while the duration of the negative effect of a pandemic flu on life expectancy might be short-term, the magnitude of that effect could be dramatic.

Physiological Constraints on Duration of Life

It has been suggested that there is no demographic evidence from recent trends in mortality for the existence of limits on the life expectancy of human populations, or that low mortality populations are approaching such limits if they do exist (Manton et al. 1991; Wilmoth 1997, 1998). It has been further suggested that there are no biological or demographic reasons why death rates for humans cannot decline to zero (Wilmoth 2001). If death rates for humans can decline to zero, then limits cannot exist for either the life span of individuals or the life expectancy of populations. Further, if most humans are biologically capable of living to say 100 years or more, then there should be little evidence of significant functional decline or pathologic anomaly among people living to average survival times (75–80 years) that are already being attained. The same logic should apply to other species as well.

In a recent publication, Carnes et al. (2003) examined age-related changes in reproduction, physiological function and the pathology observed at death of the mouse, dog and human in order to determine whether biological changes consistent with the effects of aging could be detected. The goal was to determine whether this biological evidence was more consistent with bodies capable of much longer survival as anticipated by the optimists and futurists, or with bodies that the realists suggest have approached or are approaching the expiration date of their biological warranty period (Olshansky et al. 1998).

The data for female mice demonstrate that indicators of reproductive senescence (diminishing litter size, increasing pre-weaning pup mortality and parity intervals) were detectable at ages that were only 1/3 of the median age at death for the mouse strains examined. The reproductive data for human females from a broad range of fertility and mortality backgrounds demonstrate that by 35 years of age approximately 75 per cent of the reproduction that will ever be accomplished, has been accomplished. Just like female mice, this reproductive age window (and its associated reproductive physiology) for human females opens and closes at ages that are far younger than the life expectancy at birth currently achieved by women in low mortality countries (80 years). In addition, this age pattern of female fertility is remarkably similar for high mortality, low mortality and natural fertility populations. These data suggest that like female mice, the reproductive biology of human females is well defined and follows a stable and highly predictable time course. If evolutionary theories of aging are correct, the temporal dynamics of aging and death are intimately linked to the reproductive components of a species life history strategy (Stearns 1992). The largely immutable reproductive biology observed for female mice and humans and the predictable age patterns of their respective mortality (Carnes et al. 1996) are consistent with bodies that are subject to biological warranty periods.

The post-reproductive period is a segment of the life span typically associated with a loss of functional integrity (Fries 1980). Consistent with this expectation, studies on a wide range of physiological parameters reveal that approximately 80 per cent of functional capacity in humans is lost by age 80. Because there is no aging or death program (Hayflick 2000), the age-dependent rate of loss of some but not all of this lost functional capacity can be reduced through exercise, diet and with medications (Fiatarone and Evans 1990; Bortz 1982). Nevertheless, the biological evidence seems clear; the widespread degradation of physiological function (vital capacity) over time is yet another finding that is consistent with the existence of biological warranty periods.

The data on the pathology burdens observed at death provide incontrovertible evidence that age takes a severe toll on the bodies of dogs, mice and humans. Using nothing more than this pathology profile, we demonstrated that it is possible to statistically distinguish animals that died old from those that died young. Although death certificate data for humans are far less reliable than the pathology diagnoses available for laboratory animals, the pathology implications are no less conclusive. For humans dying over the age of 80, every organ system has a greater burden of disease involvement (abnormal pathology) than was observed in people dying before age 50. As with the reproductive and physiology data, humans have an age-related pathology burden that is consistent with bodies that are subject to biological warranty periods that limit the duration of life.

In summary, extrapolation models have been used to argue that there are no biological, demographic, or other reasons why death rates cannot decline to zero and that there is no reason why life expectancies for human populations cannot rise to 100 years or more. We have provided biological evidence for the mouse, dog and human that leads to the conclusion that there are biological warranty periods for living things that influence how long they are capable of living. The reproductive biology of mice and humans and the duration of life estimates derived from these data do not support predictions of human life expectancies rising to 100 years in this century.

From the evidence available, implied warranty periods exist for the duration of life. Although aging and death cannot be programmed by natural selection, they are a predictable byproduct of stable life history strategies that evolved under environments far less conducive to survival than those experienced today. The relatively benign environments that have been created through human ingenuity (e.g., public health, medical care, technology) are already permitting people to achieve and even exceed the expiration dates of their personal warranty periods. The fact that aging is not programmed and bodies are not designed to fail makes it possible to exploit loopholes in the biological contract of life in order to alter many of the parameters of aging and manufacture survival time (Olshansky et al. 1998). However, once most people have achieved their personal life span potential, it becomes extremely difficult to overcome the inherent limitations of their biology. Although life expectancy limits for humans have certainly not yet been reached, the evidence suggests that the biological warranty periods for human bodies are considerably lower than the estimates of 100+ year life expectancies generated by purely mathematical models.

Biodemographic Constraints on Duration of Life

The measure of period life expectancy at birth is calculated from age-specific death rates for a country observed during a calendar year. At its heart, life expectancy is based on the number of person-years-of-life lived in successive age groups by a hypothetical cohort. This number can increase rapidly, as it did in the early 20th century in today's developed nations, when it begins from a lower level and when declines in death rates occur at younger ages. As life expectancy at birth reaches higher levels, it becomes increasingly more difficult to raise it further as person-years-of-life must then be added by reducing death among middle aged and older persons (Olshansky et al. 1990).

One argument used by the optimists to support their view that life expectancy will rise to 100 years in this century is that large reductions in death rates, just like those observed in the 20th century, are on the verge of occurring again. Although the optimists never specify how or why such declines in death rates might occur, they nevertheless make the argument that they are a predictable outcome of forthcoming advances in the biomedical sciences. We have demonstrated that if the large declines in death rates that occurred in the past were to occur again, including large declines in death rates at middle and older ages, then the rise in life expectancy today would be much smaller in the future than what was observed during the 20th century (Olshansky et al. 2001). For example, if all of the reductions in death rates observed throughout the 20th century occurred again from levels of mortality present in 1995, life expectancy at birth would rise by only 10.1 years instead of the 30.1 years experienced during the previous century. If a third equivalent set of large declines in mortality occurred again, the rise in life expectancy would be only 6.1 years.

Finally, a third way to illustrate biodemographic constraints on human life expectancy is to illustrate how much death rates would have to decline in order to raise life expectancy at birth from current levels, to much higher levels. According to Olshansky et al. (1990), death rates at all ages would have to decline by more than 85 per cent from all causes combined in order for life expectancy at birth to rise to 100 years – a feat requiring more than the hypothetical elimination of cancer, all cardiovascular diseases and diabetes combined. Thus, the prediction by Oeppen and Vaupel (2002) that life expectancy will reach 100 years in the U.S. by 2060 requires not only the development and widespread dissemination of currently non-existent ways of slowing the process of aging in people, but humanity would also have to discover a cure for the vast majority of the chronic killer diseases that exist today.

Biomechanical Constraints on Duration of Life

The human body can be thought of as a collection of pulleys, pumps, levers and hinges that operate much like a machine (Olshansky et al. 2001). While a mechanic can repair worn out parts of a car, a bewildering array of coordinated biological processes exist to maintain and repair the human body. Despite this remarkable teamwork, our maintenance and repair capacities are both limited and imperfect. Constraints on the duration of life imposed by body design and the biology that animates it should be obvious to even the most casual reader. For example, humans begin losing bone density (osteopenia) at about age 30. Although this process can be slowed and with medication bone loss can even be reversed, the significant loss of bone density that has already occurred among middle aged and older persons today will hamper their prospects for dramatic increases in duration of life. In addition, two types of essential cells in the body have either a limited or no capacity for regeneration – muscle cells and nerve cells in the brain. At present, the only known way to partially compensate for the age-dependent loss of muscle mass (sarcopenia) is through exercise. However, this intervention cannot reclaim lost muscle cells (it increases the size of those that remain), nor can it reverse the inevitable transition from fast twitch to slow twitch muscles fibers that occurs as we age. Similarly, the age-dependent loss of neurons and a suite of related neurological disorders are largely untreatable at this time. The current reality of aging is that age-determined immutable and progressive degradations of function like those just described are characteristic of virtually every aspect of human biology. There is, therefore, overwhelming scientific evidence for the existence of intrinsic biological constraints on the duration of life – evidence

that directly contradicts the suggestion that there are no biological reasons why death rates cannot decline to zero (Wilmoth 2001).

Is There a Biological Limit to Life?

This question and its answer are perhaps two of the most misunderstood concepts in the field of aging today. Some scientists and many in the lay public have come to a mistaken belief in the existence of a genetically determined biological barrier or wall that precludes further increases in human life expectancy (for a summary of this view see Carnes and Olshansky 2007). In attempts to refute the evolutionary biology perspective of senescence, some researchers (e.g., Vaupel 1997) misinterpreted the theory by incorrectly predicting that a "black hole" of genetic diseases should exist at the beginning of the post reproductive region of the lifespan. Both views are incorrect. In an attempt to prevent the perpetuation of these mistaken beliefs, we will take a moment to explain the evolutionary theory of senescence and briefly discuss its implications for the future of human life expectancy.

The origin of modern evolutionary theories of senescence dates back to the theory of aging set forth by biologist August Weismann (1891). According to Weismann, the one aspect of life that could not be avoided was the inevitable exposure of individuals to forces within the world around them that produce a constant barrage of small but accumulating injuries to the body. In his view, it was also unrealistic to expect that these injuries could be repaired perfectly. This logic led him to the realization that the solution to this dilemma was to replace old worn out bodies with new undamaged ones. In other words, reproduction is the solution to the inevitability of aging and death. Thus, even if immortality was theoretically possible, it could never be realized in the real world where the external forces of injury and death were (and still are) ubiquitous and unavoidable.

Another advance for theories of senescence was provided by the late Nobel laureate Sir Peter Medawar (1952), who combined genetics and evolutionary theory in order to propose a mechanism of aging. Like Weismann, Medawar invoked the importance of the ever-present external force of mortality, which was identified as the primary reason why most organisms in nature do not live long enough to experience senescence. Like other scientists then and now, Medawar considered mutations (departures from the normal state) to genes as almost always deleterious to the health and vigor of the individual carrying that mutation. His unique contribution was thinking through the ramifications of the timing of gene expression. For example, a mutated gene (allele) expressed before the age of sexual maturation would likely diminish the ability of the individual carrying that allele to reproduce. As such, the frequency of this allele in the gene pool of the population should be lower than related alleles having less or no negative impact on health and vigor. In fact, the rarity of these early expressing alleles should be inversely proportional to the severity of their effect. In essence, natural selection punishes alleles (i.e., reduces their frequency) that have negative impacts on reproduction with a severity that diminishes to a vanishing point as the time of gene expression reaches the ages when reproduction ceases.

Medawar recognized the implications of this selection scenario for senescence. The post-reproductive period is characterized by evolutionary neglect because selection is blind to the consequences of allelic variations in gene expression at these ages. Medawar's language was more colorful, he described the post-reproductive period as a "genetic dustbin" where adverse gene expression, good or bad, has no effect on reproduction. It is, however, easy to see how adverse gene expression could contribute to the senescent diseases and disorders occurring at these ages. The effectiveness of selection is a diminishing trajectory, not a step function of either being present or absent. Further, genetic variation is just that, variation that exists among alleles within a gene locus as well as variation in expression that exists between gene loci. The temporal dynamics of this genetic scenario are simply incompatible with the prediction of deleterious effects concentrated within a "black hole" at the beginning of the post-reproductive period.

Williams (1957) provided an important extension of Medawar's view of aging when he hypothesized that some of the genes that have adverse health effects later in the lifespan may exist because they play important roles in growth and development early in the lifespan. His insights provided a second genetic modality for senescence. In addition to mutated genes expressed later in life, senescence could also be the result of normal genes being expressed at

abnormal times (e.g. oncogenes are often involved in growth and development). Williams described this phenomenon of early beneficial effects and late damaging effects as antagonistic pleiotropy. Antagonistic pleiotropy could also be achieved by a normal gene being inappropriately turned on (i.e. loss of regulation) in the post-reproductive period. This latter modality was referred to as the disdifferentiative hypothesis of aging and cancer by Cutler and Semsei (1989).

One of the more recent extensions of the evolutionary theory of senescence appeared in a series of articles published by Kirkwood (1977) and Kirkwood and Holliday (1979). Like Weismann and Medawar, Kirkwood also argued that the inevitable forces of external mortality play a crucial role in the timing of senescence. As discussed earlier, the solution to the inevitability of death is reproduction. Sexually reproducing organisms must invest energy into converting a fertilized egg into a sexually mature individual within a timeframe where the probability of successful reproduction exceeds the risk of death established by the forces of external mortality. This biological imperative creates a balancing act between investment in either reproduction or the maintenance and repair needed for longer life. Thus, species experiencing high levels of mortality (most organisms) must invest more into reproduction and less into somatic maintenance. Whereas species facing lower levels of mortality (e.g., predators and animals that have found ways to evade predators) can lessen their investment in reproduction and spend more of their physiological capital on processes necessary for longer life. This economic perspective of aging is called the "disposable soma" theory of senescence and it has made it possible to organize existing theories of senescence into a more coherent and integrated conceptual framework.

In summary, the argument that natural selection alters the genetic composition of a population through the differential reproductive success of individuals is a basic tenet of modern evolutionary biology. The corollary of this tenet is that the opportunity for selection to alter gene frequencies is greatest before individuals begin reproducing, diminishes as the cumulative reproductive potential of individuals is achieved and becomes weak or nonexistent once reproduction has ceased. This age-based gradient for the effectiveness of selection has an extremely important consequence; it permits the life course of species to be partitioned into biologically meaningful and comparable time periods – the pre-reproductive, reproductive and post-reproductive periods.

The biological consequences of this partition are equally profound. When the normally high force of external mortality is controlled and survival beyond the end of the reproductive period becomes a common occurrence, senescence and senescent-related diseases and disorders have the opportunity to be expressed. Since selection does not operate in the post-reproductive period, there can be no genetic basis for either immortality or senescence that arises from the direct action of natural selection. As such, organisms are not designed to fail but neither are they designed for extended operation. Instead, senescent-related diseases and disorders are an inadvertent byproduct of a rare and irrelevant event in nature – survival into the post-reproductive period of the life span (Hamilton 1966). Investing physiological capital into maintaining the soma beyond the ages needed for reproduction, nurturing offspring and improving the reproductive success of those offspring (grandparenting) would be an unnecessary and unwise investment. Thus, from a biological perspective, aging arose as an inevitable and inescapable byproduct of life's ingenious and necessary solution to the inevitability of death.

Are there genes that influence aging? The answer to this complicated question is important to understanding the prospects for genetic interventions that the optimists and futurists are depending on to produce large increases in life expectancy. As we have demonstrated, duration of life is dictated by the time needed for maturation, reproduction, nurturing and grandparenting for some species. This race between reproduction and death is so crucial that it cannot be left up to chance. As a result, growth and development involve highly regulated genetic programs (Carnes et al. 1996). Since it is a race against time, there is no question that the tempos of these growth and development programs are driven by extremely precise and highly coordinated biological clocks. It is easy to see how these clocks could be misinterpreted as clocks for aging. However, every gene involved in this exquisitely complex process is designed for health and vigor, not sickness and decay. You can think of the duration of this process as a biological warranty period. As such, aging or senescence is the unintended byproduct of bodies surviving

to and/or beyond the expiration of this warranty period (Carnes et al. 2003).

Thus, while there are no genes whose purpose is to establish a biological limit to life, neither is there a biology whose purpose is to achieve indefinite survival. As such, the bodies produced by this biology have a characteristic period of operation that in the collective can be expressed as probabilistic limits on duration of life.

Genetic interventions that extend life by influencing the expression of specific gene-linked diseases will undoubtedly be discovered. Aging, however, is a systemic process affecting every molecule of the human body. Battles against specific diseases will be won, the life span potential of humans will be extended but in the end, entropy will still win the war (Carnes et al. 2008). The feasibility, ethics and desirability of interventions capable of dramatically extending human life will be a never ending subject of intense debate.

Conclusions

There is an appealing but superficial logic that permeates the purely mathematical approaches to forecasting human life expectancy and investigating limits on the life spans of individuals and the life expectancy of populations. In all of the purely mathematical approaches there is no age when the probability of survival becomes zero. In other words, no matter how old an individual becomes, there is a non-zero probability that the individual can survive one more day. When taken to its illogical extreme, this reasoning leads to the biologically untenable conclusion that there are no limits on how long individuals can live and therefore there can be no limits on how high the life expectancy of populations can climb.

The optimists have suggested that human life expectancy has no biological limits and that the pathway to projecting the future is to simply extend the historical trend forward in time. Their approach to extrapolation has led them to predict that life expectancy at birth in the United States will rise to 100 years in this century. As a result, they have recommended that governments should raise their forecasts of life expectancy to be in accord with their prediction. It is our contention that the data and methods used by the optimists are inappropriate, their assumptions are unrealistic and their predictions are biologically implausible. By ignoring the extensive biological evidence that duration of life is limited; the optimists also reject the unavoidable demographic conclusion derived from that evidence – namely, that life expectancy must also be limited. Their misunderstanding of evolutionary theories of senescence has led them to invalid predictions about the temporal kinetics of genetic diseases in humans. By ignoring the relationship between form and function; optimists also ignore the currently unavoidable biomechanical senescence (enervation, sarcopenia, osteopenia) of the human body that imposes limits on the functioning of both the body and mind. Their optimist predictions are driven by assumptions that as yet undiscovered advances in the biomedical sciences will simultaneously: 1) lead to the near elimination of the main causes of death today, 2) delay senescence for most people in developed countries and 3) be provided on such a broad scale as to influence a population-level measure such as life expectancy. Finally, their optimistic mortality scenarios for the future ignore a global obesity epidemic that is already in progress, alarming increases in infectious diseases and the threat of an anticipated pandemic that is overdue; all of which represent formidable obstacles to uninterrupted future increases in life expectancy.

It is important to recognize that the optimists assume that when the historical trend in a particular variable associated with life expectancy favors a projected increase – as in the case of creating a record composite life expectancy at birth – then the presumption is that the future will be like the past. However, when the historical trend in a particular variable associated with life expectancy favors a projected decline – as in the case of undeniable and measurable increases in the risk of death from diabetes, obesity and infectious diseases – the optimists invoke the anticipated development of hypothetical advances in biomedical technologies to fix the problems. If the historical record of health and longevity is to be used to inform forecasts of life expectancy, it should not be invoked selectively to favor one particular point of view – it should be invoked without bias.

Finally, it is important to acknowledge that the optimists and futurists have one argument in their favor – it is impossible to know with certainty whether anticipated advances in the biomedical sciences will yield an intervention that slows aging in people and if it does how much it might influence life expectancy.

What is known is that there is a concerted effort to find the means to slow aging in people and now there is reason to be optimistic that such developments will occur in this century (Olshansky et al. 2006). Exactly how much of an impact such an advance will have on life expectancy is uncertain but what should be encouraging for all three camps is that our mutual dream of a shift in the pattern of old-age mortality may be on the horizon. On this most important of all points, it is evident that the proponents of all three views of the future of human longevity can come together in agreement.

References

Allard M, Lebre V, Robine JM (1998) The longest life: the 122 extraordinary years of jeanne calment. W.H. Freeman and Co, New York

Armstrong GL, Conn LA, Pinner RW (1999) Trends in infectious disease mortality in the United States during the 20th century. JAMA 281(1):61–66

Austad S (1999) Why we age: what science is discovering about the body's journey through life. John Wiley and Sons, New York

Bell FC, Miller ML (2002) Life tables for the United States social security area 1900–2100. Actuarial Study No. 116, Social Security Administration, Washington, DC

Bender R, Jockel KH, Trautner C, Spraul M, Berger M (1999) Effect of age on excess mortality in obesity. JAMA 281:1498–1504

Bongaarts J (2006) How long will we live? Popul Dev Rev 32(4): 605–628

Bortz WM (1982) Disuse and aging. JAMA 248(10):1203–1208

Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath, Jr. CW (1999) Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 341:1097–105

Carnes BA (2004) Darwinian bodies in a Lamarckian world. Gerontologist 44:274–279

Carnes BA (2007) Senescence as viewed through the lens of comparative biology. Ann NY Acad Sci 114:14–22

Carnes BA, Olshansky SJ (1997) A biologically motivated partitioning of mortality. Exp Gerontol 32:615–631

Carnes BA, Olshansky SJ (2001) Heterogeneity and its biodemographic implications for longevity and mortality. Exp Gerontol 36:419–430

Carnes BA, Olshansky SJ, Grahn D (2003) Biological evidence for limits to the duration of life. Biogerontology 4(1):31–45

Carnes BA, Olshansky SJ, Grahn D (2007) A realist view of aging, mortality, and future longevity. Popul Dev Rev 33(2):367–381

Carnes BA, Olshansky SJ, Grahn D (1996) Continuing the search for a law of mortality. Popul Dev Rev 22(2):231–264

Carnes BA, Holden LR, Olshansky SJ, Witten TM. Siegel JS. (2006) Mortality Partitions and their relevance to research on senescence. Biogerontology 7:183–198

Carnes BA, Statts DO, Sonntag, WE (2008) Does senescence give risk to disease? Mech Aging Dev (in press)

Cutler RG, Semsei I (1989) Development, cancer and aging: possible common mechanisms of action and regulation. J Gerontol: Biol Sci 44(6):25–34

de Grey A (2005) Foreseeable and more distant rejuvenation therapies. In: Rattan S (ed) Aging interventions and therapies, World Scientific, Singapore

de Grey A et al (2002) Time to talk SENS: critiquing the immutability of human aging. Ann NY Acad Sci 959:452–462

Diekema DJ, Beekmann SE, Chapin KC, Morel KA, Munson E, Doern GV (2003) Epidemiology and outcome of nosocomial and community-onset bloodstream infection. J Clin Microbiol 41(8):3655–3660

Ebbeling CB, Pawlak DB, Ludwig DS (2002) Childhood obesity: public-health crisis, common sense cure. Lancet 360:473–482

Fiatarone MA, Evans WJ (1990) Exercise in the oldest old. Topics Geriatr Rehabil 5(2):63–77

Finch CE, Crimmins EM (2004) Inflammatory exposure and historical changes in human life-spans. Science 305:1736–1739

Flegal KM, Carroll MD, Ogden CL, Johnson CL (2002) Prevalence and trends in obesity among US adults, 1999–2000. JAMA 288:1723–1727

Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB (2003) Years of life lost due to obesity. JAMA 289:187–193

Freedman DS, Khan LK, Serdula MK, et al (2002) Trends and correlates of class 3 obesity in the United States from 1990 through 2000. JAMA 288:1758–1761

Fries JF (1980) Aging, natural death, and the compression of morbidity. N Engl J Med 303:130–135

Gruman GJ (1966) A history of ideas about the prolongation of life: the evolution of prolongevity hypotheses to 1800. Trans Am Phil Soc 56(9)

Gungor N, Thompson T, Sutton-Tyrrell K, Janosky J, Arslanian S (2005) Early signs of cardiovascular disease in youth with obesity and type 2 Diabetes. Diabetes Care 28:1219–1221

Hamilton WD (1966) The moulding of senescence by natural selection. J Theor Biol 12:12–45

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

Holliday R (2007) Ageing: the paradox of life. Springer Publishing, New York

Jee SA, Sull JW, Park J, et al (2006) Body-mass index and mortality in Korean men and women. NEJM 355:779–787

Karon KM, Fleming PL, Steketee RW, De Cock KM (2001) HIV in the United States at the turn of the century: an epidemic in transition. Am J Public Health 91:1016–1017

Kirkwood TBL (1977) Evolution of aging. Nature 270:301–304

Kirkwood T (2003) Time of our lives: the science of human aging. Oxford University Press, Oxford

Kirkwood T, Finch C (2000) Change, development and ageing. Oxford University Press, Oxford

Kirkwood TBL, Holliday R (1979) The evolution of ageing and longevity. Proc R Soc Lond B Biol Sci 205:531–546

Kuriyama S (2006) Impact of overweight and obesity on medical care costs, all-cause mortality, and the risk of cancer in Japan. J Epidemiol 16(4):139–144

Kurzweil R, Grossman T (2004) Fantastic voyage: live long enough to live forever. Rodale Press, Emmaus, PA

Kurzweil R (2005) The singularity is near: when humans transcend biology. Viking Press, New York

Manton KG, Stallard E, Tolley HD (1991) Limits to human life expectancy. Popul Dev Rev 17(4):603–637

Manton KG, Stallard E, Corder LS (1995) Changes in morbidity and chronic disability in the us elderly population: evidence

from the 1982, 1984, and 1989 national long term care surveys. J Gerontol B Psychol Sci Soc Sci 50(4):S194–S204
Manuel DG, Schultz SE (2004) Health-related quality of life and health-adjusted life expectancy of people with diabetes in Ontario, Canada, 1996–1997. Diabetes Care 27(2):407–414
McNeill WH. (1976) Plagues and peoples. Anchor, Garden City
McTigue K, Larson JC, Valoski A, et al (2006) Mortality and cardiac and vascular outcomes in extremely obese women. JAMA 296(1):79–86
Medawar PB (1952) An unsolved problem of biology. Lewis, London
Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP (2001) The continuing epidemics of obesity and diabetes in the United States. JAMA 286:1195–2000
Morgan E (1994) The scars of evolution: what our bodies tell us about human origins. Oxford University Press, Oxford
Muennig P, Lubetkin E, Jia H, Franks P (2006) Gender and burden of disease attributable to obesity. AJPH 96(9):1662–1668
Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH (1992) Long-term morbidity and mortality of overweight adolescents. A follow-up of the harvard growth study of 1922 to 1935. N Engl J Med 327:1350–1355
Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH (1999) The disease burden associated with overweight and obesity. JAMA 282:1523–1529
National Center for Health Statistics (1999) United States life tables eliminating certain causes of death, 1989–1991, vol 4, No. 1. DHHS (PHS) 99-1150-4
Nemetz PN, Roger VL, Ransom JE, Bailey KR, Leibson CL (2007) Recent trends in the prevalence of coronary disease: a population-based autopsy study of non-natural deaths. Arch Intern Med 261, 264–270
Oeppen J, Vaupel J (2002) Broken limits to life expectancy. Science 296(5570):1029–1031
Ogden CL, Flegal KM, Carroll MD, Johnson CL (2002) Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA 288:1728–1732
Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM (2006) Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 295:1549–1555
Olshansky SJ, Carnes BA (2001) The quest for immortality. Norton, New York
Olshansky SJ, Persky V (2007) The canary in the coal mine of coronary Artery Disease. Arch Intern Med 168(3):261
Olshansky SJ, Carnes BA, Cassel C (1990) In search of methuselah: estimating the upper limits to human longevity. Science 250:634–640
Olshansky SJ, Carnes BA, Rogers RA, Smith L (1997) Infectious diseases: new and ancient threats to world health. Popul Bull 52(2):1–58
Olshansky SJ, Carnes BA, Grahn D (1998) Confronting the boundaries of human longevity. Am Sci 86(1):52–61
Olshansky SJ, Rogers RG, Carnes BA, Smith L (2000) Emerging infectious diseases: the fifth stage of the epidemiologic transition? World Health Stat Q 51(2,3,4):207–217
Olshansky SJ, Carnes BA, Butler R (2001) If humans were built to last. Sci Am 284(3):50–55
Olshansky SJ, Carnes BA, Désesquelles A (2001) Prospects for human longevity. Science 291(5508):1491–1492
Olshansky SJ, Hayflick L, Carnes BA, et al (2002) Position statement on human aging. Sci Am (June), http://www.sciam.com/agingstatement.cfm (Also published in the J Gerontol: Biol Sci 57A(8):B1–B6)
Olshansky SJ, Passaro D, Hershow R, Layden J, Carnes, BA, Brody J, Hayflick L, Butler, RN, Allison, DB, Ludwig, DS. (2005) A potential decline in life expectancy in the United States in the 21st century. New Engl J Med 352:1103–1110
Olshansky SJ, Perry D, Miller RA, Butler RN (2006) In pursuit of the longevity dividend. Scientist 20(3):28–36
Omran A. (1971) The epidemiologic transition: a theory of the epidemiology of population change. Milbank Mem Fund Q 49:509–538
Osmon S, Warren D, Seiler SM, Shannon W, Fraser VJ, Kollef MH (2003) The influence of infection on hospital mortality for patients requiring greater than 48 hours of intensive care. Chest 124(3):1021–1029
Schwimmer JB, Burwinkle TM, Varni JW (2003) Health-related quality of life of severely obese children and adolescents. JAMA 289:1813–1819
Shock N. (1957) Age changes in some physiologic processes. Geriatrics 12:40–48
Stearns SC (1992) The Evolution of Life Histories. Oxford University Press, New York
Thompson DW (1942) On growth and form. Dover Publications, New York
Tuljapurkar S, Li N, Boe C (2000) A universal pattern of mortality decline in G7 countries. Nature 405:789–792
United Nations (2003) The impact of AIDS. Population Division, ESA/P/WP.185, New York
Van Dam RM, Willett WC, Manson JE, Hu FB (2006) The relationship between overweight in adolescence and premature death in women. Ann Intern Med 145:91–97
Vaupel J (1997) Trajectories of mortality at advanced ages. In: Wachter K, Finch C, (ed) Between zeus and the salmon. National Academy Press, Washington, DC, pp 17–37
Warner H et al (2005) Science fact and the SENS agenda: what can we reasonably expect from ageing research? EMBO Rep 6:1006–1008. Doi: 10.1038/sj.embor.7400555
Wearing SC, Hennig EM, Byrne NM, Steele JR, Hills AP (2006) Musculoskeletal disorders associated with obesity: a biomechanical perspective. Obes Rev 7:239–250
Weismann A (1891) Essays upon heredity and kindred biological problems. Clarendon Press, Oxford
Williams GC (1957) Pleiotropy, natural selection and the evolution of senescence. Evolution 11:398–411
Wilmoth J (1997) In search of limits. In: Wachter K, Finch C, (ed) Between zeus and the salmon, Washington, DC, National Academy Press, pp 38–64
Wilmoth J (1998) The future of human longevity: a demographer's perspective. Science 280:395–397
Wilmoth J (2001) How long can we live? Science debate; http://www.sciencemag.org/cgi/eletters/291/5508/1491
Wilmoth JR, Deegan LJ, Lundstrom H, Horiuchi S (2000) Increase of maximum life-span in Sweden: 1861–1999. Science 289:2366–2368
World Health Organization (1999) Influenza pandemic plan. The role of WHO and guidelines for national and regional planning. WHO/CDS/CSR/EDC/99.1

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