From Michelangelo to Darwin: The Evolution of Human Longevity

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"What is the natural, usual, and normal duration of the life of man?" [1]. When Florens asked this question in his 19th century book *Human Longevity and the Amount of Life Upon the Globe*, he was seeking an answer to an age-old question that has been the subject of inquiry and debate for thousands of years. Throughout history, the greatest thinkers of every era not only speculated about the duration of life [2,3], but many also devised what they believed were methods of modifying how long people are capable of living [4]. Questions of this sort are no longer esoteric, for how long we live as individuals and populations has important public policy implications. For example, the future solvency of age-entitlement programs (such as those involving retirement and health) is heavily dependent on how many people will live to retirement age and how long they will draw benefits from such programs. As such, forecasts of the duration of life have taken on new meaning in the public policy arena [5–8].

Although some researchers have used mathematical extrapolation models to forecast that human life expectancy at birth will rise steadily to 100 years by the year 2060 [9], others have suggested that such models, and the assumptions upon which they are based, are unrealistic because they completely ignore the underling biological forces that influence (and limit) the duration of life [10,11]. Furthermore, there is now strong theoretic and empiric evidence suggesting that the lifespans of individuals and the life expectancy of populations are fundamentally influenced and limited by biological forces that represent currently immutable genetic characteristics of the species [10]. In this review I will summarize these arguments briefly and suggest that in low mortality/high life expectancy populations, an effective biological barrier to further dramatic increases in human life expectancy is being approached.

The evolutionary model of senescence

When Michelangelo painted the Creation on the ceiling of the Sistine Chapel in Rome in the 16th century, he portrayed the Renaissance view of mankind as having been molded by the hand of its creator, in his image, as a "perfect" physical specimen. When Charles Darwin was drafting his theory of evolution in the late 19th century, it was ironically the imperfections in the anatomic structures and functions of humans and other living things that were presented as the strongest evidence for his theory [12]. Based on theoretic and empiric evidence from modern evolution biology and biogerontology, it now appears that *both* Michelangelo and Darwin were right.

The artistic-like perfection of the human body is exemplified by the near flawless maintenance and perpetuation of the immortal germ line through sexual reproduction. However, the price paid for this form of immortality is a suite of anatomic structures and functions that, when used beyond what may be thought of as their biological or Darwinian warranty period [10,13], inevitably lead to many of the diseases and disorders now commonly associated with aging or senescence. The divergent but intimately linked views of Michelangelo and Darwin exemplify the importance of a biological perspective on aging, the diseases that accompany it, and ultimately the forces that influence and limit the duration of life of individuals and populations.

In order to understand why species live as long as they do, it is important to recognize and appreciate the evolutionary theory of senescence. At the heart of this theory is a fundamental biological link between the timing of reproduction and death. According to evolution theory, the force of natural selection begins to decline rapidly once reproduction commences at puberty, approaching negligible levels at the end of the reproductive window (at menopause) [14]. What is meant by "the force of natural selection" is the ability of selection to influence the distribution and frequency of alleles in subsequent generations.

According to Medawar [15], natural selection operates not just on individuals, but also on all of the genes in our bodies. As the force of selection wanes following the onset of puberty, it then becomes possible for harmful alleles to accumulate in the gene pool because under normal living conditions there is no penalty for detriments to health occurring in older regions of the lifespan where only a few members of the species normally survive [15–18]. Thus, genes that prove to be harmful are figuratively 'pushed' by natural selection to later and later ages, where they have less of an effect on reproduction. Over many generations, harmful alleles will tend to have their age of expression accumulate at or near the end of the reproductive window and beyond [15,16]. Williams [18] later extended this theory by suggesting that natural selection would favor the accumulation of genes that do beneficial things early in

life, even if they are known to be harmful later in life. This concept, known as antagonistic pleiotropy, operates under the same premise that there would normally be no penalty for favoring genes with harmful effects expressed later in life, as long as they enhance reproductive fitness.

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

Empiric tests of these hypotheses have shown that the age trajectory of death is, in fact, a species-specific phenomenon that, as predicted from evolution theory, is calibrated to the onset and length of a species' reproductive window [19,20]. This means that sea turtles, whales, elephants and humans – species that experience an extended period of growth and development, a significant delay in puberty, and a longer time window within which reproduction can occur – live longer than species that reproduce early and for shorter time periods.

It is important to remember that the reproductive window is a genetically determined and fixed attribute that is established as part of every species' life history strategy that was molded by the environment within which species evolved. If aging is indeed an inadvertent byproduct of genetically fixed programs for growth, development and reproduction, then there can be neither death genes nor longevity genes that evolved under the direct force of natural selection. In the absence of such genes, it is unlikely that researchers will ever find a master aging switch that can be manipulated in order to make us live longer. The good news is that in the absence of a genetic program for aging, its manifestations (e.g., many of the physiologic parameters that change with the passage of time and which cause both frailty and death) are inherently modifiable. This is why exercise, diet and pharmaceuticals have been used successfully to modulate both physical and physiologic attributes of our bodies.

How much do we control our aging destiny?

A persistent concept that emerged from the major World religions and has appeared repeatedly in legends from almost every culture dating back to antiquity [4] is the idea that humanity is in control of our own aging destiny. Familiar examples include an immortal Adam in the Garden of Eden before his fall from grace, and biblical patriarchs like Methuselah who was said to have lived 969 years. The most common historical explanation for the loss of immortality, the lack of perfect health, and the steady decline in human longevity since the time of the patriarchs has been that each new generation has adopted increasingly more decadent lifestyles. Roger Bacon, an influential English philosopher and scientist of the 13th century was the first to popularize this view [21]. However, he also believed that the trend toward shorter lifespans could be reversed by invoking the "secret arts" of the past – namely, the adoption of more restrained lifestyles and the ingestion of foods and other substances believed to have life-extending properties. Thus, the perspective that aging and diseases are amenable to modification through changes in lifestyles, which is the basis for contemporary medical and epidemiologic views of chronic degenerative diseases, has its origins in thinking that extends back in time at least one thousand years, and perhaps as far back as the golden mean in Greek philosophy.

These persistent beliefs about aging and disease that have been passed down through time have spawned two other positions that continue to have a significant philosophical and practical influence on contemporary scientific views of mortality. The most important of these is the belief that aging and disease is unnatural and are, therefore, somehow avoidable. The second is the notion that the health and longevity consequences associated with perfection can be reclaimed through human actions. These beliefs and the quest for longer lives that arise from them have become a central part of the paradigm of modern medicine and the effort of epidemiologists to understand how risk factors alter death rates.

On the surface, this philosophy of personal empowerment is seductive. After all, people want to believe that they have some control of their own aging destiny. However, an evolutionary perspective suggests that aging and many of the diseases that accompany it are not deviant departures from perfection, or even the sole consequence of moderately decadent lifestyles. Instead, they are primarily the consequence of operating our living machines beyond their biological warranty period [10] (e.g., beyond the end of the reproductive window, and for some species, into a region of the lifespan where grandparents can contribute to reproductive fitness of offspring). Thus, the romantic philosophy that people are empowered to control their own aging destiny becomes, in modern times, an ideology of personal blame. In effect, we are inappropriately held responsible for many of the diseases and disorders that we experience as we age, and more importantly, are led to believe that aging and the diseases that accompany it are largely avoidable. An evolutionary view leads to the realization that even though aging, disease, and death are not programmed into our genes, once the engine of life is switched on at conception, our destiny as an aging animal is written in stone. Our bodies fail over time not because they were designed to fall victim to aging and disease at a predetermined age [22], or because of the acquisition of decadent lifestyles, but because they were not designed for extended use.

Will there be another quantum leap in life expectancy?

Rapid declines in infant, child, maternal, and late-life mortality led to an unprecedented 30-year increase in human life expectancy at birth in the 20th century. The vast majority of this increase reflects dramatic declines in mortality risks in childhood and early adult life. Since the young can only be saved once and because these risks are now so close to zero, further improvements in this age range, even if they occurred, would have little effect on life expectancy. Future gains in life expectancy will, therefore, require adding decades of life to people who have already survived seven decades or more. Since the processes of aging impede mortality declines among people living into older ages in a fundamentally different and far more insidious way by comparison to the impact of infectious

diseases on early age mortality, most biogerontologists now believe that another quantum leap in human life expectancy can occur only if it becomes possible to intervene in the fundamental processes of aging [23]. Although it may eventually become possible to alter the biological processes that contribute to aging, that day has not yet dawned.

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