

# Biological Aging Is No Longer an Unsolved Problem

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**ABSTRACT:** The belief that aging is still an unsolved problem in biology is no longer true. Of the two major classes of theories, the one class that is tenable is derivative of a single common denominator that results in only one fundamental theory of aging. In order to address this complex subject, it is necessary to first define the four phenomena that characterize the finitude of life. These phenomena are aging, the determinants of longevity, age-associated diseases, and death. There are only two fundamental ways in which age changes can occur. Aging occurs either as the result of a purposeful program driven by genes or by events that are not guided by a program but are stochastic or random, accidental events. The weight of evidence indicates that genes do not drive the aging process but the general loss of molecular fidelity does. Potential longevity is determined by the energetics of all molecules present at and after the time of reproductive maturation. Thus, every molecule, including those that compose the machinery involved in turnover, replacement, and repair, becomes the substrate that experiences the thermodynamic instability characteristic of the aging process. However, the determinants of the fidelity of all molecules produced before and after reproductive maturity are the determinants of longevity. This process is governed by the genome. Aging does not happen in a vacuum. Aging must be the result of changes that occur in molecules that have existed at one time with no age changes. It is the state of these pre-existing molecules that governs longevity determination. The distinction between the aging process and age-associated disease is not only based on the molecular definition of aging described above but it is also rooted in several practical observations. Unlike any disease, age changes (*a*) occur in every multicellular animal that reaches a fixed size at reproductive maturity, (*b*) cross virtually all species barriers, (*c*) occur in all members of a species only after the age of reproductive maturation, (*d*) 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, (*e*) occur in virtually all animate and inanimate matter, and (*f*) have the same universal molecular etiology, that is, thermodynamic instability. Unlike aging, there is no disease or pathology that shares these six qualities. Because this critical distinction is poorly understood, there

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is a continuing belief that the resolution of age-associated diseases will advance our understanding of the fundamental aging process. It will not. The distinction between disease and aging is also critical for establishing science policy because although policy makers understand that the funding of research on age-associated diseases is an unquestioned good, they also must understand that the resolution of age-associated diseases will not provide insights into understanding the fundamental biology of age changes. They often believe that it will and base decisions on that misunderstanding. The impact has been to fund research on age-associated diseases at several orders of magnitude greater than what is available for research on the biology of aging. There is an almost universal belief by geriatricians and others that the greatest risk factor for all of the leading causes of death is old age. Why then are we not devoting significantly greater resources to understanding 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?"

**KEYWORDS:** aging; age-associated disease; longevity

## INTRODUCTION

As his inaugural professorial lecture in 1951 at University College London, Sir Peter Medawar gave one of the most influential discourses on the biology of aging. It was entitled, "An Unsolved Problem in Biology."<sup>1</sup> The unsolved problem was the failure to understand how and why biological aging occurs.

In the more than half century that has elapsed since Medawar's notable lecture, research on the biology of aging has gone from virtual obscurity to a level of popularity that today can only be characterized as remarkable.

For the first 25 years after Medawar's lecture most studies on aging were descriptive. But, in the subsequent 25 years the enormous advances that have been made in our understanding of fundamental biological mechanisms has been exploited by biogerontologists to provide us with new insights into the immediate cause of age changes. As these insights emerged, the field of aging research became inundated with many theories on the cause of aging. See, for example, Hayflick (1985).<sup>2</sup> So many theories were formulated that cynics remarked that there are as many theories of aging as there are biogerontologists.

However, that belief is no longer true. Of the two major classes of theories, the one class that is tenable is derivative of a single common denominator that results in only one fundamental theory of aging. I will discuss these two classes of theories subsequently. The huge body of knowledge in biogerontology that has been revealed in the last 25 years has resulted in a high level of confidence that the cause of biological aging is now understood. This knowledge is the result of the work of many researchers.

In order to address this complex subject it will be necessary to first define the four phenomena that characterize the finitude of life. These phenomena are aging, the determinants of longevity, age-associated diseases, and death. I will not discuss the biology of death other than to say that even for this concept there is no single universally accepted definition. In order to avoid a definition of biological death one was observed that death is nature's way of telling you to slow down.

## THE AGING PROCESS

Let us consider the aging process first. There are only two fundamental ways in which age changes can occur. Aging occurs either as the result of a purposeful program driven by genes or by events that are not guided by a program but are stochastic or random, accidental events. These two fundamental ways in which age changes might occur define the two classes of theories that I identified above.

It is a cornerstone of modern biology that a purposeful genetic program drives all biological processes that occur from conception to reproductive maturation. But, 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 random losses in molecular fidelity. Despite the claim by many researchers to the contrary, there is no direct evidence that genes drive age changes. I will discuss how genes are involved in the finitude of life subsequently.

I propose that the phenomenon that we call aging, which commonly appears after reproductive maturation, is driven by random events not governed by a genetic program.

The evidence for the belief that aging is a stochastic process is, first, that everything in the universe changes or ages in space-time without being driven by a purposeful program. Second, there is no direct evidence that proves that age changes are governed by a genetic program. Finally, there is a huge body of knowledge indicating that age changes are characterized by the loss of molecular fidelity.

Both biological systems and inanimate objects incur change over time. But, living systems are, among other properties, distinguished from inanimate objects because a purposeful genetic program governs the changes that occur from their origin until reproductive maturation. In inanimate objects, change is continuous and never ending. Whether the changes that occur in inanimate objects are called age changes or not is the result of the tendency of humans to view the physical world in anthropomorphic terms. I will return to this concept again when I discuss longevity determination.

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

be called increasing loss of molecular fidelity or increasing molecular disorder. It can be viewed as an increase in entropy which adheres to the more recent interpretations of the Second Law of Thermodynamics that do not include the necessity for a closed system.<sup>3</sup>

Entropy is the tendency for concentrated energy to disperse when unhindered. The hindrance is the relative strength of chemical bonds that are formed by what is called activation energy. The prevention of chemical bond breakage is absolutely necessary for the maintenance of the life of individuals and the continuity of species—at least until reproductive maturation. The tendency for molecules to lose energy is never entirely eliminated but it can be blocked for varying periods of time by replacement or repair. Although the loss of molecular energy may result in a biologically inactive or disordered molecule, from the standpoint of a physicist this lowered energy state is not necessarily disorder because it simply results in a molecule with a different energy state. The fact that such a molecule might be biologically inactive does not concern the physicist. It definitely does concern the biologist and the biogerontologist.

Biological aging is more than simply the occurrence of random changes in molecules. It also includes the role of the many repair systems found within cells. Thus, a more complete, but less concise, explanation of the first causes of aging in biological systems is the following:

Aging is an increase in molecular disorder. It is a stochastic process that occurs systemically after reproductive maturity in animals that reach a fixed size in adulthood. This escalating loss of molecular fidelity ultimately exceeds repair and turnover capacity and increases vulnerability to pathology or age-associated diseases.<sup>4,5</sup>

The fundamental cause of molecular disorder is rooted in the intrinsic thermodynamic instability of most complex biological molecules whose precise three-dimensional folded structures cannot be maintained with accuracy indefinitely. These losses in fidelity can lead, for example, to covalent modifications such as glycation, conformational alterations, aggregation and precipitation, amyloid formation, changes in protein degradation, synthesis rates, and nuclear and mitochondrial DNA damage and alterations. The impact of these changes can be local or systemic.

The loss of fidelity in complex biological molecules is inevitable over relatively short time periods compared to the changes that occur over long periods of time in the molecules that compose inanimate objects.

In its present state, nothing lasts forever. Despite the common belief that there are some immortal biological systems (sea anemones are often cited as an example) there is no evidence to support this belief. The only biological property that is long lasting on an evolutionary time scale is the information coded in the genome and mitochondria, but even that information is subject to mutation or change.<sup>6</sup>

Immortality 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 exist in that lineage when it reaches Avogadro's Number of about  $6 \times 10^{23}$  cells.

If the founding cell in a lineage consisted entirely of hydrogen molecules—the lightest element, none would be retained after about 50 population doublings. Because biomolecules are much heavier than hydrogen molecules their survival, if not replaced or repaired, would be lost after far fewer population doublings than 50.

Because of the randomness of the molecular disorder that underlies the aging process, the rate of molecular fidelity varies from organ to organ, from tissue to tissue, and from cell to cell making us what is analogous to a clock shop where there is little probability that all clocks record the flight of time identically.

The differences in rates of molecular disorder result in a few tissues containing cells with the greatest number, or most critical, unstable molecules. These tissues become the weakest links and their decreasing ability to function ultimately leads to greater vulnerability to pathology and death of the organism.

This phenomenon is analogous to what occurs in the varying rates of aging in components of complex inanimate objects such as, for example, automobiles. 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 objects. The components of a system in which these molecules are a part then become the weakest link in the entire system.

For example, in an inanimate object, such as an automobile of a particular make, model, and year of manufacture, there may be a greater probability of failure in a common weak link in 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 in the probability of failure in some common component in similar complex entities. In the vernacular of engineers, the time when the weakest link in a complex system fails is called the “mean time to failure.” For a cheap car, it might be 6 or 7 years, and for newborns today in developed countries their mean time to failure is in the range of 75–83 years.

In developed countries, the weakest links in humans are the molecules in cells that compose the vascular system and the cells in which cancer is most likely to occur. The molecular instability, or aging process, that occurs in the molecules composing these tissues are the weakest links. Their weakness increases vulnerability to vascular disease and cancer—the two major pathologies that are the leading causes of death in developed countries.

Biomolecules, like the proteins that constitute most of our tissues, are extraordinarily complex entities. The cause of the molecular instability that characterizes the aging process is the inevitable loss of the energy necessary

to maintain the structural and functional integrity of virtually all molecules that are synthesized during life. The fidelity of this vast array of different biomolecules can last from picoseconds to several thousand years after death in the case of some molecules, such as DNA. Although bone may survive for millions of years it is not a complex biomolecule.

It is critical to point out that the repair, turnover, and replacement processes referred to above and which are so well described in an enormous literature, are themselves composed of complex biomolecules. Consequently the molecules that compose these vital systems also succumb to the same instability that occurs in the substrate molecules that they are involved in repairing or replacing.

We spend the first 20 years or so of our lives producing, ordering, and replacing our molecules with close to absolute fidelity. Through natural selection, that fidelity must be maintained until reproductive success or our species would vanish. Thus, through evolution, natural selection has favored energy states capable of maintaining molecular fidelity until reproductive success, after which there is no species survival value for those energy states to be maintained indefinitely.

It is a certainty that losses of molecular fidelity must also occur frequently well before reproductive maturation and it must be equally certain that the repair and turnover systems must be capable of maintaining the integrity of the system until reproductive maturation. Because there is no species survival value for repair or replacement systems to operate as perfectly after reproductive maturation as they do before, repair systems become less and less capable of maintaining molecular order.

Consequently, the random downward spiral of molecular disorder gradually exceeds repair or turnover capability and this results in changes at the cell, tissue, and organ levels that we call aging. The proof is clear. Humans have survived with a life expectation of about 25 years or less for 99.9% of the several million years that we have been a species. No prehistoric human remains have been found to be older than about 50 years.

If the time in which the human species has existed could be imagined on a 24-h time scale, the revelation of aging as a process that most of the population experiences would occur only a few seconds before midnight.

## **THE DETERMINANTS OF LONGEVITY**

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

Potential longevity is determined by the energetics of all molecules present at and after the time of reproductive maturation. Thus, every molecule, including those that compose the machinery involved in turnover, replacement, and repair, becomes the substrate that experiences the thermodynamic instability described earlier. This energy loss is the hallmark of the aging process.

However, the determinants of the fidelity of all molecules produced before and after reproductive maturity are the determinants of longevity. This process is governed by the genome.

Aging does not happen in a vacuum. Aging must be the result of changes that occur in molecules that have existed at one time with no age changes. It is the state of these pre-existing molecules that governs longevity determination. The pre-existing state is, as I have already described, maintained by repair and turnover systems that themselves eventually succumb to irreparable age changes. Longevity determination is the state of all molecules prior to succumbing to irreparable loss of molecular structure.

The genome directs events from life's beginning until reproductive maturation after which the events that it continues to govern are overtaken by the aging process. The imbalance that occurs in youth where the repair and maintenance of molecules exceeds any loss of fidelity slowly shifts after reproductive maturation to a state where the loss of molecular fidelity begins to exceed repair capacity.

This occurs because species survival is guaranteed when most members reach reproductive maturity. Natural selection does not favor the survival of species members who have incurred the liabilities of aging. Modern humans have not only learned how to reduce deaths that occur in youth but also those that occur after reproductive maturity. This is also true for the animals that we choose to protect. 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.

Unlike the stochastic process that characterizes aging, longevity determination is not a random process. It is governed by the excess or reserve physiological capacity reached at the time of sexual 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 that is to reach reproductive maturity. Thus, the genome only indirectly governs longevity.

Genes do not drive the aging process but by governing the levels of excess physiological capacity, repair, and turnover they indirectly determine potential longevity. There are no genes that specifically drive longevity but there are genes that govern biological processes that increase the likelihood of survival to reproductive maturity. The variations in excess physiological capacity, repair, and turnover accounts for the variations found in longevity both within and between species.

Longevity determination is an entirely different process from aging and is independent of it. One might think of longevity determination as the energy state of molecules before they incur age changes. It follows then that one might think of aging as the state of molecules after they have incurred an irreparable state of disorder.

Aging then is a catabolic process that is chance driven. Longevity determination is an anabolic process that, indirectly, is genome driven.

The studies in lower animals made in recent years that have led to the view that genes are involved in aging have not revealed a reversal or arrest of the inexorable expression of molecular disorder that is the hallmark of aging. These studies are more accurately interpreted to have impact on our understanding of longevity determination because all of the experimental results have altered biological variables before the aging process begins. None of these studies in invertebrates has demonstrated that the manipulation of genes has slowed, stopped, or reversed recognized biomarkers of the aging process.

Just as a blueprint is vital to manufacture a complex machine and contains no information that describes a system that causes the aging of that machine, the genome is necessary to govern biological development and maintenance but it contains no instructions that cause the animal to age. The animal and the machine ultimately fail because of the thermodynamics that drive losses in molecular fidelity.

Contrary to the pronouncements made by several of those who have lead the human genome project, genes do not drive the aging process, consequently an understanding of the human genome, even beyond what is known today, will not provide insights into a process that is random and thermodynamically driven.

### AGE-ASSOCIATED DISEASES

The third and last of the four aspects of the finitude of life that I will discuss is age-associated disease.

Although this is in some dispute, my view and that of many others, is that aging is not a disease and that it and longevity determination must be distinguished from disease.

The distinction between the aging process and age-associated disease is not only based on the molecular 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.

There are hundreds of easily recognizable manifestations of the aging process that few would consider to be pathologies or diseases in need of a cure. Emergency room personnel would not look kindly on patients who seek admission because of complaints that their hair is turning gray, wrinkled skin has just been observed, reaction time has increased, short-term memory losses have been noted, grip strength has decreased, or presbyopia or presbycusis has been experienced.

The 25-year-old Olympic champion sprinter is not encouraged to see his or her physician to complain that he or she could no longer reach the running speed that, at age 19, won the gold. These examples are representative of the hundreds of thousands of systemic losses in molecular fidelity that lead to nonpathological age changes.

For most of the time that we have been a species the loss of sprinting speed or long distance running ability that would have occurred during aging could have resulted in death. Speedier predators or those with greater stamina would have been our undoing. Our species has survived because most reproductive successes in the last two million years occurred well before the decrements of aging occurred.

But, in more recent times when molecular disorder occurs in cells, or cell products that results in the loss of running speed, grip strength, or jumping agility, death is not imminent. However, when the disorder occurs in a vital organ and accumulates sufficiently to increase vulnerability to pathology, a trip to the emergency room today may, indeed, become a necessity.

The inexorable loss in molecular fidelity that defines aging can either lead to changes that may be an affront to vanity, an inconvenience, or simply uncomfortable. When the same kind of molecular mischief occurs in the cells of vital organs, and then leads to an increase in vulnerability to disease or pathology, treatment of that pathology is required because life may become threatened.

These examples in which true pathology is easily distinguished from the nonpathological aspects of the aging process form the basis of distinguishing between the phenomena of aging and age-associated diseases.

## **CONSEQUENCES OF THE FAILURE TO DISTINGUISH AGING FROM AGE-ASSOCIATED DISEASES**

The fundamental aging process is not a disease but it increases vulnerability to disease.

Because this critical distinction is poorly understood, 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 concept is analogous to the efforts made to resolve childhood pathologies, such as poliomyelitis, Wilms' tumors, and iron deficiency anemia.<sup>7</sup> When the resolution of all of these diseases or pathologies occurred it did not advance our understanding of childhood development.

A good example of the phenomenon in which many mistakenly believe that the resolution of disease will advance our knowledge of the fundamental biology of aging is where more than one-half of the budget of the National Institute on Aging in the United States is spent on Alzheimer's disease research. Yet, accidents cause ten times as many deaths,<sup>7</sup> and from the age of 65 years heart and cerebrovascular disease cause ten times as many deaths as does Alzheimer's disease and cancer causes more than five times as many deaths.<sup>7</sup> Alzheimer's disease is the sixth leading cause of death in people over the age of 65 years although the disease is rarely authoritatively diagnosed by postmortem examination and in 2001 the Alzheimer's disease category was suddenly inflated by 10,000 people by including in it other dementias of unknown etiology.<sup>8,9</sup>

The resolution of Alzheimer's disease will add approximately 19 days onto average life expectation<sup>10</sup> and even if that enormous accomplishment occurs it will not bring us any closer to understanding the fundamental biology of aging. The distinction that must be made between the phenomena of aging and age-associated diseases is critical to an understanding of why many of the claims made by practitioners of antiaging medicine are spurious.

The distinction between disease and aging is also critical for establishing science policy because although policy makers understand that the funding of research on age-associated diseases is an unquestioned good, they also must understand that the resolution of age-associated diseases will not provide insights into understanding the fundamental biology of age changes. They often believe that it will and base decisions on that misunderstanding. The impact has been to fund research on age-associated diseases at several orders of magnitude greater than what is available for research on the biology of aging.

There is a universal failure by science policy makers to understand that the basis for all age-associated disease might lie in discovering why age changes increase vulnerability to all of those diseases.

### **WHAT CAN BE PERTURBED?**

Of the three aspects of the finitude of life that I have discussed only one has been successfully manipulated to increase human life expectancy. I must define life expectancy because there is no commonly accepted definition and I have seen it used to express fundamentally different concepts that have created enormous misunderstandings. By life expectancy, I mean the probability that 50% of a population of a particular age will reach a later age. For newborns life expectancy is the age at which 50% of the population is likely to reach. On the other hand, life span is the maximum time that any member of a species

is known to have lived. The frequently cited example for humans is Madam Calmant who lived for 123 years and some months.

There is only one aspect of the finitude of life that humans have learned to manipulate. That aspect is the prevention, elimination or delay of age-associated disease. No one has demonstrated how aging or the longevity determining processes in humans can be manipulated to extend life expectancy. We know of no intervention that will slow, stop, or reverse the aging process in humans.

From 1900, when life expectancy at birth in developed countries was about 49 years, until today, there has occurred a 27-year increase in life expectancy at birth.<sup>11,12</sup> This increase is equivalent to the gain in life expectancy that occurred during the previous 2000 years.

This gain was due substantially to the resolution of deaths caused by infectious diseases that occurred from birth to young adulthood. They were eliminated by the discovery of the microbial basis for disease and then the implementation of better hygienic conditions and later the discovery of antibiotics and vaccines.

It is the chronic diseases: cardiovascular, cerebrovascular disease, and cancer that have replaced infectious diseases as the main causes of death today and these remain largely unresolved.

Twenty-one of the 27-year increase in life expectation that occurred during the 20th century took place during the first 70 years. Only a 6-year increase in life expectation occurred in the following 27 years.<sup>11,12</sup> For an increase of even 10 more years in human life expectation to occur in any developed country in the next 50 years, mortality rates will have to decline to a level that has never before been achieved.<sup>13</sup>

Even if biomedical research is completely successful in eliminating all causes of death currently written on death certificates, human life expectancy could only be extended by about 15 years.<sup>10</sup>

When this miracle occurs, the aging process will still manifest itself and we will then reveal that the underlying cause of all age-associated diseases are the physiological decrements characteristic of the aging process. We will not become immortal because the inexorable loss in physiological capacity—the hallmark of the aging process—will cause most deaths and this will require a new vocabulary for writing causes of death on death certificates.

## **WHAT IS THE PURPOSE OF DOING RESEARCH ON AGING?**

The notion that aging requires treatment is because aging is a negative term that connotes deterioration, approaching pathology, and death.

The hundreds of thousands of septuagenarians who follow the sun in their recreational vehicles, or sail away on cruises, no longer have child-rearing responsibilities, have good health, and a modest income will disagree. To them,

and others, who believe that their intellectual growth does not stop, arresting adult development at an earlier age would be unthinkable.

It is more likely that it is not the fear of aging but the fear of approaching death that motivates the prolongevists. Why then is it useful to pursue research on aging if the goal is not to intervene in the process? It is useful for the same reason that research in other areas of biological inquiry are useful and where there is an implicit and easily understood appreciation that intervention is not a goal.

Research conducted on embryogenesis or fetal, childhood, or adult development is not conducted with the goal of understanding how to stop, slow, or reverse the development of embryos, fetuses, or the maturation of children. It is conducted to satisfy the human need to understand the processes and to learn how the pathologies associated with young cells and their role in developmental processes might be prevented.

Similarly, the goal of research on aging should be to answer similar fundamental questions that may hold the key to an understanding of all of the causes of death presently written on the death certificates of older people.

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

Why then are we not devoting significantly greater resources to understanding 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?"

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