

Aging is not a Process of Wear and Tear

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Abstract:

The idea that bodies wear out with age is so ancient, so pervasive, and so deeply rooted that it affects our thought in unconscious ways. Undeniably, many aspects of aging, e.g. oxidative damage, somatic mutations and protein cross-linkage are characterized by increased entropy in biomolecules. However, it has been a scientific consensus for more than a century that there is no physical necessity for such damage. Living systems are defined by their capacity to gather order from their environment, concentrate it, and shed entropy with their waste. Organisms in their growth phase become stronger and more robust; no physical law prohibits this progress from continuing indefinitely. Indeed, some animals and many plants are known to grow indefinitely larger and more fertile through their lives. The same conclusion is underscored by experimental findings that various insults and challenges which directly damage the body or increase the rate of wear and tear have the paradoxical effect of extending life span. Hyperactive mice live longer than controls, and worms with their antioxidant systems impaired live longer than wild type. Fundamental understanding of aging must proceed not from physics but from an evolutionary perspective: the body is being permitted to decay, because systems of repair and regeneration that are perfectly adequate to build and rebuild a body of ever-increasing resilience are being held back. Regardless of the reason for this retreat, it should be more fruitful to focus on signaling to effect their ongoing activity than to attempt repair of the manifold damage left in the wake of their failure.

Introduction

It is an idea so common, so embedded in the thought process of gerontologists and medical practitioners that it is seldom questioned: Aging is a physical process of deterioration, as damage accumulates faster than it can be repaired. At least since the Renaissance, scientists and philosophers, poets, doctors and laymen have adopted this

understanding of aging. It remains the basis of a great deal of medical research today, and it is at the core of the SENS program.

But despite its ubiquity and commonsense appeal, this idea was thoroughly discredited by physicists of the nineteenth century, and their analysis remains cogent. Evolutionary biologists, who claim the high ground in understanding of deep causes in biology, have for the last century regarded damage as a result, not a cause of aging.

In this article, the theoretical relationship between life and the Second Law of Thermodynamics will be clarified, and reasons to suppose that physics requires living things to age will be deconstructed. Some predictive failures of the 'Damage Theory' will be catalogued. Finally, if the enormous range of natural aging rates – at least six orders of magnitude – is not sufficient reason to discredit the idea that aging is inevitable, then certainly the existence in nature of organisms that do not age at all must be a disproof.

History of Thermodynamics

The idea that order spontaneously and universally dissolves to disorder is very old, but it was not until 1850 that this notion was codified quantitatively as the Second Law of Thermodynamics. Clausius [1, 2] is credited with incorporating entropy as a quantitative physical variable. He distinguished ideal 'reversible' processes from the 'irreversible' processes that take place in the real world, and demonstrated that ideal processes conserve entropy, while in realistic cases, entropy must always increase.

The Second Law of Thermodynamics is sometimes stated thus: *In any closed physical system, the entropy will increase, until it attains its maximum value. The state of the system in which entropy realizes its maximum value is called 'equilibrium'.*

The second law explains why a rock tumbles down a hill, turning its potential energy of gravitation into low-grade heat. Metal fatigue and oxidation are familiar examples of irreversible processes, in which entropy accumulates.

But the law applies only to closed (isolated) systems, and it is possible for processes to accumulate information in one object, while entropy is dispersed elsewhere. For example: As a pool of water evaporates, the liquid can cool (lower entropy) because the gas disperses, with higher entropy that more than compensates. If there is salt in the water, the salt may congeal into a crystal as the water disappears. The crystal has much lower entropy than the dissolved species. It is the water vapor that carries the higher entropy. The disequilibrium between the liquid water and warm, dry air above it was sufficient to drive the process, and create the crystal in its highly ordered state.

Living things have taken this loophole in the Second Law and developed it as a specialty. The ongoing ability to gather free energy from the environment and concentrate it as order within, while discarding entropy as waste is a defining property of living systems.

Every multicellular organism is capable of growing from seed into a fertile adult. Typically, the mortality risk of the adult is lower than the immature stage, and certainly the fertility is (by definition) higher. So growth and development constitute “negative aging” in both the biological and the thermodynamic senses.

There is no theoretical reason this process could not continue indefinitely. The organism could continue to grow larger, more fertile, and more resistant to mortality of all sorts after it attained maturity, and some, in fact, do just this [3]. For an explanation of senescence, we should be appealing to evolutionary theory, not to thermodynamics.

Weismann’s Role

If living organisms wore out like machines, there would be no need for an evolutionary account of aging. But multicellular life succeeds in the remarkable feat of constructing a complex system from fragments found in the environment, using only a genetic blueprint – only to fail at the seemingly much more modest task of maintaining the completed soma in reasonable working order. In the generation after Darwin, Weismann articulated the essential biological conundrum of aging, and sought an explanation not from physics but from evolution. Weismann is credited with the first evolutionary theory of aging, but his departure from physical wear and tear was not so clean. His original theory [4] was based on a presumption that damage to the adult soma was unavoidable, and that damage must accumulate over time.

Weismann backed away from this theory later in his life, and wrote instead of the loss of immortality in somatic cells, as it became an unnecessary luxury. But it was not until Medawar that the essential logical flaw in Weismann’s original hypothesis was articulated: ‘Weismann assumes that the elders of his race are worn out and decrepit—the very state of affairs whose origin he purports to be inferring— and then proceeds to argue that because these dotard animals are taking the place of the sound ones, so therefore the sound ones must by natural selection dispossess the old.’ [5]

Medawar realized full well that there is no thermodynamic necessity for wear and damage to accumulate. He sought not a physical explanation for aging, but an evolutionary explanation, grounded in the declining force of natural selection with age. The evolutionary community has not looked back, and today there is broad agreement that aging cannot be explained as a physical necessity, but must be understood like every other biological phenomenon in terms of natural selection.

Is somatic repair a difficult or expensive process?

It has been argued (most famously by Hamilton) [6] that repair of the adult organism cannot be perfect, and that errors in repair and maintenance must inevitably accumulate,

leading eventually to the organism's demise. This is also a premise of the Disposable Soma theory of Kirkwood [7]. But the reasoning is logically flawed, as Vaupel [3] has demonstrated. There is nothing perfect about a freshly-minted adult, and the maintenance of that adult is not a process that demands perfection. For example, when a bone is broken, it knits back together in a few weeks' time. The bone was not perfect before it was broken, and it is not perfect after it heals. But mended bones are stronger than the original, and will not break again in the same place. Bone repair may be said to be better than 100% efficient, and clearly requires a finite amount of free energy.

The mammalian body is equipped with an impressive array of repair mechanisms, from the molecular level up to the tissue level. Proteins are recycled into constituent amino acids when they become damaged; it is only in aged animals that this process becomes inefficient [8]. DNA is constantly monitored and repaired. Under-performing mitochondria are eliminated and replaced under control of the cell nucleus [9]. And whole cells are routinely destroyed via apoptosis and replaced when they become damaged [10]. All these processes are adequate in youth to maintain the organism without loss of function, and they fail progressively *as a result* of aging, causing aging damage to progress. But their efficiency in youth attests to the fact that aging is not *caused* by shoddy repair.

Loose analogies may suggest that at some point in the life of an organism, damage accumulates to the point where repair of the organism is energetically less costly than replacement through reproduction. This idea is implicit in the foundation of the Disposable Soma theory [11-13]. Our experience with man-made appliances lends credibility to the idea; but many of the reasons that a ten-year-old car can be replaced more cheaply than it can be repaired do not have analogs in the world of biology: Autos must be dismantled before they can be repaired and re-assembled afterward, while for biological organisms repair themselves from the inside out. Auto manufacturers price the new car with a low profit margin, and overcharge for replacement parts, since the customer has nowhere else to go. Auto repair is purchased at market rates for European or American labor, while cheap Asian labor and cheaper robots are used by factories in which the autos originate. Thus we should not expect our intuitions about automobiles to apply to living bodies.

The energetic cost of repairing an aging soma are substantially less than the the total energetic cost of reproducing one new adult. Repairing DNA and stringing together amino acids are both processes with low intrinsic thermodynamic costs, and both have been highly optimized for energy efficiency. In contrast, the cost of anabolism is quite substantial, and the cost of reproduction is magnified by high mortality rates of the immature. For example, a female mouse consumes twice as much food energy while pregnant and lactating [14]. All this suggests that an enormous quantity of resource has been consumed in order to create a single mature adult, and evolutionary pressure to protect and preserve that investment ought to be correspondingly high.

A few mammals and many lower animals are capable of regenerating whole body parts after dismemberment. Heber-Katz [15, 16] has shown that this capability is latent in

mammals as well, and can be switched back on with a simple blood factor. Almost all plants and many animals can regenerate. The process is expensive relative to repair, but cheap compared to the full cost of reproducing a new adult individual. Starfish have legendary capacity for regeneration, and half a starfish can readily grow back its other half. And yet, starfish age with a life expectancy of about eight years. If a limb is severed from a six-year-old starfish, it regenerates a full animal that remembers its age, so that it has two years remaining in its life expectancy. The persistence of senescence even in the presence of extensive regenerative capacity poses a conundrum: How is the memory of the starfish's age carried into the young, regenerated tissue?

Tooth wear is an example of true damage accumulation leading to senescence of the elephant. Elephants can grow six full sets of teeth in a lifetime, but if he should outlive his last set of teeth (and some have been found in nature to do so), he will become toothless, and must starve to death. It is a strange wear-and-tear theory that can explain how it is that the elephant's capacity for regeneration ends after its sixth set of teeth.

Somatic mutations

There is an exception to the thesis that all damage is avoidable, and in any case should be easily and cheaply repaired. This occurs in somatic mutations, where genetic information may be irretrievably lost. This process certainly occurs, but whether it has observable consequences for real organisms, and whether it is related to the phenotype of aging is unknown. Curiously, somatic mutation is out of fashion, and seldom mentioned nowadays as a primary cause of aging.*

Somatic cells are descended directly from a single gamete that contained a pristine copy of the organism's genome. When mutations inevitably occur in this lineage, they affect all descendant cells further down the line. The problem can only be resolved by a process of selection, weeding out cells with damaged genomes. It is not known whether such a mechanism exists for stem cells in modern mammals.

The Hungarian-American physicist Leó Szilárd first proposed[17] that somatic mutations were the cause of aging in 1959. Szilárd had difficulty accounting for the accelerating onset of senescence and the fact that the range of life spans around a species mean is typically narrow. Szilárd's intellectual heir was Leslie Orgel, who theorized[18] not about copying errors (mutations) but transcription errors. The attraction of the Orgel theory was that transcriptional errors could conceivably affect, among other things, the faculty of transcription itself, so that the process has the potential to be self-reinforcing.

* This is mutation accumulation, but it is not the well-known "Mutation Accumulation Theory of aging". The standard theory by this name is about mutational load: mutations accumulate in the germ line over evolutionary time because the speed of natural selection is less than the rate at which new deleterious mutations occur. The Mutation Accumulation Theory should not be confused with the phenomena of somatic mutations discussed in this section.

This would explain the rapid onset of aging and narrow range of life spans that Szilárd's mutational theory failed to account for.

Orgel's theory was abandoned when experimental evidence failed to support it. Mice deliberately fed misformed proteins do not age any faster than control mice[19]. And direct tests of the hypothesis in cell colonies indicate that transcription errors do not increase in frequency as a lineage ages [20].

Szilárd's theory of copying errors also suffers from lack of experimental support. The theory predicts that tissues that are self-renewing on a short time scale should be a central locus of failures with age. But in humans, the heart and the brain suffer particular aging damage, and both these organs have minimal rates of cell renewal. The immune system is the only organ with a high turnover rate that is also a hot spot for aging problems, but the immune system is a special case in that B- and T-cells *depend on* mutation in order to maintain their sensitivity to a diverse universe of antigens.

Szilárd formulated his theory at a time when stem cells were unknown, and he imagined that terminally differentiated somatic cells were the reservoir for their own renewal. In fact, the mechanism of stem cells substantially mitigates the problem of somatic mutation, and this may, in fact, be related to the evolutionary reason that stem cells are deployed by the body instead of simply allowing terminally differentiated cells to clone themselves [21].

Mutations in the mitochondrial DNA has also been the subject of speculation as a primary origin of aging damage[22]. This is an attractive hypothesis because mitochondrial DNA must survive in a highly oxidizing environment, and mitochondria reproduce at a much more rapid rate than do cells. Furthermore, it was thought possible that mitochondria reproduce in a competitive environment, so that they may be subject to selection not for efficiency of their function for their cell, but for their (selfish) rate of growth and reproduction. This combination appeared to offer the means, the motive, and the opportunity to resolve the mystery of aging.

However, ingenious experiments by Hayashi[23] have indicated that mitochondrial reproduction takes place not in a competitive environment, but under tight regulation from the cell nucleus. Damaged mitochondria do not reproduce excessively (like an intracellular cancer), but are efficiently weeded out and destroyed. Somehow, the internal evolution of mitochondria is managed and directed for the benefit of the whole cell, and not mitochondrial selfishness is not permitted to prevail.

In summary, while there were good theoretical reasons to believe that somatic mutations, including mitochondrial mutations, could be keys to the process of aging, the evidence indicates that they are not, and this kind of damage is no longer the subject of a vigorous research program.

Theories of Oxidative Damage

It is over fifty years since Denham Harman [24] first proposed that aging is caused by progressive damage to the body's chemistry from the reactive oxygen species (ROS) that are an inescapable byproduct of respiration. The theory has inspired thousands of research projects, and continues to have great currency today. The ongoing attraction of the theory is that there is broad evidence that oxidative damage to key proteins accompanies aging. Extensive experimentation has explored the use of antioxidants as an anti-aging intervention, both in the laboratory and in human epidemiology. The results of these studies have been disappointing, with the largest studies actually showing *increased* mortality for subjects ingesting antioxidants [25]. The emerging picture of the relationship between oxidation and aging is complex: peroxide is an important signal in the pathways connected to apoptosis [26] [27]. Apoptosis has two faces: it is both an essential mechanism for cleansing the body of infected, cancerous and damaged cells, and also implicated in the wasting of sarcopenia [28, 29], the loss of brain cells in Alzheimer's [30, 31] and Parkinson's diseases [32, 33]. The body's important antioxidants are expressed at lower levels with age, which both accounts for the observed increase in oxidative damage [34, 35], and suggests that oxidative damage is secondary effect rather than a root cause of aging.

Theories of oxidative damage are elegant and attractive, but some of the experimental results seem almost to mock the predictions of the theory. Physical activity generates copious free radicals, and yet high levels of physical activity are generally associated with longer, not shorter average life spans. Hanson and Hakimi [36] report on a genetically modified mouse that has extra mitochondria. These mice are phenomenally active, eat much more than wild type and burn it all up, yet they live almost two years longer than wild type, and remain reproductively active two years longer. Two of the body's most essential antioxidants are superoxide dismutase (SOD) and ubiquinone. Mice in which one copy of the gene for SOD has been knocked out have half as much SOD in their tissues, and measurements of oxidative damage to DNA show that it is far higher than controls; yet the heterozygous *Sod2*^{+/-} mice lived slightly longer than controls [37]. SOD knockout worms also have extended lifespan, coupled with enhanced markers of oxidative stress [38].

CLK-1 is a gene originally discovered in worms [39], inactivation of which increases life span by an average 40%. The homologous gene in mice is MCLK1, and its deletion also leads to enhanced life span [40]. Only later was it discovered that the action of CLK-1 is essential for synthesis of ubiquinone, and, as a result, CLK-1 mutants are *less* able to quench the ROS products of mitochondrial metabolism – yet they live longer [41]. The first data was reported for heterozygous CLK-1 ^{+/-} worm, and it was thought that the homozygous ^{-/-} mutant was not viable. More careful experimentation revealed that the ^{-/-} worm would develop on a delayed schedule, and subsequently lived to a record ten times the normal *C. elegans* life span [42]. This worm has no capacity to synthesize ubiquinone, and its prodigious life span is truly a paradox from the perspective of the damage theories of aging.

Naked mole rats live eight times longer than mice of comparable size, though the latter seem to be better protected against oxidative damage [43, 44]. And life spans of mice are generally a few years, while bats for decades, despite a higher metabolic rate and greater load of mitochondrial ROS [45].

The laboratory of Arlan Richardson at the Barshop Institute of the University of Texas reports on the results of an eight-year, systematic study of a wide variety of genes coding for antioxidant enzymes. For each target gene, they studied both knockout mice and mice with extra copies of the gene, and assayed life spans under standard conditions. The only intervention that affected life span was the SOD1 gene. They published their study under the provocative title, “Is the oxidative stress theory of aging dead?” [46]. Circling for the wounded beast, LaPointe and Hekimi draw a parallel conclusion from their own experiments in an article titled, “When an aging theory ages badly.” [47]

It is certainly true that much of the damage we associate with senescence can be traced back to oxidative damage from ROS created as a byproduct of mitochondrial processes; but biochemical protections could be adequate to protect against these hazards with essentially perfect efficiency.

Disposable Soma Theory

Kirkwood’s Disposable Soma theory is the only mainstream evolutionary theory that connects to the idea of accumulated damage. The thrust of Kirkwood’s idea is that damage accumulates because the body must budget caloric energy, and skimps on repair in order to enhance reproduction, in a compromise that optimizes net reproductive fitness.

The biggest problem with the Disposable Soma theory is what it predicts about the relationship between food energy and aging. If aging were primarily a matter of insufficient food energy to both reproduce and repair, then more food energy would lessen the need for compromise, and the body should be able to both live longer and increase fertility. The Caloric Restriction effect is the oldest, most robust and best-known intervention to *increase* life span, and it is absolutely irreconcilable with the Disposable Soma theory [48].

It is also a robust prediction of the Disposable Soma theory that life span should be shortened by the energetically expensive act of reproduction. In animals, there is no evidence that this is the case [45, 49], and in humans, there seems to be a small *positive* correlation between fertility and life span [50-53].

Pre-senescence, Negligible Senescence, Negative Senescence, and Post-Senescence

If aging were a process of stochastic damage, then that damage would be accumulating inexorably, regardless of species, of environment, or time of life. The many examples of non-aging in nature attest to the fact that aging is not a physical necessity.

All multicellular life is capable of building itself up from seed. During the process of growth, aging is typically absent. In fact, if aging be defined demographically as increasing mortality rates along with decreasing fecundity, then the early period of growth is a time of negative senescence.

Semelparous animals from may flies to octopi may be distinguished as a subcategory of animals that suffer no (or negative) actuarial senescence before they die precipitously [45]. Many plants and some animals do not age measurably over hundreds of years [45]. Vaupel has collected examples of animals that enjoy negative senescence, including coral, sea urchins, some mollusks and desert lizards [3]. Fahy offers unique details and adds many more examples, including cartilaginous fish and turtles [54].

The phenomenon of late life mortality plateaus was not predicted by any of the evolutionary theories of aging, and certainly not by wear-and-tear theories. It was discovered in the 1990s that in *Drosophila*, *C. elegans*, and humans mortality rates cease their exponential growth and level off late in life. (These are the only three animals for which sufficiently large samples have been studied to detect this phenomenon.) The phenomenon is difficult to reconcile with damage theories of aging. It must be considered paradoxical that damage should cease its relentless advance at a point in the life cycle when repair mechanisms are at their weakest [55].

If not damage, what then?

The thesis of this work has been negative: aging of living organisms is essentially different from the process of accumulated damage that causes inanimate machines to wear out over time. If aging cannot be explained as a process of accumulated damage, what then is its cause? The answer must be sought in the evolutionary process that created life. Since the aging phenomenon is so ubiquitous in the biosphere, and since genes that cause aging are related over widely separated taxa, it makes sense to seek a unified answer to the question why organisms age.

But the phenomenology of aging is diverse and often paradoxical, refusing to be tamed by simple, unifying hypotheses. The community of evolutionary theorists has no consensus about the ultimate provenance of aging; instead there are competing theories, all growing from Medawar's original insight about the declining force of natural selection [56]. It may be that the paradoxical phenomenology, including results cited herein, is inconsistent with prevailing notions of individual fitness, and that evolutionary theory will have to stretch to accommodate the evidence [57] [58].

Fortunately, there is a clear message for anti-aging research which does not depend on which evolutionary theory is favored. The message is that aging is under the body's control. If there is no physical necessity for damage to accumulate, there is also no necessity for bioengineers to invent elaborate solutions for repairing that damage. It should be far easier to reprogram the body's signaling apparatus, turning on mechanisms that are perfectly capable of maintaining the body in a state of youthful vigor.

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