LONGEVITY DETERMINATION AND AGING

(Adapted and updated from "The Future of Aging", L. Hayflick, Nature, 408, 37-39, November 9, 2000)

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ABSTRACT

Advances in our knowledge of age-associated diseases have far outpaced advances in our knowledge of the fundamental aging process that underlies the vulnerability to these pathologies. If our goal is to increase human life expectation beyond the fifteen-year limit that would result if the leading causes of death were resolved, more attention must be paid to fundamental research on aging. Longevity determination must be distinguished from aging to take us from the common question: Why do we age, to a more revealing question that is rarely posed: Why do we live as long as we do? However, if the ability to intervene in aging processes ever becomes a reality, it will be rife with many undesirable and unintended consequences.

KEY WORDS: aging, senescence, longevity determination, disease, life span, life expectation, genes

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INTRODUCTION

Research on aging entered the main stream of biological inquiry about thirty years ago but few notable advances have occurred in our understanding of the fundamental human aging process. Notable success has only been achieved in our knowledge and treatment of age-related diseases.

The failure to distinguish between aging research (biogerontology) and research on age-associated diseases (geriatric medicine) has been, and still is, the source of many

misunderstandings that have led to important scientific, political and societal decisions that have yet to be fully appreciated. There is little evidence that these misunderstandings, with their serious consequences, will soon be rectified. Thus, the present imbalance will continue in which resources available for research on the diseases of old age far exceed those available to increase our understanding of the ultimate question: Why are old cells more vulnerable to disease than are young cells?

Policy makers, properly impressed with the future demographics of the graying of all economically developed countries, are basing important policies and decisions on a flawed understanding of
what constitutes aging research and what they believe might be accomplished.

DISEASE AND AGING

Aging is not a disease and the distinction is central to an understanding of why the resolution of the leading causes of death in old age, - cardiovascular disease, stroke, and cancer, will tell us little about the fundamental biology of age changes. The resolution of all three causes will result only in an increase of about fifteen years in human life expectation (Anderson, 1999a). Then, aging, or the inexorable loss in physiological capacity that underlies the cause of these pathologies will be revealed as the leading cause of death.

Resolution of age-associated diseases will advance our knowledge of aging processes to the same extent that the resolution of pediatric associated diseases such as poliomyelitis, acute lymphocytic leukemia, Wilms' tumors and iron deficiency anemia advanced our knowledge of childhood development. That is, no advancement occurred at all.

Disease processes can be distinguished from age changes for at least five reasons. Unlike any disease, age changes occur in every animal that reaches a fixed size in adulthood. Unlike any disease, age changes cross virtually all species barriers. Unlike any disease, age changes occur in all members of a species only after the age of reproductive success. Unlike any disease, aging occurs in animals removed from the wild and protected by humans even when that species has not experienced aging for thousands or even millions of years. Finally, unlike any disease, aging occurs in both animate and inanimate objects.

Today, the study of age-associated diseases and manipulating biological development in lower life forms dominates what many in the scientific community consider to be the field of aging research. It is not. One example is that more than half the budget of the National Institute on Aging in the United States is spent on Alzheimer's disease research, yet motor vehicle accidents cause twice as many deaths(Adelman, 1998; Anderson, 1999a) and from age 65 on, it is not even one of the five leading causes of death (Hobbs and Damon, 1996). The likelihood of dying from Alzheimer's disease is 0.7%(Anderson, 1999b) and the complete resolution of this disease will add about 19 days onto average life expectation (Anderson, 1999a).

Nor will that accomplishment advance our knowledge of the fundamental biology of aging.

In the minds of the public, policy makers and many biomedical scientists, no one suffers or dies from aging. We suffer and die from the diseases associated with the aging process. Yet, the aging process is the underlying cause of the increase in invulnerability to everything that is written on the death certificates of the elderly.

No one over the age of, say 75, has, or will die from what is written on his or her death certificate. Death results from the inevitable increase in systemic molecular disorder that living long enough incurs. That disorder simply increases vulnerability to whatever was, or will be, written on death certificates. There is an almost universal belief that the greatest risk factor for the three leading causes of death is the aging process yet that risk factor, aging, receives only a microscopic portion of the biomedical research budget. This illogical state of affairs must be reversed if we are to make any progress in understanding why old cells are more vulnerable to pathology than are young cells.

The hallmark of extreme old age is the presence of multiple pathologies making the determination of the cause of death difficult. Because autopsies of old people have become increasingly rare, the cause of most deaths in old age is still hidden in the proverbial black box.

AGING AND LONGEVITY DETERMINATION

If aging research is to advance, it will not only be necessary to distinguish biogerontology from geriatric medicine but it will also be necessary to distinguish aging from longevity determination. Failure to do so often results in research interpreted to bear on aging when, in fact, the results impact on our knowledge of longevity determination.

Aging is a stochastic process that occurs after reproductive maturation and results from increasing systemic molecular disorder. This disorder has multiple etiologies, including damage by reactive oxygen species, but generally from the diminishing loss of energy states necessary to maintain molecular fidelity.

Longevity determination, on the other hand, is not a random process. It is governed by the excess physiological capacity reached at the time of sexual maturation that, through natural selection, was achieved to better guarantee survival. Thus, longevity is only indirectly determined by the genome.

Species survival depends on a sufficient number of members living long enough to reproduce and, if necessary, to raise progeny to independence. Natural selection favors animals that have greater survival skills and, especially, redundant physiological reserve in vital organs beyond the minimum needed to survive the damage that might be exacted by predators, disease, accidents or environmental extremes.

Physiological capacity, beyond the minimum required for life, increases the chances for animals to survive long enough to achieve reproductive success just as redundant vital systems in complex machines, better insures that they will achieve their goals. The amount of excess physiological capacity, like the amount of redundancy engineered into space vehicles, provides the potential for continued function beyond the primary goal (Hayflick, 1996; 1998).

Because living long beyond reproductive success has diminishing value for the survival of a species, weakened members will be culled by natural selection. Energy is better spent on guarantying reproductive success than it is for increasing individual longevity. The molecular order achieved from conception to sexual maturation becomes increasingly disordered after reproductive success. Systemic molecular disorder, or aging, increases in spite of the presence of repair processes because these too incur disorder. In this way the acceleration of molecular disorder, or aging, increases vulnerability to predation, accidents and disease.

The developmental events that lead to the survival of animals to reproductive success are determined genetically but the survival of animals beyond sexual maturation is determined only indirectly by the genome. It is for this, and other reasons, that biogerontologists may be asking the wrong question: “Why do we age?" The right question could be: “Why do we live as long as we do?"

GENES DO NOT GOVERN AGING

Aging is not a programmed process governed directly by genes. Studies in lower animals that have led to the view that genes are involved in aging have not shown a reversal or arrest of the inexorable expression of molecular disorder that is the hallmark of aging. Those studies are more accurately interpreted to have impact on longevity determination because the results alter physiological capacity and occur before the aging process begins.

Another argument against the direct role of genes in programming the aging process is that animals do not age at the same rate nor are the patterns of age changes identical. This results in the variations found in age of death. When the random events characteristic of aging are compared with the orderly, virtually lock-step, changes that occur during genetically driven embryogenesis and development, the orderliness and precision stands out in stark contrast to the quantitative and qualitative disorder of age changes. The variability in the manifestations of aging differs greatly from animal to animal but the variability in developmental changes differs trivially. Humans from conception to adulthood are virtually identical in respect to the stages and timing of biological development but from about thirty on, age changes make humans more heterogeneous.

Just as a blueprint is vital to manufacture a complex machine and contains no information to cause the aging of that machine, the genome is necessary for biological development but unnecessary to cause the animal’s aging. The animal and the machine fail as a result of increasingly irreparable loss of molecular fidelity, which in living systems increases

vulnerability to predation, accidents or disease and in inanimate objects increases vulnerability to analogous failures in some vital component.

Longevity determination in higher animals has been a profoundly neglected area of research. One class of animals that may provide some answers to the determination of longevity are those animals that do not reach a fixed size in adulthood and age slowly or not at all. If these animals do age, the process is either negligible or it occurs below the limits of detection. Animals of this class include some tortoises, many sport and cold-water deep-sea fish, some amphibians and the American lobster. Even telomerase expression, the hallmark of immortal cells has been found at extraordinary high levels in the cells of negligibly aging animals like the American lobster (*Homarus americanus*) and the rainbow trout (*Onchorhynchus mykiss*)(Klapper et al., 1998a, 1998b). Whether these animals age at all, and the reasons for this, have been almost entirely neglected. They are not immortal because, like animals that do age, there is a constant threat of disease, predation and accidents (Hayflick, 2000a). The time is long overdue for more intense study of the phenomenon of negligible aging.

The aging of living things is not unlike the aging of everything in the universe including the universe itself. The molecular disorder that defines biological aging might occur passively by increasing decrements in the energy necessary to maintain molecular fidelity or actively through, for example, the action of reactive oxygen species.

Although biological aging occurs in an open system, the Second Law of Thermodynamics applies in that entropy increases despite the constant availability of energy in the form of food. Entropy increases in biological systems because natural selection has not favored systems that can maintain molecular fidelity indefinitely. Energy is better spent on strategies that insure reproductive success in order to perpetuate the species rather than spending it on post reproductive longevity that has little species survival value. The verity of this statement can be found in the observation that, for feral animals that reach a fixed size in adulthood, death will occur from predation, accident or disease shortly after the period of reproductive success that, through natural selection, favors species survival.

AGING IN FERAL ANIMALS

Aging rarely if ever occurs in feral animals because it is unusual for them to live long enough to experience the phenomenon. The same observation can be made for prehistoric humans who also never lived long enough to experience aging. Natural selection could not select for a process like aging that has no species survival value especially when few, if any, animals ever lived long enough to participate in the selection process.

If, through human intervention, feral animals are kept as pets or deposited in zoos and thus protected from predation, disease, and accidents, age changes that may never have been experienced in the wild will be unmasked. The resulting greater longevity

is not caused by the expression of new genes but by the protection provided by human intervention. Any finding of old feral animals usually results from the enormous increase in the human population that has disturbed their ecological niches.

Most animals do not die immediately after reproductive success because it is prohibitively costly in energy to evolve such a system. The class of animals generally referred to as “big bang animals” represented by the Pacific salmon and the marsupial male rat may appear to be an exception to this notion. However, it is more likely that the deaths that occur in these animals after reproductive success result from their unique expenditure of enormous amounts of energy that precedes mating (Hayflick, 1996). It is questionable whether the biological changes that precede their deaths are age changes because there is no necessity for death to be preceded by age changes.

AGING AS AN ARTIFACT OF CIVILIZATION

Aging is a phenomenon unique to the human species because it is a consequence of our advancing knowledge of hygiene and biomedicine. The resulting increase in the numbers of older people in developed countries is, to a large extent, an unintended consequence of these advances and an artifact of human civilization (Hayflick, 1996, 1998, 2000).

Humans, and the animals we chose to protect, are the only species in which large numbers experience aging. Furthermore, old humans, or old animals, are not essential for the survival of any species. The evidence for this is that humans had a life

expectation at birth of thirty years or less for more than 99.9 percent of the time that we have inhabited this planet. Prehistoric human remains have never revealed individuals older than about fifty years of age. There appears to be no selective advantage favoring the survival of old animals or old humans.

Members of exotic feral animal species, who for millions of years have not experienced aging, reveal those changes when protected by humans as pets or in zoos. It would be difficult to explain how evolution could have selected for a process like aging that could be made to appear in all members of a species after, perhaps, millions of years of suppression.

Because modern humans, unlike feral animals, have learned how to escape death long after reproductive success, we have revealed a process that, teleologically, was never intended for us to experience. Again, one might properly conclude that aging is an artifact of civilization.

THE PROBABILITY OF LIVING TO 100 AND BEYOND

Life expectation is the 50% likelihood of how long a human of any age might live, given current environmental conditions. This is fundamentally different from life span, which is the maximum number of years that a human has been proven to live. The human life span has remained unchanged for the past 100,000 years at about 125 years (Hayflick, 1996,1998). What has changed is life expectation that, at birth in the United States and other developed countries, has increased from about 49 years in 1900 to about 76 years in 1997 (Anderson, 1999c). This 27-

year increase in life expectation is equivalent to the increase in life expectation that occurred from the time of ancient Rome until the year 1900. This astounding improvement is due substantially to the resolution of deaths from birth to young adulthood. The main causes were infectious diseases that have been substantially eliminated by implementation of better hygiene and the discovery of antibiotics and vaccines. It is the chronic diseases, - cardiovascular disease, stroke, and cancer that remain unresolved and that dominate today as the causes of death in the elderly. Twenty-one of the 27-year increase in life expectation that occurred during the twentieth century took place during the first 70 years. Only a six-year increase in life expectation occurred in the following 27 years (Hayflick, 2000b).

If all causes of death currently appearing on death certificates are resolved from what will we die? All successful biomedical research, and its' implementation, results in adding time up to the fifteen-year limit of what remains for extending human life expectation.

To know what the future societal impact might be of a fifteen-year increase in life expectation, one might consider the changes that have occurred from 1931 until the present, which spans a period of time in which an approximate fifteen-year increase in life expectation has occurred (Anderson 1999d). Of the many observations that could be made, three are: the increase in the proportion of older people, the greater time spent in frailty and dependency in old age and the political and

economic consequences that both have had (Crimmins, Hayward and Saito, 1994).

What then are the possibilities of extending life expectation once the present causes of death are resolved? The possibilities are near zero because very little research is being conducted on the fundamental biology of age changes. The possibilities are almost nil because virtually all research conducted under the aging rubric is research on the diseases of old age or on modifications of developmental processes that increase or decrease longevity in lower animals. Despite the likelihood that biological aging, like the aging of everything else, is inexorable and inevitable, is the power to manipulate the human aging process a desirable goal?

One might view the goal of arresting the aging process in the same light that we view arresting developmental processes. Arrested physical or mental development in childhood is viewed universally as a serious pathology. If retarding the development of a seven-year-old for ten years in order to have the child live then arresting one's aging processes in later life should not be attractive for the same reasons. Other scenarios have been described where the power to arrest the aging process would have different negative impacts on society (Hayflick, 2000c).

Perhaps the least imperfect scenario would have everyone living until his or her 100th birthday in good physical and mental health and then dying at the stroke of midnight.

FUTURE POSSIBILITIES

We know of no way in which the human aging process is likely to be slowed with the probable exception of caloric restriction. However, the results might also be interpreted to suggest that overeating diminishes longevity (Hayflick, 1998). Although demonstrated in many species, including its' likely occurrence in non-human primates, it has yet to be demonstrated conclusively in humans (Roth, Ingram and Lane, 1999). Even if demonstrated, a near starvation diet is unlikely to be acceptable to most people whose quality of life is more important than is their quantity of life.

In developed countries more than 75% of all deaths now occur in those over the age of 75. If the causes of these deaths are resolved we will not become immortal but we will have revealed how death occurs in the absence of disease. What will be found is that the underlying cause of these deaths is the inexorable loss of physiological capacity that results from increasing molecular disorder in the cells of vital organs. This is the hallmark of aging and it will appear on all death certificates once the present leading causes are resolved.

There is no evidence to support the many outrageous claims of extraordinary increase in human life expectation that might occur in our lifetime or that of our children or their children. Even if the miracle of eliminating the three leading causes of death were to occur tomorrow a maximum of 15 years would be gained in average life expectation. Any increase beyond that

number will depend on slowing or stopping the fundamental processes that produce molecular disorder. The likelihood that that can be done is remote if not impossible.

One must eliminate almost all mortality risks from 1995 levels before age 85 to achieve a life expectation greater than 100 (Olshansky, Carnes and Désesquelles, 2001). The 1995 death rates would have to decline by more than 50% at every age in order for life expectancy to reach 85 years in the United States (Olshansky, Carnes and Désesquelles, 2001). Even among Japanese women who are the longest lived sub-group in the world, total mortality at every age would have to drop 20% in order to raise life expectancy by 2 years from its' current 83 years. The mortality reductions at every age required to achieve a 1-year increase in life expectancy at birth today are more than twice those needed to achieve the same gain early in the 20th century (Olshansky, Carnes and Désesquelles, 2001). It is not possible to reach life expectations of 100 or more today by life style modifications unless those modifications will completely eliminate all causes of death currently appearing on death certificates and the discovery of an intervention to slow the fundamental aging process.

Thus, the approximate 25-year increase in life expectancy that occurred in the United States from 1900 to 2000 will be impossible to achieve in the 21st century even if all causes of death currently appearing on death certificates were to be resolved. Even if that miracle were to occur the maximum extension of life expectation that could be achieved is about 15 years.

Those who predict enormous gains in life expectation in the future based only on mathematically sound predictions of life table data but ignore the biological facts that underlie longevity determination and aging do so at their own peril and the peril of those who make health policy for the future of this country.

It is likely that a natural increase in the human life span is presently occurring but so slowly that our ability to detect it will only be made after millennia of careful record keeping. This belief is based on persuasive evidence in the fossil record that suggests that the life spans of most animals increase as evolution proceeds (Hayflick, 1996).

As some civilizations have, our society must learn that aging and youth should be valued equally if for no other reason than the youth in developed countries have an excellent chance of experiencing the phenomenon that they may now hold in low esteem. Then, the misplaced passion for cosmetic surgery, anti-aging nostrums and similar snake oil remedies touted to arrest aging will be recognized for what they truly are, - at best, a cover-up
for an irreversible and inexorable process and, at worst, a delusion and waste of money by the uninformed.

If the main goal of our biomedical research enterprises is to resolve causes of death, then every old person becomes a testimony to those successes. Biogerontologists have an obligation to emphasize that the goal of research on aging is

not to increase human longevity regardless of the consequences but to increase active longevity free from disability and functional dependence.

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