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REVIEW

Can Aging Be Programmed?

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Abstract—Aging diminishes individual fitness, and aging could never evolve as an adaptive program according to the most prevalent model of evolutionary theory. On the other hand, some mechanisms of aging have been found to be conserved since the Cambrian explosion, and the physiology of aging sometimes looks like programmed self-destruction. Biostatisticians find evidence of an epigenetic aging clock, extending the clock that controls the growth and development into a realm of inexorably increasing mortality. These and other observations have suggested to some biologists that our understanding of aging is being constrained by restrictive evolutionary paradigms. Several computational models have been proposed; but evolution of an aging program requires group selection on a scale that goes beyond the theory of multilevel selection, a perspective that is already controversial. So, the question whether plausible models exist that can account for aging as a group-selected adaptation is central to our understanding of what aging is, where it comes from and, importantly, how anti-aging medicine might most propitiously be pursued. In a 2016 *Aging Cell* article, Kowald and Kirkwood reviewed computational models that evolve aging as an adaptation. They find fault with each of these models in turn, based on theory alone, and on this basis, they endorse the standing convention that aging must be understood in terms of trade-off models. But consideration of the corpus of experimental evidence creates a picture that stands in counterpoint to the conclusions of that review. Presented herein is a broad summary of that evidence, together with a description of one model that Kowald and Kirkwood omitted, the demographic theory of aging, which may be the most conservative, and therefore most plausible of the alternative evolutionary theories, and which is the subject of a book by the present author, published contemporaneously with Kowald and Kirkwood.

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This question was posed in the title of the 2016 *Aging Cell* review [1]. Formulating the question in this way implies that it is to be resolved by theory, and indeed publication of this article in a prominent experimental journal suggests a dictum that experimental results are to be interpreted in the light of well-established evolutionary theory. But there is a great deal of experimental evidence that bears on the question whether aging is an evolved program, and it is a reversal of normal scientific priorities to impose a strict theoretical framework in the face of substantial contravening evidence. It is the job of theorists to explain experimental results, not to constrain them.

The article goes on to review and critique six theoretical models, from verbal reasoning and agent-based computations, demonstrating proposed evolutionary mechanisms by which aging might have evolved as an adaptation. The plausibility of these models must be considered in light of biological phenomena that they are designed to explain. In proposing their models or mechanisms, each of the reviewed authors describes the empirical evidence that led them to the conclusion that aging has been shaped as an evolutionary adaptation. Many other bench scientists have also noted evidence that there is a programmed aspect to aging.

Libertini [2] was first in a century to propose a mechanism for programmed aging, led to his hypothesis by a dissatisfaction with the prevailing theories' ability to account for species that do not age and for time scales of those that do. Bredesen [3] wrote about programmed aging, based on biochemical similarities between metazoan aging and programmed cell death. Skulachev [4] was led to his theory by pioneering work on the biochemistry of mitochondria, which retain from their origin as infectious bacteria the capacity to assassinate the cell. Goldsmith [5] places aging in the context of multiple group-selected evolvability traits. Longo [6] directly observed programmed death while documenting altruistic apoptosis in yeast cells. Travis and Dytham [7] came to

their view of aging by noting the ecological role of predictable death rates. Fahy [8] and Bowles [9] regard aging as programmed based on hormonal changes that drive human aging. (Bowles credits the pioneering research of Dilman a generation earlier on the neuroendocrine basis of aging [10].) Blasco [11], Andrews [12] and Fossel [13, 14] drew the conclusion that aging is programmed based on the role of (easily avoidable) telomere shortening in driving the mortality increase with age. Kornfeld (personal communication) has noted that the lifespan and other aspects of *C. elegans* life cycle are exquisitely adapted to exploit intermittent food availability. Barja [15, 16] detects programmed aging in the signaling role of mitochondrial reactive oxygen species (ROS). Pepper [17] realized that predators protect their prey through restrained reproduction before extending his study of altruism to include aging. Goodnight's study of population control through cannibalism in beetles [18] led him to population control through senescence as a natural extension. Partridge and Gems [19] considered the broad homology of aging genes across the biosphere as *prima facie* evidence, and arrived at a nuanced view that the regulation but not the origin of aging is a genetic program. Guarente [20] and especially Kenyon [21] draw closer to a position that aging is programmed based on the same evidence. Werfel, Inger and Bar-Yam [22] describe being motivated by the wide range of lifespans in nature (~7 orders of magnitude): what unifying physical or chemical process could produce effects on such different timescales? Informally, Kenyon (personal communication) has cited this as a one-line proof that aging is programmed. Mitteldorf [23] became an advocate of programmed aging through study of hormesis and caloric restriction. De Cabo [24] was led to appreciate the power of group selection after surveying the plasticity of aging under various simple interventions. Katcher [25] saw evidence that aging is programmed in the response of old tissue cells to a young signaling environment in parabiosis experiments. Horvath [26] used statistical methods to derive an "aging clock" based on DNA methylation, and he has recently taken the position [27] that epigenetic methylation is not merely a marker but a programmed driver of aging in mammals. Finch [28] has chronicled evolutionary implications of diverse aging phenotypes, and Church [29] is at the forefront of biochemical interventions to slow or reverse aging; both these scholars have communicated to me privately that their investigations have led them to the perspective that aging is an epigenetic program akin to development, but that making this point in public would only distract from the substance of their work.

Diverse empirical evidence for programmed aging stands against a requirement of powerful group selection for its evolution and a conventional theoretical skepticism of group selection. But whether or not a particular model holds the explanation for the evolution of aging, empirical evidence demands a theoretical accounting. Some of this evidence is reviewed below, and we refer the reader to a recent book for more evidence and fuller detail [30].

- There is a conserved genetic basis for aging, and the persistence of any trait in homologous forms through the biosphere is generally interpreted as evidence for an adaptive origin of the trait.
- Lifespan increases in response to diverse hormetic challenges, which is to say that the body is tuned to senesce more rapidly in the absence of challenge. This fact is difficult to reconcile with models where the body is adapted to protect itself to the best of its ability (always subject to constraints).
- There are two modes of indisputably programmed aging in *protoctista* namely apoptosis [6] and cellular senescence [31], where theory insists there should be no aging at all; both these mechanisms have been preserved through 500 million years of evolution, and they now contribute to senescence in multicelled eukaryotes, including mammals.
- Many single gene deletions have been identified that extend lifespan in diverse species; indeed, these have become so common that we may have forgotten that the impossibility of such genes was put forward as a core prediction in the seminal paper that inspired the entire corpus of evolutionary theory for aging that has emerged in the last 60 years [32]. For some of these "aging genes", pleiotropic tradeoffs have been identified, but for others, there are no known downsides. Of course, it is never possible to prove there are no detrimental pleiotropic effects because we cannot reproduce environmental conditions in which these organisms evolved; but we can say that the long-lived variants have no obvious defects.

The question whether aging is programmed should be resolved on the basis of empirical evidence, and no biological theory is so well-established as to provide an ironclad authority on the subject. Indeed, the essence of scientific method is that empirical observation of nature should always be the ultimate arbiter, rather than any theory or institutional authority. If the existence of a heritable, lifespan-limiting program can be established experimentally, theorists should accommodate this conclusion, with a preference for the most conservative model that departs minimally from well-established theory. I have proposed that the most conservative path is the demographic theory of aging [30, 33, 34], a model that was omitted from the review of Kowald and Kirkwood.

A CONSERVED GENETIC BASIS FOR AGING

There are homologous families of genes that regulate aging across a wide range of eukaryotes, from yeast cells to mammals [19-21]. The existence of such pathways implies that they have been conserved by natural selection, presumably from an origin in a common eukaryotic

ancestor more than half a billion years in the past. Of course, there are very many genes that have been conserved since the origin of eukaryotic life, but they all have core metabolic functions that are essential to life. Natural selection has treated aging with the same conservatism as these other essential biological functions.

The best-known of the conserved pathways involves insulin/IGF-1. Almost all animals detect an abundance of food through insulin signaling, and shorten their lifespans in response, and single-cell consumer species perform the same function through alternative pathways. This is demonstrated by the well-known response to caloric restriction [35, 36], and life extension in times of scarcity is only possible because life is shortened when abundant food is detected. The latter adaptation reduces fitness of individuals, presumably for the sake of moderating population growth at times when overshoot poses a collective, existential danger.

Other conserved mechanisms of aging include the TOR pathway, SIR2/SIRT, and the transcription factor known as DAF16 in nematodes and FOXO in mammals.

Evidence that programmed aging in protists has evolved into senescence of animals. Two special cases of the conserved genetic basis involve mechanisms of senescence that evolved in ancient protists and have propagated into today's multicelled life forms, where they now have more roles, including the original role of programmed death. These are cellular senescence and apoptosis.

The loss of telomere length with cell replication is a purely mechanical consequence of the way in which DNA polymerase functions; however, the enzyme telomerase could, in principle, be deployed with sufficient frequency that cells never need to suffer from telomere shortening. Rationing of telomerase appears in ciliates, where the sexual function (conjugation) is independent of the reproductive function (mitosis). In *Paramecia* among other ciliates, telomerase is not expressed during mitosis, but only during conjugation. Thus, telomeres are permitted to shorten, and a lineage will die out if it does not conjugate at least every hundred generations. This is programmed aging in an early form [37, 38]. Rationing of telomerase can only serve to lessen the reproductive fitness of individual cells, but as an adaptation, it contributes to the fitness of the community by enforcing the imperative to share genes via conjugation. (In higher organisms, sex is tied tightly to reproduction, enforcing the imperative to share genes via a different mechanism.)

Telomerase rationing persists in multicellular organisms, and cellular senescence contributes to rising mortality rates with age in humans [40, 41], horses, and dogs (but not in mice, pigs or cows). It appears that telomere attrition is entirely optional, from the evolutionary perspective, but that it shortens lifespan in those animals where it has been retained by natural selection.

The second mode of programmed death in protists is apoptosis, and it is even older than cellular senescence. The possibility of apoptosis in unicellular organisms has been long regarded as a logical absurdity. Since altruistic apoptosis in yeast was documented by Longo [6], a number of other examples have been discovered (reviewed in [42, 43]). In humans, apoptosis is related to sarcopenia [44-46] and plays a role in Alzheimer's dementia [47, 48]. Shen [49] describes a generalized role for programmed cell death in senescence of animals.

Programmed cell death in bacteria has been known since the early 1990s, and its function is generally to regulate population [50], once again foreshadowing a principal function of aging in higher organisms [33].

HORMESIS IMPLIES THAT AGING IS PROGRAMMED

Hormesis is the extension of lifespan in the presence of challenging environmental conditions. There are many examples of hardships to which the metabolism responds in a way that lengthens life expectancy. This is difficult to reconcile with the notion that the body is doing its best to live as long as possible, and in fact, the very existence of hormesis was contested for decades before plentiful examples and robust evidence overwhelmed the skeptics. If the body is capable of living longer when challenged by hardship, we must ask why it does not choose to do so when resources are plentiful, and survival is less demanding. This is direct evidence for programmed aging. The subject is reviewed by Neafsey [51], Luckey [52] and Calabrese [53], and its relationship to evolution is discussed by Forbes [54] and Blagosklonny [55].

Life extension can be achieved with heat stress [56], cold stress [57], action of chemical toxins [58], oxidative stress [59, 60], and ionizing radiation [52, 61].

The best-documented example of hormesis is caloric restriction [36]. It is true in most cases that underfed animals live longer, and this has been interpreted as an evolutionary adaptation to protect populations from famine [35, 62, 63]. But caloric restriction is seldom considered from a converse perspective: why should lifespan be shortened when food is abundant (or just adequate)? Posing the question in this way [23] suggests a role for evolved aging in the stabilization of population dynamics, avoiding extinction [33].

Life extension from caloric restriction poses a particular challenge to the disposable soma theory of aging [64], which attributes aging to a necessity for rationing caloric energy. Surely, more caloric energy should mean less rationing, so the disposable soma theory predicts that a starved animal should suffer a shortened lifespan. There has been one attempt to reconcile the disposable soma theory with the calorie restriction phenomenon for the special case of pregnant mice [65], but it fails even in this

case, and certainly the generality of life extension in starved animals is powerful evidence against the central hypothesis of the disposable soma theory.

Another familiar example of hormesis is that exercise increases mean (but not maximum) lifespan in humans [66] and other species [67, 68]. Since exercise expends energy and generates damage in the form of muscle tears, microscopic bone fractures, and free radical oxidation, the increase in lifespan must be regarded as a paradox from the perspective of the disposable soma or any of the wear-and-tear theories of aging. The hormetic nature of the metabolic response to exercise is underscored by the ability of antioxidant vitamins to subvert the benefit [69].

SINGLE GENE DELETIONS THAT EXTEND LIFESPAN: "AGING GENES" OR PLEIOTROPY?

When Williams proposed a pleiotropic basis for the evolution of senescence [32], he extracted predictions from the new theory, one of which was "Senescence should always be a generalized deterioration, and never due largely to changes in a single system.... Any such small number of primary physiological factors is a logical impossibility if the assumptions made in the present study are valid". When T. E. Johnson [70] discovered the first point mutation that substantially extended lifespan in *C. elegans*, he reported that his long-lived mutants were defective in fertility, as pleiotropy theory would predict. However, further investigation revealed that the longevity mutation (AGE-1) and the fertility mutation (FER-15) were linked but separable [71], highlighting the paradox of cost-free life extension. Since that time, many single gene deletions and mutations have been discovered that extend lifespan in worms and other model organisms [72]. Another of the worm longevity genes has been shown to carry pleiotropic costs [73], but for many other genetic variants, no cost has yet been identified.

Long-lived mutants have been discovered in the insulin and TOR signaling pathways, in growth [74] and pituitary hormones [75], in SIR and other transcription factors [76, 77], and more surprisingly, by sabotage of the antioxidant metabolism [78]. Do all these long-lived mutants have lower overall fitness? Many theorists take it as a matter of faith that they must, but evidence is lacking in most cases, and there are at least some examples where the animals seem to be otherwise healthy and fertile [79].

THE DEMOGRAPHIC THEORY OF AGING

I have advocated a theory for the evolution of aging based on the ability of programmed lifespan to level the death rate, avoiding population overshoot and extinctions [30, 33, 34, 80]. If one accepts the empirical evidence that aging has been programmed by natural selection as an adaptation in its own right, this model is the easiest to reconcile with the classical evolutionary theory (despite the fact that it depends on strong group selection among individuals that are not necessarily related by descent). Modeling the population dynamics of the predator/prey systems, one cannot help but be struck by how robust is the necessity of restraints on reproduction and/or lifespan in order to avoid extinction [17, 81]. Indeed, in agent-based simulations, population dynamic effects are the only force that appears to be sufficiently swift and lethal as to compete effectively with individual selection, which always favors higher fertility and longer life spans.

The essence of the demographic model is that the danger of population overshoot enforces regional cooperative behavior with a threat of rapid and devastating population crashes. All evolutionary models assume a sustainable population limit; not everyone can survive. In the standard population genetic theory, it is assumed that any excess population is immediately trimmed, and those individuals whose fitness is lowest suffer most heavily. But often nature does not work this way. There is a prey species (animal or vegetable) that provides a reservoir of foodstock that permits an animal population to expand temporarily well beyond its sustainable limit. Typically, after just a few generations of exponential expansion, the foodstock is exhausted, and the population suffers a famine which takes down the fittest individuals along with the less fit. Famines can be an existential threat to an ecological community. This is a particularly rapid and powerful mode of group selection that is neglected in standard theories.

In the absence of group selection, fertility and longevity evolve inexorably upward. There are many plants that do not age, but few animals [82]. Many trees live for centuries; oaks can produce a million acorns in a lifetime, and giant sequoias a billion cones [83]. But no consumer species can afford such fertility rates. Any consumer that grows its population at an exponential rate that exceeds the producers' on which it depends by more than a factor of three faces chaotic population dynamics and swift extinction [33]. In practice, animal species tend to be much more conservative than this, and in living lightly on their prey populations, they actually maximize their own long-term average population [84], and long-term average population has been proposed as the most robust measure of (collective) fitness [85]. In the context of demographic limits on lifetime fertility, it is easy to understand the evolution of senescence as one mechanism among many that promote demographic homeostasis.

Famines cannot be avoided without individual sacrifice of energy intake and reproductive potential. Thus, the demographic model directly opposes individual selection for ever higher reproductive rates, requiring ever more intense exploitation of food resources. Demographic selection is a game-changer.

CORRECTION OF SOME MISUNDERSTANDINGS AND MISCHARACTERIZATIONS

In this section, I address several misunderstandings in Kowald and Kirkwood's descriptions of my computational models and others.

The model of Mitteldorf and Pepper [86] was borrowed from Socolar [87], who reported the same model behavior in a physics journal, but did not explore the biological implications. The driving force behind the model is the imperative to limit local population densities. High population density risks a major local extinction event that effectively wipes out offenders in a wide swath. After Socolar, I called these events "epidemics", and this conception fits as well as famines, as described above. In either case, excessive population density leads to an extinction event that wipes out an entire community and is oblivious to local variations in individual fitness. In the model, such events are found to enforce the imperative for local cooperation to keep population densities below this threshold.

Kowald notes that if an evolvable gene for mobility is added to the model, then mobility predictably evolves ever higher. But increased mobility entails a concomitant opportunity for epidemics to spread. If this change is implemented in parallel, then the need to limit population density is not eliminated, nor is the central dynamic of the model altered, but it acts on a larger scale. If the model universe is expanded appropriately so that it is always larger than the scale of typical epidemics, then the model always evolves a finite lifespan; if not, then the population destroys itself.

In the analysis of Mitteldorf and Pepper, we illustrate exactly this phenomenon by varying the size of the neighborhood from a 5-cell von Neumann neighborhood to a 9-cell or 25-cell square. Migration is not explicitly included, but the standard modeling of viscous population via reproduction within a local neighborhood accomplishes the same thing. Crucially, we allow the epidemic to spread through the same neighborhood rules as local reproduction. Under these circumstances, we demonstrate that the larger the neighborhood, the larger the scale on which the evolutionary dynamic operates. But for any given size of a neighborhood, a finite lifespan always evolves, and, in fact, larger neighborhoods tend to evolve shorter lifespans, all else being equal.

In land animals, physical limitations will always place an upper limit on mobility, but Kowald allows mobility to evolve higher without bound. As mobility increases, the model approaches a panmictic simulation, in which there can be no group selection and, of course, aging cannot evolve.

Kowald also notes that the Mitteldorf/Pepper model predicts that higher background mortality evolves a lower rate of aging. This, they claim, is at odds with most field studies, indicating that high background mortality leads to selection for shorter lifespan. They recognize *Poecilia* [88] as the sole example of a complementary relationship between the background mortality and evolved senescent mortality. In fact, *Daphnia* [89, 90] have also been reported to have longer lifespans under conditions of higher predation. The ubiquitous caloric restriction adaptation is a response that shortens lifespan just when food is plentiful and background mortality is low. And I have become convinced that selective reporting has masked a major presence of this complementary relationship in nature, based on anecdotes about unpublished data that have been shared with me verbally at conferences. (There are abundant examples of species in which incidental mortality is low evolving longer lifespans, but for intraspecific variation, the evidence is mixed.)

Kowald reports that after modifying the Mitteldorf/Martins model to include sexual gene exchange, lifespan evolves upward without limit. After conferring with Kowald, I was able to replicate this finding in my own implementation of the model. An explanation for this behavior is that shorter lifespan evolves via a mechanism akin to hitchhiking; individuals with shorter lifespan have more opportunities to increase their fitness, so fitness genes become correlated with lifespan genes. Sexual gene exchange dilutes this correlation sufficiently that the hitchhiking mechanism is no longer potent to evolve shorter lifespans. This is a problem with evolutionary mechanisms based on evolvability alone, without taking population dynamics into account. I have speculated that population dynamic mechanisms fundamentally alter evolutionary dynamics, such that evolution of aging, sex, and evolvability, among other altruistic adaptations, cannot be understood without invoking selection for demographic homeostasis [30, 91].

Kowald interprets the evolutionary mechanism of the Werfel model in terms of enhanced opportunity for spreading to another site (an individual advantage). But Werfel et al. describe the advantage instead as the (collective) necessity for the consumers to preserve their resource. This is a demographic effect, suggesting once again that population dynamics is the key to understanding the evolution of aging. In the Werfel model, it is counterproductive for consumers to reproduce at a faster rate than their resource, and the danger of exhausting resource provides a powerful incentive for local cooperation. With the rules of the Werfel model, the only way that consumers can preserve their resource is by evolving a shorter lifespan. I believe that (in nature as *in silico*) the imperative to maintain demographic homeostasis is the most robust basis for group selection. Kowald claims that "the rule for programmed death allows consumers to move, a property that they do not otherwise possess". This claim apparently derives from a misunderstanding of the simple rules in the Werfel model. All "movement" of consumers is via reproduction into a neighboring cell that contains a producer species to support them. There is no explicit pro-

scription against non-aging varieties reproducing into a neighboring cell. The viscous structure of the grid enhances the probability that the neighbor of an aging consumer will be another aging consumer, and the aging consumer is more likely to vacate the site with producer species intact than is a non-aging consumer. It is only in this sense that the Werfel model facilitates the spread of the aging variety, and indeed this feature realistically models a group advantage that we expect is realized in nature. Kowald goes on to create a variant of the Werfel model in which migration is facilitated, and they note that this vitiates the advantage of aging. As a consequence of enhanced migration, the Kowald variant becomes well-mixed, and (aging) altruists lose the advantage of being located near other altruists. It is tautological that group selection requires groups, and we should not be surprised that strong altruism fails to evolve in a well-mixed population.

Kowald criticizes proposed mechanisms of Skulachev, Goldsmith, and Libertini, which were originally presented as verbal heuristics with the support of quantitative simulations. All three are based on an enhanced adaptability (rate of evolutionary change) in a population with short lifespans. Kowald reports that none of the numerical implementations of this mechanism that he has tried result in the evolution of limited lifespan. I agree that the criticism is well-taken, and indeed my own efforts at simulating evolution of senescence based on the rate of adaptability have, with the exception of the Martins model, led to the same dead ends. This experience has strengthened my conviction that population dynamics is a key to understanding aging, altruism, and long-term effects in evolution.

WHAT IS AT STAKE?

At stake in the programmed aging debate are the foundation of evolutionary theory and the future direction of geriatric medicine.

First, for evolutionary theory:

Darwin's theoretical writings were combined with the rediscovered genetical investigations of Mendel and recast in the first half of the 20th century as a predictive, quantitative theory. This was the work of such luminaries as Lotka, Wright, Dobzhansky, Haldane, and especially R. A. Fisher. The "New Synthesis" of neo-Darwinism identifies Darwin's fitness with quantity and speed of reproduction, subsumed in the computable value of the Malthusian parameter, ***r***. Today's mainstream evolutionary theory rests on the axioms:

- that ***r*** can be associated with individual genes;
- that ***r*** measures the rate at which a gene spreads through a (constant or slowly-shifting) population;
- and that natural selection always works to maximize ***r***.

The axiom that "selection maximizes ***r***" underlies the dictum that, other things being equal, natural selection can never favor a shorter lifespan over a longer one. If we are to accept evidence that limits to lifespans have evolved as an adaptation in its own right, then this axiom of neo-Darwinism is called into question. Such profound and seismic shifts in well-established theory are not to be lightly proposed, and they should be subject to all the rigors of scientific skepticism.

However, with respect to maximization of ***r***, evidence from the science of aging is not the first to cast doubt on this axiom. Many specific instances have been reported in which the postulate is violated, including two examples cited above and two additional examples:

- *Poecilia reticulata* drawn from low-predation environments evolve shorter life spans, slower maturation, lower swimming speed, and lower fertility than their cousins just a few hundred meters away in high-predation environments [88].
- Similarly, *Daphnia pulex* in low-predation environments evolves slower maturation and lower fertility [89, 90]. Both the guppies and the fleas appear to be adjusting their rate of aging and their fertility in tandem to avoid overcrowding [92].
- *C. elegans* hermaphrodites become infertile after a few days of life when they run out of sperm, though egg production is far more metabolically costly, and plenty of eggs remain [93].
- Birds' clutch size is adjusted to match environmental resources, resulting in a net reduction in individual reproductive output. David Lack's classic finding [94] that birds lay just enough eggs to maximize the output of fledged offspring is widely cited even today, but Ydenberg and Bertram [95] followed up 40 years later, reviewing the many field studies that collectively falsify Lack's claim.

But far and away, the clearest challenge to the primacy of ***r*** is the ubiquity of dioecious sex, which has evolved and spread and persisted despite the fact that it gratuitously imposes a reduction of ***r*** by a full factor of two. The paradox of sex has inspired a large and diverse literature [96-100] but there is yet no consensus solution that reconciles the persistence of sex with the maximization of ***r***.

Perhaps the seismic shift has already occurred, and the evidence for adaptive aging is only corroborating what other evidence has already suggested: that Darwinian fitness is a complex, multi-faceted concept; that natural selection occurs simultaneously at the level of the gene, the individual, the community, and the ecosystem; that fitness (as the etymology suggests) can only be defined relative to a specific ecological context; and that ***r*** captures and quantifies but one aspect of fitness.

Second, for geriatric medicine:

As mentioned by Kowald and Kirkwood, the question of programmed aging potentially affects the direction of anti-aging medicine and related research programs for the diseases of old age. Gene expression changes with age have been noted and quantified. If we interpret these changes in gene expression as a protective response that

helps the body mitigate the damage it has suffered, then we should regard gene expression changes with age as benign and learn from them how better to protect the body. If, however, aging is an epigenetic program of self-destruction, we may pursue the restoration of a youthful epigenetic profile as a robust strategy for whole-body rejuvenation. We might expect broad health benefits to derive from epigenetic manipulations that shift the levels of transcription factors and cytokines toward their youthful levels.

In fact, evidence is already accruing for the latter case. In mice, old muscle and nerve cells have been exposed to the circulating hormones from young blood plasma, with the result that tissues are rejuvenated growth is promoted, and healing is more efficient [25, 101-104]. A few of the specific gene expression changes associated with the deficits of age have been characterized explicitly:

- Expression of pro-inflammatory cytokines (e.g., NFκB, TGF-β) increase with age, adding to the burden of inflammation that is associated with all the diseases of old age [105, 106].
- Hormones associated with menstruation (LH, FSH) increase after menopause, when they have no function but only a destructive effect [107-109].
- Production of protective anti-oxidants (e.g., glutathione, ubiquinone, SOD) decreases with age.
- P53 increases with age, placing apoptosis on a hair-trigger, destroying healthy muscle cells (sarcopenia) and nerve cells (dementia) [110-112].
- Blood levels of oxytocin [103] and melatonin [113, 114] have been shown to decrease with age, to the body's detriment.
- Levels of Neuroprotein Y in the hypothalamus decline with age, contributing to loss of proteostasis and stem cell exhaustion [115].

These changes represent both evidence for programmed aging in humans, and also an accessible point of intervention with the potential to slow or reverse aging.

DISCUSSION

A few years ago, there were two standard and commonly-accepted theoretical approaches to the evolution of aging. Pleiotropic theories are based on tradeoffs that compel compromise in late-life fitness in order to achieve higher fertility and survival value early in life. In addition, there were theories based on genetic load (mutation accumulation theory). The latter depended on the assumption [116, 117] that the fitness cost of aging in the wild is vanishingly small. As Kowald points out, we now have substantial evidence from field studies that aging takes a sizable bite out of fitness in the wild [82, 118-121]. In addition, the hypothesis that aging derives from genetic load implies a recent, stochastic origin for aging genes, that might be expected to differ widely from one lineage to the next; this proposition faces broad contradiction in the homology that speaks of an ancient origin for the regulation of aging. If accumulated mutations theory is ruled out, this leaves pleiotropy as the one theory of aging sanctioned by mainstream evolutionary science.

If we ask, which model is most consistent with present-day understanding of evolutionary dynamics, the answer is clearly pleiotropic theories, based on individual selection. But if we ask instead, which models are better supported by laboratory data, we may find a role for the programmed models. While pleiotropic theories capture some aspects of aging phenomenology, there are other areas in which the theories fail badly. There are results that baldly contradict pleiotropic theory.

A model is a cartoon version of reality. No model represents nature realistically, but that does not mean they are without merit or use. A good model captures the essence of some real-world dynamic and offers insight into an observed phenomenon of nature.

For years, evolutionary theorists have dictated to experimental scientists that there is no conceivable Darwinian process that could lead to affirmative natural selection for aging. Aging can contribute only negatively to individual fitness, and individual fitness is the only target of natural selection that their theory recognized. The significance of the models cited in Kowald is that they represent a counter-example to this dogma. They are an existence proof that evolution of aging as an adaptation in its own right, selected for its own sake, is not inconceivable. The door is open to interpreting aging phenomenology as an adaptive program, if that is what the experiments are saying.

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