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Perspective

Can Human Biology Allow Most of Us to Become Centenarians?

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Life span is a topic of great interest in science, medicine and among the general public. How long people live has a profound impact on medical costs, intergenerational interactions, and the solvency of age-based entitlement programs around the world. These challenges are already occurring and the magnitude of their impact is, in part, proportional to the fraction of a population that lives the longest. Some demographic forecasts suggest that most babies born since the year 2000 will survive to their 100th birthday. If these forecasts are correct, then there is reason to fear that the financial solvency of even the most prosperous countries are in jeopardy. We argue here that human biology will preclude survival to age 100 for most people.

Key Words: Life span—biological warranty period—longevity—life span extension—centenarian.

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FEW other subjects of scientific inquiry engender more media and public attention than aging and longevity. In fact, this intense interest has made it difficult to distinguish where the evidence-based conclusions of science end and the carnivalesque proclamations of pseudoscience begin (1). The scientific community has contributed to this atmosphere of hype and confusion by providing platforms (and thus credibility) for futurists and some scientists who agree with them to assert that the first 1,000-year-old person has already been born (2), a life span of several hundred years will soon become reality (3), bridges to immortality are already being built (4), and if the life expectancy gains observed over the last two centuries continue through the 21st century in countries that currently have high life expectancies, then most babies born since the year 2000 in those countries will celebrate their 100th birthday (5,6). Although these assertions are derived from very different arguments, they share a common conclusion; namely, that most people have the biological potential to live a century or more.

Promoters of large and rapid increases in life expectancy are not new, they are just the most recent advocates of a prolongivist argument that can be traced back to antiquity (7,8). Given the escalating costs and questionable solvency of age-based entitlement programs around the world, there is legitimate reason for concern. If the life span extensions already achieved are challenging the financial integrity of these programs, what would happen if half or more of a country's population actually did survive up to and beyond the age of 100? The credibility of this scenario depends on the question examined in this article: Can human biology, as it currently exists, allow most of us to become centenarians?

Demographic Realities

Before making biological arguments about demographic projections, we believe that there are also fundamental demographic reasons why modern prolongivist claims should be viewed with some skepticism. Between 1935 and 2000, the probability of surviving to age 100 (based on period life tables for the U.S. population) increased from 0.22% to 1.8% for females and from 0.09% to 0.49% in males (9). In Japan, where female life expectancy at birth is the highest in the world, the 2000 period life table estimate of surviving to age 100 was 4.5% (10). Based on a recently published projected cohort life table, the Social Security Administration's estimate of surviving to age 100 for U.S. females born in 2000 was 8.5% (11). A similar cohort-based projection made by the Office for National Statistics in the United Kingdom (12) estimated that 39% of females born in 2012 are expected to live to age 100. In contrast, as mentioned earlier, scientists adopting a prolongivist philosophy offer a much more optimistic demographic scenario for achieving centenarian status, one

that we believe to be fundamentally unattainable. For example, Christensen and colleagues (5) estimate that survival to age 100 for both men and women will be about 28 times greater than the period life table estimate for U.S. females in 2000, 11 times greater than the period life table estimate for Japanese females in 2000, close to 6 times greater than a cohort life table estimate for U.S. females in 2000, and 1.3 times greater than the cohort projection for U.K. females born in 2012 (Figure 1).

To provide historical perspective on these differences in modern estimates of survival to age 100, consider the fact that in 1900 cohort life expectancy for U.S. females (58.3 years) was 9.3 years higher than period life expectancy (9,11). In 2000, the gap between U.S. cohort (84.2) and period (79.4) life expectancy for females shrank to 4.8 years. In contrast, Christensen and colleagues (5) estimate suggests the gap between period and cohort life expectancy in 2000 will be 21 years—more than 4 times greater than the gap in the Social Security Administration Office of the Actuary tables (9,11). It is important to emphasize that historical cohort life tables are based on populations that have entirely died out, thus reflecting the true life expectancy of a birth cohort. However, contemporary cohort life tables remain speculative because they are based on assumptions about the future trajectories of mortality for people still alive. Within this demographic context, declaring that the probability of surviving to 100 was already 50% or more beginning in the year 2000 (based entirely on extending the historic trend of period life expectancy at birth forward in time) is not supported by either empirical evidence or historical precedent (Figure 1).

In order for most babies born in the modern era to live to age 100, death rates at older ages would not only have to fall dramatically, but they would have to do so at an accelerated pace (13). In effect, by hypothesizing that mortality beyond age 50 must decline at "a rate that yields yearly improvements in period life expectancy of 0.2 years," Christensen and colleagues ([5], p. 1196) are suggesting that it is already easier to add decades of life to older people today than it was to add decades of life to children dying from infectious diseases in the early 20th century.

The rationale used to support this demographic forecast is: (a) the claim that biological aging has already been delayed by human intervention ([6], p. 536), (b) the claim that cohort life expectancy at birth will exceed period life expectancy at birth by 21 years for babies born early in this century, and (c) the suggestion that declines in death rates for older people in the 21st century will occur faster than the reductions in death rates observed for young people during the 20th century. A more detailed demographic examination of modern prolongivist views can be found in Olshansky and Carnes (13).

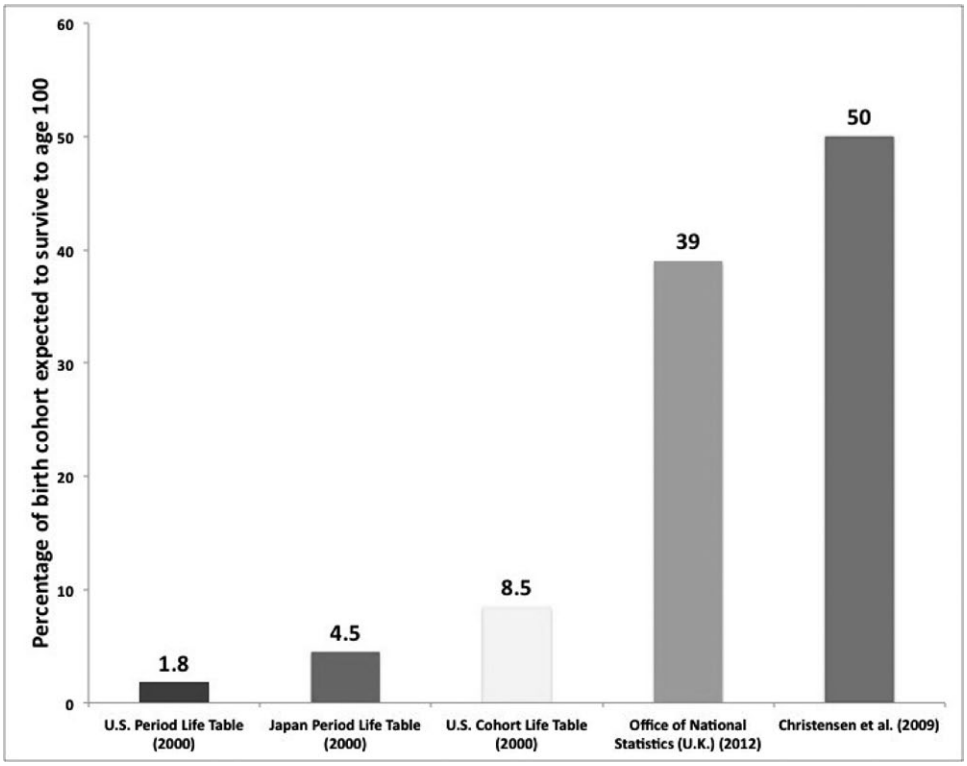

Figure 1. Percentage of birth cohorts expected to survive to age 100. *Sources*: Period life tables for females (Human Mortality Database, www.mortality.org), cohort life tables for females (SSA, www.socialsecurity.gov/OACT/NOTES/as120/LOT.html; ONS, [12]) and a period data–based prediction for both sexes combined (5).

Look Back, Not Forward

It is important to recognize that the world of today bears little resemblance to the environments of 200,000 years ago that shaped the biology we inherited from our ancient (anatomically modern) ancestors (14). Infectious and parasitic diseases, the rigors of childbirth, physical injuries, wars, predation, accidents, and hostile climatic events took a heavy mortality toll on our ancestors. Although data on survival are limited for humans living in prehistoric times, a life expectancy at birth of about 25–30 years in that era is reasonable (15), and one that is consistent with data-based estimates for ancient Rome during the 1st to 4th century AD (16) and extant hunter-gatherer societies unaffected by modernity (17).

Low life expectancies can give a false impression that high mortality populations have no long-lived members. Life expectancy at birth is heavily influenced (ie, lowered) by high early age mortality, a universal problem for humans prior to the middle of the 19th century. In extant hunter-gatherer populations, Gurven and Kaplan (17) report that there is a 57% probability of surviving to age 15, and a 37% chance of surviving to age 45, after which people are expected to experience another 20 years of reasonably healthy life.

Some might say that because modern humans have continued to evolve, they have different biological expectations for longevity and aging than our ancestors. This position, however, contradicts recent studies that apply SNP (single-nucleotide polymorphism) technology to examine evolutionary changes arising from the migration of humans out of Africa (18). Although geographic polymorphisms (genetic adaptations) related to migrations have occurred (eg, skin color, lactose tolerance, resistance to infectious disease, hypoxia mitigation), evidence suggests that most of the adaptations made over the course of human history have been cultural and technological (19). The logic for this assertion is that the slow pace of evolution could not possibly keep pace with the relative rapidity that humans populated the world.

The key point here is that modern and ancient humans share a common biology. The odds of becoming a centenarian were extremely small for our ancient ancestors, and remain so today even among the extremes of extant hunter-gatherer societies and people living in developed nations. Recall, only 5% of the Japanese babies born in 2009 are expected to survive to age 100 based on current period life tables (10). The survival disparities between hunter gatherers and populations in developed countries today are testaments to Medawar's (20) observation that aging "is in a real and important sense an artifact of domestication; that is, something revealed and made manifest only by the most unnatural experiment of prolonging an animal's life by sheltering it from the hazards of its ordinary existence."

Life Span Versus Longevity

Life span is an individual's observed duration of life from birth to death. As such, becoming a centenarian is about achieving an exceptionally long life span in a genetically heterogeneous population where this has always been a rare event, and remains so today. By way of context, the 2010 Census for the United States (21) reports that in a population of 308,745,538 people there were 9,162 males (6 per 100,000) and 44,202 females (28 per 100,000) that were 100 years or older. These are not great odds, especially if you are male, and those odds drop considerably lower for people living in countries with health care systems less advanced than those in developed countries, and they drop even further when it is recognized that "age exaggeration" is a widely documented phenomenon (22).

A focus exclusively on longevity misses several important lessons from biology. One of the most important of these is that life on earth would not exist without reproduction. The ability to reproduce, however, requires a developmental period to achieve sexual maturity and for many species also includes a period of nurturing, postreproductive parenting, and even grandparenting (23). In other words, this process takes time and time means exposure to mortality risks. There is, therefore, a race between reproduction and death where intense selection pressures mould a biology capable of achieving Darwinian fitness (24). This window of time has been given various labels such as "essential life span" (25), "biological warranty period" (26), and "longevity determination" (27), and it is so biologically critical that it must be under intense genetic regulation (28). Given the ancient mortality pressures that shaped our biology, that window probably extends, at best, to the early to mid-sixties, and it most certainly does not include age 100 or beyond.

The Right Stuff

If our species' biological warranty period for survival does not include centenarians, then there must be an alternative explanation for their existence. Obviously, there are ways to achieve exceptional longevity because an estimated 53,000 centenarians and supercentenarians were living in the United States in 2010 (29). It is probable that every pathway to surviving 100 years requires having won the genetic lottery at birth (30,31) and avoiding events that cause premature death (32–35). Being female clearly increases those odds as does a history of long-lived relatives and ancestors (36,37), with a long-lived mother appearing to be particularly important (33,38,39). Like athletic tournaments, centenarians are people who reached the finals. They are different from people who die at earlier ages and those differences likely involve genetic polymorphisms (longevity alleles) that enhance resistance to diseases and disorders that kill other people at younger ages (40). Mimicking the lifestyles of centenarians in order to live longer is unlikely to work for the rest of the population because while survival to extreme ages is not exclusively a genetic phenomenon (41), it is very likely

that the right genetic keys are required to enter those ages (42–45). Furthermore, there is no "centenarian lifestyle" that is common to all centenarians. It is this recognition that human populations are a highly heterogeneous mixture of subgroups that, besides socioeconomic, educational and ethnic diversity, also includes numerous biologically defined subgroups (of which centenarians are only one) that is missing from the information used to inform demographic models of longevity or life expectancy (46).

Interventions

If someone lacks the genetic endowment required to become a centenarian, then the only way to achieve this milestone is to find ways to manufacture large amounts of survival time (47). There are three basic ways to extend life span (in increasing order of difficulty): (1) continue reducing avoidable mortality, (2) develop pharmaceuticals that mimic the life span extension benefits of longevity genes, and (3) slow the catabolic effects of aging. Cultural adaptation and technology has taken humans from caves to temperature-regulated houses, from hunting and gathering to grocery stores containing unlimited calories, from Shamans and medicine men to physicians with access to remarkably sophisticated technology. Despite these monumental advantages of modernity, the probability of surviving to age 100 in 2006 for the most advantaged subgroup of the U.S. population (non-Hispanic whites with postgraduate educations and economic advantages) was still only 3.4% for females and 1.5% for males, approximately 15 and 33 times lower, respectively, than predicted by life extension forecasts (5) for female and male cohorts born at the beginning of the 21st century.

Most of the gains in life expectancy achieved during the 20th century were achieved by discovering new and improved ways to protect or cure children and young adults from the mortality and morbidity consequences of infectious diseases and saving mothers from dying during childbirth (48). Although ways to reduce avoidable mortality will continue to be found, they will not generate death rates that approach or reach zero. People simply do not live perfect lives in perfect environments while also avoiding the detrimental consequences of being in the wrong place at the wrong time. Modernity has also extended childhood by progressively delaying the age of "social" maturity (education completed, job, marriage, children). When childhood is extended, the mortality consequences typically associated with it (an increase in premature deaths) are also likely to be extended. If the elderly people in the future are not healthier (lower accumulated pathology burdens) versions of today's elderly people, then avoidable mortality will remain a serious threat to them in the future.

Will there be progress in manipulating human biology in order to save the lives of people who would otherwise have died at an earlier age? Currently, genetically engineered extensions of the human life span are beyond our understanding of the genetics of longevity. In the future, the question will not be can we do this, but should we artificially manipulate the human genome in order to extend life span? As progress is made toward reducing one kind of disease (eg, heart disease), another will rise up to fill the void. It is also likely that diseases that manifest at progressively older ages will be progressively more difficult to cure and/or manage because the homeostatic capacities of the body tend to be compromised at those ages. Stem cell technologies and organs created from the patient will extend life spans, but anyone who owns an old car knows that despite extensive repairs and part replacements, the car still eventually ends up in the junk yard.

Even successful extensions of life span will likely be accompanied by tradeoffs that frequently involve reductions of fecundity and/or a sacrifice of robustness (49–51). These tradeoffs will have to be weighed when deciding whether to introduce a life span extending intervention before or after the reproductive phase of the life span. How much of the intended longevity benefit will be lost if introduced postreproductively in order to avoid costs to fecundity and robustness? Finally as a caveat on upper boundaries, a single gene does not define organisms and it is unlikely that tweaking a single gene will transform noncentenarians into centenarians. As such, the odds of becoming a centenarian may be modestly increased for people who would otherwise be likely to die in their nineties, but a modest increase of a small probability is still a rare event.

If aging itself becomes the predominant mortality risk at the oldest end of the age distribution, then further life extension becomes even more difficult to achieve. There are several reasons for this. The scientific and lay literature often refers to the discovery of "aging" genes that, if manipulated, could dramatically extend life span by slowing aging. This merger of aging and genes, however, is a conflation of incompatible concepts. There is a growing body of evidence and scientific consensus that aging is largely a stochastic process (52) or complex mixture of stochastic processes (53). If true, then extending life to 100 years or more for at least half of the population by manipulating the human genome is unlikely to work. Further, if aging is a complex mixture of stochastic modalities interacting with varying degrees of interdependency (54), then it is exceedingly improbable that a "silver bullet" intervention can be created that simultaneously negates all of the catabolic modalities of aging. The stochastic and fragmented nature of aging makes it far more resistant to modification than the vulnerabilities to frailty, morbidity, and disease that accompany it.

Discussion

Demography and actuarial science are mathematical disciplines that quantify the survival and mortality characteristics of populations. There has been a long history of

inquiry into whether the data and methods of demography can provide biological insights on the organisms they model (55–58). There are several challenges to this merger of biology and demography. One of the biggest is data; linking biomedical information to life span data cannot be done with the traditional cross-sectional data (a snapshot of a population at a moment in time) most accessible to population scientists. Cohort and registry studies exist (eg, Framingham and Honolulu Heart Studies) but their sample sizes are limited and their data collection is often focused on specific diseases (eg, cardiovascular disease, neurofibromatosis 1) or ethnic groups (eg, Japanese American and Okinawan Americans in Hawaii).

Another significant impediment involves how death rates are calculated; the numerators are death counts and the denominators are time of exposure to risk of death (eg, person-years in human data). Raw age-specific death counts are easy to obtain, but for biological investigations it is necessary to know what caused or contributed to death. The latter information comes from death certificates, most of which involved no autopsy and are, therefore, considered to be highly inaccurate especially at older ages and likely to undercount less common causes of death (59). Ignoring cause of death (ie, using all-cause mortality) avoids the death certificate issues, but doing so creates a conceptual problem that has a large impact on predicting how many people in the future will survive beyond age 100.

Demographic forecasts of extreme life extension (5,6,60,61) are based on the assumption that all-cause mortality trends in the future will be an extension of those observed in the past. Because those trends have followed a downward trajectory, researchers who rely exclusively on these trends see no biological or demographic brakes operating on the life span of individuals or the life expectancy of populations. However, in terms of what we die from, the present has already departed from the past. There has been a fundamental transition from avoidable deaths that occur early in life to more intractable deaths linked to the accumulated failure (aging) of bodies that are not designed for extended operation. These latter causes can often be medically managed (ie, progression of pathogenesis delayed) but rarely cured (eg, central nervous system diseases and the majority of cancers and heart diseases). As populations move beyond the biological warranty period for humans and deeper into the unchartered waters of Medawar's unnatural experiment, the future currents of mortality will be harder to navigate and far different than a simple repetition of past trends because the old (acute) diseases we know will give way to new (chronic) diseases that are either unknown or rare today.

The hypothetical lack of demographic constraint on longevity at the population level also conflicts with what is known at the individual level; namely, that while humans are not designed to fail, neither are they designed for extended operation (26). In humans, the period of normal operation (biological warranty period) goes from conception to postreproductive parenting as well as an opportunity for grandparenting (25,28,62). Postreproductive parents and to a lesser degree, grandparents, provide cultural and demographic benefits to a population (63) that extend well beyond the purely Darwinian benefits (24) conferred on their children. The issue is when do these biological milestones occur in humans. Given that we are living in Medawar's unnatural world of "protection from the hazards of ordinary existence" (20), today is neither the right time nor the right place to identify the ages associated with these critical life history milestones.

Hunter-gatherer societies isolated from modernity provide the closest approximation to the biology we inherited from our ancient ancestors. Because menarche in hunter-gatherer societies ranges from 13 to 15 years, grandparenting would have begun as early as 30 years of age (23). Upon reaching menopausal age (~45 years), men and women in hunter-gatherer societies can expect to live another 20 years in relatively good health (17,64). Based on these documented anthropological observations, the biological warranty period for humans ends and the period of extended operation begins at about age 65. Beyond that age is a period of extended operation where mortality rates in hunter-gatherer societies climb dramatically and survivors experience precipitous declines in health and physical function. Life expectancy at birth in the United States (both sexes combined) crossed that boundary into the period of extended operation in 1944 and reached 78.3 years (80.2 for women and 75.6 for men) in 2007 (10). Although this was a remarkable extension of the human life span beyond the warranty period, it still requires all the major causes of death that appear on death certificates to be eliminated (65) or all avoidable mortality to be eliminated (26) in order to have life expectancy extended to about 90 years for men and women combined.

The reality, however, is that avoidable mortality will always be a significant contributor to the human mortality burden, genetic engineering will always be accompanied by unintended biological consequences, and the stochastic and fragmented nature of aging will continue to be an elusive target for interventions. Scenarios of extreme or radical life extension must overcome two inescapable biological realities: (1) the only longevity that matters is the shortest one (warranty period/essential life span) that permits Darwinian fitness to be achieved, and (2) as age increases so does the pathology burden and the resulting degradation of biological function (66). Life expectancy and maximum life span are demographic metrics that are clearly useful for developing social policies in an aging world. Thus, they are concepts worthy of scientific examination and debate. However, it is equally important to put them in their proper context. In the modern world, both demographic metrics have become measures of how far human intervention has already extended survival beyond the human warranty period. As such, if reaching a life expectancy of 90 requires successfully

managing the imploding biology of bodies not designed for extended operation, then having 50% or more of populations in developed countries becoming centenarians will remain as elusive as the Fountain of Youth was for Ponce de León.

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