What is healthy aging in the 21st century?1–4

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ABSTRACT
In the coming years, human aging will be one of the biggest challenges faced by industrialized countries. The average life expectancy is continuously increasing and we may be faced with spending more years in poor health. Because aging is a relatively modern phenomenon, we lack knowledge for a proper understanding of this process. Current biological thinking emphasizes that organisms are encoded for early survival and reproduction, humans not excluded. Aging is not programmed nor is it inevitable. Life span is the result of the interactions between genes and the environment in which we live. In the original habitat, genes encoding early survival and reproduction were optimized in an everlasting attempt to increase fitness and prevent the species from extinction. Aging is best explained as a cost of optimizing fitness because investments in body maintenance and repair cannot be maximized. The environment also determines how a gene influencing life span is expressed over a lifetime. When the conditions in which we live significantly improve, mortality decreases, evolutionary pressures for early survival and reproduction relax, and further resources can be invested in body maintenance and repair, which increases both average life expectancy and maximum life span. Increasing our understanding of the aging process and applying available interventions will help to protect and preserve healthy aging. Am J Clin Nutr 2006;83(suppl):404S–9S.

KEY WORDS Aging, morbidity, mortality, proinflammatory response, antiinflammatory response, disposable soma, evolution, genetics, life span, longevity, genome, Darwinian fitness, early survival, environment, TNF-α, IL-10

INTRODUCTION
Editor’s Note: This article is based on the Keynote Address at the Living Well to 100 Conference held at Tufts University. The author was specifically asked to review the current issues influencing healthy aging and future directions to set the tone for the emerging science on nutrition and genetics as presented in the remaining session. As such, this article should be viewed as laying the practical foundation for the science presented.

In the years to come, addressing the cumulative damage associated with aging will be one of the biggest challenges faced by industrialized countries. Since the industrial revolution in the middle of the 19th century, average female life expectancy has increased in Western societies from ≈45 y to currently >80 y, which corresponds to an increase of 2.3 y per decade (1). Life expectancy has also risen for men, although more slowly; over the years, the gap between females and males has extended from 2 to 6 y (1). The increase in life expectancy since 1850 is a straight line, and there are no indications that life expectancy is leveling off (Figure 1), despite the estimates of the United Nations, who predicted the rate of increase to plateau (2).

The curve for Japan provides a key to what drives life expectancy. No other country has seen such a dramatic increase in life span. From 1900 until the Second World War, life expectancy in Japan lagged behind other countries by as much as 30 y. At that time, Japan was an economically poor, agricultural society. Since World War II, Japan has experienced unprecedented economic and social development and now has the highest life expectancy in the world. Although debate exists as to the specific elements involved, wealth and an affluent environment correlate closely with life expectancy. Improvements in sanitation, education, nutrition, and medicine afforded by increased wealth are positive indicators of long-term health and decreased early mortality for entire populations.

LONGER WELL OR POORLY LONGER?
The increase in average life span observed in all developed countries is accompanied by an incremental burden of age-associated diseases. The expectation is that scientific advances will prevent disease from occurring or, if disease does strike, will protect us from permanent damage. Over the last 20 y, the United Kingdom has gained about 4 y in both female and male life expectancy, but only 2 y in healthy female life expectancy (3). The overall increase is far greater than that for healthy living, and this contradicts recent thinking. In 1980, Fries (4) published the concept of compression of mortality and morbidity, on the basis of survival curves. Juxtaposing curves from 1900 and 1980, it appeared that the curve became rectangular with increasing survival to higher age (Figure 2).

Projecting the same curve forward in time, it was expected to become even more rectangular, to a point where individuals all survive to a similar age. Mortality would be compressed into a shorter period; individuals born around the same time would die over the same 5–15-y period instead of being threatened over the...
lifetime. And, as Fries concluded, because there is no mortality without disease, compression of mortality also implies compression of morbidity; individual suffering before death would also be limited to those 5–15 y.

The difficulty with this concept is that it assumes a fixed maximum human life span. It became clear in the 1980s that this is not the case. The concept also fails to consider the effects on survival of the extreme environmental change that occurred during the 80 y between data sets, therefore assuming that survival was independent of environmental factors.

When we examine age at death in Sweden over the last 140 y, we notice a steep increase over the last 40–50 y. Examination of trends in the improvement of survival show that the tendency of the survival curve to become rectangular existed only for the period between 1860 and 1950. From then on, there was a parallel shift of the curve to the right (5; Figure 3).

In 2000, using the same data sets, Wilmoth et al (6) further calculated that the rise in the maximum age at death in Sweden from the 1860s to the 1990s was due primarily to reductions in mortality at older ages. Of the total increase, 72.5% was attributable to decreased mortality above the age of 70 y. The increasing size of successive birth cohorts and decreased mortality below the age of 70 y accounted for the balance. It is known that a reduction in old-age mortality has been a primary factor behind population aging and the proliferation of centenarians during recent decades. Wilmoth et al also showed that the mortality decline above the age of 70 y has been the main cause of a gradual increase in maximum achieved life span over more than a century. Only a minor part of this increase is due to the larger size of recent cohorts, which are defined either as numbers of children born each year or numbers of survivors to old age. It appears that, although the maximum age has increased more slowly than the average, the entire distribution of age at death has been shifting upward for more than a century in industrialized countries.

Current biological thinking emphasizes that organisms are encoded for early survival and reproduction to prevent the species from extinction. Humans are unlikely to be excluded from this evolutionary program. In contrast with the strict control over the first one-half of (human) life history, aging is not programmed. Because a mortality program is absent, aging is not inevitable (7). The rightward shift of the survival curves and analyses of changes in mortality patterns from the last half-century are in line with the basic idea that there is no biological limit to life. Therefore, compression of mortality and morbidity is not valid either. It may even be, because we still suffer from disease in middle age, that there is actually a decompression of morbidity, as the trend in the United Kingdom suggests. Analysis of death registries in the Netherlands corroborates the UK findings.

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1989 to 2000, average life expectancy increased by 2 y accompanied by an increase in the number of years with disease, hence, decompression of morbidity. Under current conditions, we are going to live longer with more years spent in poor health (9).

**THE KNOWLEDGE SHADOW**

On further improvement of our environmental conditions, with a continuous increase in average life expectancy and no biologically determined limit, the question becomes one of disease-related morbidity. How do we optimize an increasingly aging population’s health such that we don’t simply spend more years in misery before we die? The answer lies in a thorough understanding of the aging process and how available interventions may be applied to protect and preserve health.

Of immediate concern for health of the ever-increasing numbers of elderly is our constrained knowledge domain. The bulk of medical research has been invested in early development, adulthood, and middle age. Scientific and medical advances in the past century targeted prevention and control of diseases that threatened survival through the “prime” years, and these represent enormous contributions to the quality of life we now enjoy in youth and middle age. While this was happening, however, we were not investing in our understanding of the natural consequence of this, ie, a growing elderly and aging population. Data from Sweden and the Netherlands show that ≈80–90% of deaths now occur after the age of 75 y. The problem is that deaths at this age are actually occurring in a “knowledge shadow.”

**WHY WE AGE: THE DISPOSABLE SOMA THEORY**

The process that underlies the likelihood of disease and death in old age is considered to occur through the accumulation of environmentally influenced molecular and cellular damage. Host response mechanisms responsible for the maintenance and repair of somatic cells and tissues are limited because they occur at a cost of investments in early survival and reproduction (10). Accumulated molecular and cellular damage causes cellular and tissue dysfunction that, in the organism as a whole, will lead to disease, disability, and death (11). As we age and accumulate “scars” of incomplete repair, we become brittle, more susceptible to disease, frail, and thus more likely to die. In humans, such degenerative processes were seldom seen within the age ranges commonly experienced until improvements in survival extended the average life span. In the “original” environment, under adverse conditions, there was no advantage in investing in higher levels of maintenance than were required to keep the body in good condition for as long as it needed to reproduce an offspring that had a reasonable chance of remaining alive. As a result, Darwinian fitness has biased the population genome we carry toward early development and reproductive effort. The theory of disposable soma suggests that if the finite metabolic resources are used for somatic repair, eg, to extend healthy age, then an earlier fitness attribute, ie, reproduction, must be killed to compensate. This has proven to be the case in *Drosophila* and *Caenorhabditis elegans* (11).

An illustration of the disposable soma theory in humans is shown in Figure 4, in which death age versus reproductive patterns in a closed and environmentally uniform society, ie, the British aristocracy, is plotted (12, 13). Reproductive success was low in women who died young and increased with increasing age at death to late middle-age. From then on, however, it declined again in women who survived to ≥80 y. This was most pronounced in the period before 1700 when living conditions were relatively poor and life expectancy was ≈40 y. The trade-off is unlikely to have been an intended effect: family planning, either to control family size or to promote maternal longevity, was not in practice at the time. Apparently, women with more durable
the new objective of late survival (14). Late in life, a proinflammatory response mode has been associated with high body mass index, cholesterol, lipids, and risk of cardiovascular disease, stroke, and dementia (17).

REGULATION OF THE INFLAMMATORY HOST RESPONSE

Cytokines, which are the signaling peptides of various cells of the immune system, are important regulators of the type of host response the organism will produce. Compounds such as the proinflammatory cytokine tumor necrosis factor α (TNF-α) mediate the inflammatory response to fight infection. Regulatory signals such as interleukin 10 (IL-10) switch off the inflammatory response to reduce collateral damage.

Aging is associated with chronic, low-grade inflammatory activity; systemic chronic inflammation has been found to be related to mortality risk from all causes in older persons (18). Age-related diseases such as Alzheimer disease, atherosclerosis, diabetes mellitus, sarcopenia, and osteoporosis are initiated or worsened by systemic inflammation, which suggests the critical importance of unregulated systemic inflammation in old age (18–20). Accordingly, proinflammatory cytokines are believed to play a pathogenic role in age-related diseases, and genetic variations located within the promoter regions of these genes have been shown to influence the susceptibility to age-related diseases by increasing gene transcription and therefore cytokine production (20, 21).

Conversely, genetic variations determining increased production of IL-10 or decreased production of TNF-α have been shown to be associated with healthy aging, which suggests a role for the control of the proinflammatory mode in older age (22). Predetermination of inflammatory or antiinflammatory mode is genetically controlled and is likely a result of Darwinian fitness pressure. Humans have been programmed for a proinflammatory response mode sufficient to survive long enough to reproduce without too high a risk of death from infection (Figure 5).

However, when we invest more heavily in the proinflammatory mode, we sacrifice fertility, because successful pregnancy requires an antiinflammatory phenotype (23). The investment in proinflammatory mode by our natural genome, then, must have a limit. If it moves too far to the right, the fitness cost in reproductive capability discourages survival of the species. This concept may explain why British aristocrats who lived longer were less likely to reproduce. Their innate proinflammatory immune system favored resistance to infection. At the same time, it prevented pregnancy from proceeding, a trade-off that became more pronounced under poor environmental conditions. It also explains why a genotype associated with impaired fertility persisted despite its obvious disadvantage with respect to evolutionary fitness. Selection for resistance to infection was traded against selection for fertility, which resulted in a compromise that was optimal for the fitness of the species in the particular environment.

ORIGINAL GENES IN A NEW ENVIRONMENT

Currently, we have a fairly solid understanding of the evolutionary mechanisms that make us age and also allow us to survive in such disparate environments as Greenland and the Sahara. Darwinian fitness constantly shapes the genome to better adapt
the organism to its habitat. Our mounting life span is determined by genes that were originally selected for survival in an adverse environment and are now expressed under completely new affluent environmental conditions. This may result in different, sometimes opposing biological effects. For instance, the *Drosophila melanogaster* gene chico encodes an insulin receptor substrate that functions in the insulin/insulin-like growth factor (IGF) signaling pathway. Fruit flies with a chico mutation have reduced insulin signaling and a longer life span when the adults are fed a concentrated food diet mimicking affluent environmental conditions (24). This coincides with evidence that reduced insulin signaling is associated with longevity in a variety of species. Recently, we found evidence that reduced insulin signaling is also associated with longevity in humans (25).

The chico mutant, however, shows a shorter life span than wild-type flies when kept under diluted, natural food conditions (26). This interaction between genes and environment had remained unnoticed under standard affluent laboratory conditions. The lower survival probabilities under low food conditions explain, from an evolutionary point of view, that the chico mutant did not emerge in the natural habitat but only under experimental affluent conditions. It also explains why humans were selected for insulin sensitivity, improving handling of scarce food and survival probabilities (27). Now it appears that high insulin signaling under affluent environmental conditions is suboptimal (25) but was never optimized to match a surplus of food.

ENVIRONMENTAL IMPRINTING

An open issue in aging research is the extent to which responses to the environment during development can influence variability in the life span in animals and the health profile of the elderly in human populations. Both affluence and adversity in human societies have profound effects on survivorship curves, and some of this effect may be traceable to effects in utero or in infancy. Data from human observational studies suggest that a pregnant woman’s diet affects not only the health of her children but also that of her grandchildren (28). The idea, known as the Barker Hypothesis, links diet in very early life to disruptions in glucose-insulin metabolism in later life and has attracted much attention, as well as some controversy, in medical circles.

One crucial mechanism by which animals can respond in an adaptive manner to adverse conditions, for example in nutrition or infection, during development is phenotypic plasticity, which describes the ability of a genotype to express different phenotypes in response to different environments. However, phenotypic plasticity is only rarely considered by evolutionary biologists or by biogerontologists studying model organisms such as *C. elegans* or *Drosophila*. Recently, we started a discussion of adaptive plasticity in animals, asking what such a phenomenon may reveal that is relevant to the rate of aging in animals and in humans, and to gather the evidence that environmentally mediated events taking place very early in life may determine the biological status of an individual at the end of life (29).

The biological mechanisms underlying this heritable, epigenetic information have yet to be understood. The findings, however, corroborate findings concerning the regulation of life span in ants and honey bees. Secretion of larvae juvenile hormone (corresponding to thyroid hormones in humans) is food-dependent. Should it be stimulated at a critical time in development, the larvae develop into diploid queens with a prolonged life span. In the absence of this food-triggered hormonal signal, the same larvae will develop into haploid workers with a short life span (30). This signaling by the environment to invest particular attributes in the new organism is an example of early environmental programming. Applied in humans, and given our much longer average life span relative to ants and honey bees, depending on early environmental programming of food, a life history of 100 y could only be an average. There is enormous potential plasticity in our life history, but we have not yet identified the signals controlling it.

CONCLUSIONS

Aging is under environmental and genetic control, but it is not programmed nor is it inevitable. As evolutionary pressures for early survival and reproduction decrease, more metabolic resources can be invested in soma maintenance and repair, which
increases both average life expectancy and maximum life span. Aging is best explained as the balance between investments in fitness and investments in body maintenance: if investment in body maintenance is not optimal, aging occurs. Increasing our understanding of the aging process and applying available interventions will greatly enhance healthy aging.

The author had no conflicts of interest to report.

REFERENCES