The Biology of Human Longevity, Aging and Age-Associated Diseases

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Presented at the Living to 100 and Beyond Symposium

Orlando, Fla.

January 7-9, 2008

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Abstract

In order to better understand the finitude of life it must be divided into its four components: aging, longevity determination, age-associated disease and death.

Age changes result from the increasing rate of biomolecular disorder that, after reproductive maturation, exceeds repair and turnover capacity. These are stochastic or chance events governed by entropy or the tendency for concentrated energy to disperse when unhindered. The hindrance is the relative strength of chemical bonds. The maintenance of chemical bonds until reproductive maturation is absolutely necessary for species survival.

Genes do not cause aging but genes do indirectly govern longevity by determining the energy status of biomolecules before age changes occur, or to reproductive maturation. Longevity is indirectly governed by genes because the strategy of producing excess physiological capacity to better ensure survival to reproductive maturation allows life to continue beyond that crucial point.

Through natural selection biomolecules must retain structure and function until reproductive success or the species will vanish. Selection for the maintenance of molecular fidelity beyond reproductive success is unnecessary for species survival. Thus, the aging process begins.

The failure to distinguish age changes from disease or pathology is a fundamental problem that has not only blurred efforts to understand the biology of aging and the determination of longevity but it has profound political and economic consequences.

Aging is not a disease because, unlike any disease, age changes

(1) occur in every animal that reaches a fixed size in adulthood.

(2) cross virtually every species barrier.

(3) occur in all animals that reach a fixed size in adulthood and only after sexual maturation.

(4) occur in animals removed from the wild and protected by humans even when that species has not been known to experience aging for thousands or millions of years.

(5) increase vulnerability to death in 100 percent of the animals in which they occur.

(6) occur in both animate and inanimate objects.

Of the four aspects of the finitude of life, the only aspect that humans have manipulated is disease or pathology and that has a significant limit. If all causes of death currently written on death certificates were to be resolved, average human life expectancy at birth could not exceed about 93 years. The only way that this number can be exceeded is if we could intervene in the fundamental aging process itself or in the determinants of longevity. These possibilities are presently remote if for no other reason than the research investment in this effort is orders of magnitude less than what is available for research on age-associated diseases. The widespread belief that the resolution of age-associated diseases will increase our understanding of the fundamental aging process is spurious.

Aging is a process that is only experienced by humans and the animals that we choose to protect like zoo and domestic animals. We, and those animals, now survive well beyond young adulthood. That did not occur for the majority of time that we have been a species and it is, in fact, an aberration of civilization attributable to our discovery of how to eliminate many causes of death.

Immortality does not exist in biology because cells and their constituent molecules turn over or are replaced. The only long-lasting biological property on an evolutionary time scale is the information coded in the DNA of the genome and mitochondria, but even that information is subject to mutation or change.

There is an almost universal belief by geriatricians and others that the greatest risk factor for all of the leading causes of death is aging.

Why then are we not devoting significantly greater resources to understand more about the greatest risk factor for every age-associated pathology by attempting to answer this fundamental question:

> "What changes occur in biomolecules that lead to the manifestations of aging at higher orders of complexity and then increase vulnerability to all age-associated pathology?"

1. Introduction

Communication in the field of biogerontology is a minefield because all of the commonly used terms have no universally accepted definitions.

In a series of five annual meetings that I chaired in an attempt to define common terms, the dozen or more experts who attended could not agree on the definition of almost all of them, including "aging." The committee was disbanded and the communications dilemma remains.

Not only does the problem result in communication failures, it also produces erroneous interpretation of research results, illogical allocation of research funds and misdirected scientific, economic, social and political policy decisions [1-3].

There is no other field of science in which a similar situation exists.

Consequently, I will define three of the four aspects of the finitude of life: aging, the determinants of longevity and age-associated diseases. I will not define death although even this word defies a universally accepted definition.

2. The Aging Process

Age changes can occur in only two fundamental ways: by a purposeful program driven by genes or by random, accidental events.

It is a cornerstone of modern biology that a purposeful genetic program drives all biological processes that occur from the beginning of life to reproductive maturation. However, once reproductive maturation is reached, thought is divided in respect to whether the aging process is a continuation of the genetic program or whether it is the result of the accumulation of random, irreparable losses in molecular fidelity.

The deterministic dream of 19th century physicists was torpedoed in the 20th century with Heisenberg's discovery of the uncertainty principle. In fact, the fundamental laws of physics can only be expressed as probabilities. The most compelling evidence for the belief that biological aging is also a random process is that everything in the universe changes or ages in

space-time without being driven by a purposeful program. Although there is no direct evidence that genes drive age changes, their critical role in longevity determination is indisputable.

There is a huge body of knowledge supporting the belief that age changes are characterized by the random loss of molecular fidelity [4] and, as they accumulate, slowly overwhelm maintenance systems [1-3].

Both biological systems and inanimate objects incur change over time. Living systems however are, among other properties, distinguishable from inanimate objects because a purposeful genetic program governs the changes that occur from their origin until reproductive maturation. In inanimate objects, change is not programmed. It is continuous and never ending. Whether the changes that occur in inanimate objects are called age changes or not occurs because of the tendency for humans to view the physical world in anthropomorphic terms.

The common denominator that underlies all modern theories of biological aging is change in molecular structure and, hence, function.

This can be viewed as an increase in entropy which is supported by the recent reinterpretation of the Second Law of Thermodynamics where the belief that it only applies to closed systems has been overturned [5]. Entropy is the tendency for concentrated energy to disperse when unhindered regardless of whether the system is open or closed.

The hindrance is the relative strength of chemical bonds. The prevention of chemical bond breakage, among other structural changes, is absolutely essential for life. Through evolution, natural selection has favored energy states capable of maintaining fidelity in most molecules until reproductive maturation, after which there is no species survival value for those energy states to be maintained indefinitely.

The dispersal of molecular energy may result in a biologically inactive or malfunctioning molecule. Dispersal is never entirely eliminated but it can be circumvented for varying time periods by repair or replacement processes. The internal presence of these processes represents a major difference between living and inanimate forms. From the standpoint of a physicist a lowered energy state is not necessarily disorder because it simply results in the identical molecule with a lowered energy state. The fact that such a molecule might be biologically

inactive may not concern the physicist but it definitely does concern the biologist and, especially, the biogerontologist.

The aging process occurs because the changed energy states of biomolecules render them inactive or malfunctioning. Identical events also occur before the aging phenotype appears but repair and replacement processes are capable of maintaining the balance in favor of functioning molecules or the species would vanish. After reproductive maturation this balance slowly shifts to one in which molecules that lose their biologically active energy states are less likely to be replaced or repaired. This occurs because the enormously complex biomolecules that compose maintenance systems also suffer the same fate as their substrate biomolecules.

When the escalating loss of molecular fidelity ultimately exceeds repair and turnover capacity, vulnerability to pathology or age-associated diseases increases [1,3,6].

Immortal biological systems cannot exist if for no other reason than molecular turnover (or dilution) ensures that the molecules present at the beginning of a biological lineage are unlikely to be present in that lineage when it reaches Avogadro's Number of about 6×10^{23} cells. The only biological property that is long lasting on an evolutionary time scale is the message coded in information containing molecules but even that data is subject to mutation or change [7].

Although the loss of molecular fidelity is a random process, there is, nonetheless, a strong element of uniformity in that errors will occur first in the same families of the most vulnerable molecules in similar cells, organs or objects. The components of a system in which these molecules are a part then become the weakest link in that system. This accounts for the similarity in the aging phenotype as it progresses within species members.

Similar events occur in aging inanimate objects where, for example, automobiles of a particular make, model and year of manufacture may have a greater probability of failure in a common weakest link such as the electrical system. In another car of similar manufacture but different make, year or model, molecules in the cooling or exhaust system will suffer age changes fastest and become the most probable system to fail first. There is, inevitably, a weakest link with the probability of failing first in a similar component of all complex entities. This

“mean time to failure” for a cheap car might be six or seven years, and for newborns today in developed countries their mean time to failure is in the range of 75–85 years.

In humans in developed countries, the weakest links are the cells that compose the vascular system and those in which cancer is most probable. The molecular instability, or aging processes which occur in these cells, are the weakest links that increase vulnerability to these two leading causes of death. This is why knowing how fundamental age changes occur could lead to a better understanding of the etiology of all of the leading causes of death.

3. The Determinants of Longevity

The second aspect of the finitude of life is longevity determination, a process that is completely different from aging.

Unlike aging, the genome governs the processes that determine longevity. These are the systems that synthesize molecules and repair or replace them. When they are unable to maintain the positive balance that existed prior to reproductive success, a tipping point is reached and the aging phenotype slowly becomes manifest.

Aging must occur in molecules that previously existed with no age changes. It is this prior state of molecules and the efficiency of their maintenance that govern longevity determination.

Unlike the stochastic process that characterizes aging, longevity determination is not a random process. It is governed by the level of physiological reserve reached at the time of reproductive maturation that, through natural selection, was achieved to better guarantee survival to that age. The determination of longevity is incidental to the main goal of the genome, which is to govern events until reproductive maturity occurs. Thus, the genome only indirectly governs longevity.

The variations in excess physiological capacity, repair and turnover account for the differences found in longevity both within and between species. One might think of longevity determination as the energy state of molecules before they incur age changes and aging as the state of molecules after energy dissipation results in an irreparable state of functional loss.

Longevity determination is a genome driven anabolic process that answers: "Why do we live as long as we do?" Aging is a chance driven catabolic process that answers: "Why do things finally go wrong?"

Furthermore, genes that govern the aging process are unnecessary for it to occur. Just as blueprints are vital to construct a complex machine and contain no information describing a system to cause its aging, the genome is necessary to govern biological development and maintenance but it contains no instructions to cause the animal to age. Automobiles know how to age without requiring instructions. Both ultimately fail because of changes in molecular fidelity driven by increasing entropy.

4. Age-Associated Diseases

The third aspect of the finitude of life is age-associated disease. The distinction between the aging process and age-associated disease is not only based on the definition of aging described above but it is also rooted in several practical observations.

Unlike any disease, age changes:

(1) occur in every multicellular animal that reaches a fixed size at reproductive maturity.

(2) cross virtually all species barriers.

(3) occur in all members of a species only after the age of reproductive maturation.

(4) occur in all animals removed from the wild and protected by humans, even when that species probably has not experienced aging for thousands or even millions of years.

(5) occur in virtually all animate and inanimate matter.

(6) have the same universal molecular etiology, that is, thermodynamic instability.

Unlike aging, there is no disease or pathology that shares these six qualities.

The inexorable loss of molecular fidelity that defines aging can either lead to changes that may be non pathological affronts to vanity, inconveniences or simply uncomfortable. When the same kind of molecular mischief occurs in the cells of vital organs leading to an increase in vulnerability to disease or pathology, treatment is required because life may be threatened.

The fundamental aging process is not a disease but it increases vulnerability to disease. Because this critical distinction is generally unappreciated, there is a continuing belief that the resolution of age-associated diseases will advance our understanding of the fundamental aging process. It will not. This is analogous to believing that the successful resolution of childhood pathologies, such as poliomyelitis, Wilms' tumors and iron deficiency anemia advanced our understanding of childhood development. It did not.

The failure to distinguish the fundamental biology of aging (biogerontology) from age-associated pathology (geriatric medicine) and both from longevity determinants is the most serious impediment to our understanding of the aging process. This failure is exemplified best by realizing that under the rubric "Aging Research," misled policy makers have appropriated most available funds to research on age-associated diseases. Yet no advance in geriatric medicine will add to our knowledge of the fundamental biology of aging [1-3].

References

l. Hayflick, L. 2007. Biological aging is no longer an unsolved problem. Ann. New York Acad. Sci., 1100, 1-13.

2. Hayflick, L. 2004. “Anti-Aging” Is An Oxymoron. J Gerontol: Biol. Sci. 59A, No. 6, 573-578.

3. Hayflick, L. 1995. How and Why We Age. Ballantine Books. New York.

4. Finch, C.E. and Kirkwood, T.B.L. 2000. Chance, Development and Aging. Oxford. Univ. Press, New York.

5. Lambert, F.L. 2007. Entropy and the second law of thermodynamics. www.entropysite.com. July.

6. Hayflick, L. 2000. The future of ageing. Nature 408: 37–39.

7. Hayflick, L. 2000. The illusion of cell immortality. Br J Canc 83: 841–846.

Previously published material used to prepare this report may be found in reference 1.