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Programmed and Non-Programmed Theories of Aging

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Abstract—There are compelling reasons to regard aging as an evolved adaptive program. The evidence is diverse, deriving from genetics, breeding experiments, and plasticity of life span in stressful environments. But based on the classical neo-Darwinian understanding of population genetics, there are powerful theoretical reasons to believe that aging could not have evolved as an adaptation. This paradox is one of the most challenging scientific problems of our age.

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INTRODUCTION

The prevailing evolutionary theories of aging have been shaped by history. The roots of the theories derive from R.A. Fisher's [1] work in the 1930s, formulating Darwin's theory of evolution in quantitative terms, and founding the modern science of *population genetics*. Fisher was neither an experimental scientist nor a field biologist, but a mathematician, and population genetics remains the only biological science with a mathematical rather than an empirical foundation. Evolutionary theory has been derived from axioms, and imposed from the top down.

Programmed aging is fundamentally inconsistent with this prevailing view of natural selection. A genetic program for aging can only exist so far as it has been favored by natural selection. But aging may be defined as the loss of viability and reproductive capacity over time, and it follows that the impact of aging on *individual* fitness must be negative. It is a robust deduction of population genetic theory that natural selection can act directly only to lengthen life span and never to shorten it. Hence the three well-accepted theories of aging all regard aging as a side-effect, or incidental consequence of natural selection. Direct natural selection for aging would contradict fundamental precepts of population genetic theory.

There are deep theoretical reasons to deny the possibility that aging could be a genetic program; yet empirical support for the notion of an aging program is robust, rooted in many kinds of observations.

– Single genes have been identified which, when removed through genetic manipulation, extend life span significantly.

– Some such genes are closely related over widely-separated taxa, suggesting that aging mechanisms have been conserved by natural selection.

– Animals extend their life spans under stress (*hormesis*), which implies that when they are not stressed, life span is not maximized.

– In population genetic theory, additive genetic variance is the accepted signature of an adaptation, and by this measure age-related mortality is an adaptation.

It is not an exaggeration to say that 80 years of population genetic theory will stand or fall on whether it can be reconciled with an aging phenomenology that appears to contradict its fundamental precepts.

Four Perspectives on Evolution of Aging

Ideas about the evolutionary origin and significance of aging may be broadly categorized in four camps. We will review the history of each of the four camps in turn, examine the logical connections among them, and summarize the evidence for each.

1. Aging as the accumulation of damage. The "entropic" theory of aging. This is the oldest idea about what aging is, and remains the most prevalent among scientists and non-scientists alike. Ideas of accumulated damage are seductive, though they have no support within classical evolutionary theory.

2. Aging as irrelevant to evolution. Natural selection has had no chance to affect the dynamics of senescence, because so few organisms in nature ever attain to an age at which they are affected.

3. Aging as the result of evolutionary tradeoffs. Natural selection optimizes individual fitness, but life span is only one component of individual fitness. Life span may have been curtailed because genes that enhance fertility early in life have detrimental side-effects that accumulate over time. In another variant, the tradeoffs are metabolic: The organism forgoes some necessary repair and maintenance in order to devote more energy to metabolism and reproduction.

4. Aging as a genetic program, evolved independent of side-effects and selected for its own sake. Though there is broad empirical support for such theories, they conflict deeply with the standard framework of population genetics.

1. Theories of Aging Based on Accumulated Damage

It is an ancient and enduring misconception that aging derives from a physical necessity. The Second Law of Thermodynamics is a deep cause for the rusting of metal, and even for the decay of dead organic matter. These systems are "closed" in the sense that they have no outside source of free energy, and the Second Law prescribes that their entropy must increase over time.

Living things, however, are different. It is a defining characteristic of life that it is capable of gathering free energy from the environment, creating new order and structure within itself, while dumping its waste entropy back into the surroundings. Green plants take in free energy in the form of sunlight. Animals take in chemical free energy in their food. Both are able to build up from seed to a fully robust soma.

This initial feat of anabolism is far more impressive than anything that could be demanded in the way of repair. Somatic repair can be a very energy-efficient process because it is performed from the inside out. Cells can be discarded, recycled and replaced one-by-one, with stem cells serving as the source of fresh, young muscle, bone and nerve tissue. Individual protein molecules can be recycled into amino acids, and new, perfect proteins grown from ribosomal templates. DNA repair is an ongoing process in cell nuclei. In terms of free energy, these continuous processes are enormously more economical than the creation of a new soma from seed. In addition, there is inevitable attrition, as young animals and seedlings grow into mature adults with very low rates of success. As an energy investment, it is always more efficient to expend resources in repairing damage to a mature, proven parent than to build a new, mature and fertile adult from seed.

This reasoning demonstrates that accumulated damage is not a sufficient evolutionary explanation for aging. It is not to say that aging has nothing to do with physical and chemical wear. Certainly much of the degradation that characterizes senescence is fairly characterized as wear or stochastic chemical damage. But in principle, there is no reason the body could not repair this damage to its original standard of perfection, and the body should be highly motivated to do so.

In writing theoretically about aging, Hamilton [2] assumed that repairing a tissue "perfectly" is a standard that can only be approached asymptotically, and which would, theoretically require an infinite amount of energy. The idea of a high energy cost of repair later became the basis of Kirkwood's [3] Disposable Soma theory for the evolution of aging. But Hamilton's assumption was fallacious. Building the tissue the first time did not require infinite energy, and the body's ongoing repair and recycling systems are far more energy-efficient than its developmental anabolism. Based on the infinite energy assumption, Hamilton claimed to "prove" that somatic degradation at each moment in time is implied by evolutionary theory. Later, Vaupel [4] exposed this fallacy, introducing a metabolically reasonable model that posited a finite marginal cost of ongoing growth, increasing fertility, and lowered mortality risk. Retracing Hamilton's logic, he "proves" that natural selection on the individual level should favor ever-increasing fertility and ever-decreasing mortality.

To their credit, most evolutionary theorists today do not fall into the trap of believing that accumulated damage is a sufficient evolutionary theory of aging. In fact, it was almost a century ago that August Weismann [5] helped to establish the idea that damage to living things is *not* a viable basis for an evolutionary theory.

In addition to these theoretical reasons for believing that accumulated damage to a living thing is not inevitable, there is evidence from the phenomenology of aging that mechanisms of repair are shut down

progressively in aged individuals. For example: Reactive oxygen species generated as by-products of the Krebs cycle are quenched by the enzymes catalase and ubiquinone. Expression of all three have been found to decline with age in humans [6, 7]. Similarly, expression of anabolic enzymes tends to decline with age, while that of catabolic enzymes trends upward [8]. There is evidence, too, that DNA damage does not simply accumulate with age, but that repair mechanisms are progressively shut down [9, 10]. As a primary mechanism of aging, accumulated oxidative damage has attracted more attention and more support than any other metabolic theory; yet there is reason to believe that oxidative damage is not the root cause 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 [11, 12]. And life spans of mice are generally a few years, while bats live for decades, despite a higher metabolic rate and greater load of mitochondrial ROS [13]. It is certainly true that some 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. That these protections are rationed, allowing the damage of senescence to accumulate: this is the primary dynamic of aging that cries out for explanation [14].

The most compelling counter-example to the view that aging is a consequence of free radical damage is the life span of *C. elegans* worms in which both copies of their CLK1 gene have been disabled. These animals are unable to synthesize ubiquinone, and yet live ten times longer than wild type [15].

2. Aging Because There is No Selection Pressure Against It

The theory that aging exists because there is no effective selection against it still has currency, despite definitive evidence to the contrary. The idea originated with Medawar [16], who argued purely on theoretical grounds that the force of natural selection must decline with age. Edney and Gill [17] noted that if selection pressure is truly close to zero, then mutational load alone would be a sufficient explanation for the evolutionary emergence of aging. This is the Accumulated Mutation theory.

Two independent areas of study compel the conclusion that this is not the primary explanation for aging: First, demographic surveys indicate that aging does indeed take a substantial bite out of individual fitness in nature [18]; and second, that the genetic basis for aging has been conserved over æons of evolutionary history indicates that natural selection has not neglected senescence, but on the contrary has shaped aging programs to exacting specifications [19, 20].

Nesse [21] was the first to report evidence for aging in natural populations, interpreting it as evidence against the Accumulated Mutation theory, and therefore (?) supporting the pleiotropic theory (see section on tradeoffs, below). Promislow [22] surveyed field data on 56 species of small mammals, concluding that mortality increase with age was readily observable in the wild. Ricklefs [18 31] proposed to measure the impact of senescence as the proportion of deaths in the wild that would not have occurred but for senescence. He derived statistical methods for extracting this number from animal demographics, and found a huge range, from less than 2% to more than 78% senescent deaths, with the higher numbers corresponding to long-lived species. Bonduriansky and Brassil [23] applied a similar methodology in an intensive study of a single species, the antler fly. They estimated the impact of senescence on the fly's individual fitness as 20%. Thus senescence presents a surprisingly large target for individual selection, despite a short (6 day) life span. Ricklefs [24] compared causes of bird and mammal mortalities in captivity and in the wild, and concluded "Similar patterns of ageing-related mortality in wild and captive or domesticated populations indicate that most ageing-related death is caused by intrinsic factors, such as tumours and cardiovascular failure, rather than increasing vulnerability to extrinsic causes of mortality." This pulls the legs from under the Accumulated Mutation theory.

A second line of evidence against the theory is the existence of a conserved genetic basis for aging. Homologous genes associated with aging have been discovered in all laboratory species in which they have been sought, from protists through worms and flies to mammals. The idea behind the *AM* theory is mutational load, i.e., that selection pressure for the genes that cause aging is so weak that they have not yet been selected out of the genome. It follows that aging genes are expected to be random defects, recently acquired and differing widely from one species to the next. This is the opposite of the observed situation.

A conserved family of aging genes codes for components of the insulin/IGF signaling pathway [19, 20, 25]. These hormones affect the timing of growth and development, and also the metabolic response to food. Part of their function signals the soma to age more rapidly in the presence of abundant food. This is true in *C. elegans*, where the link to aging was first characterized, and also in yeast, in fruit flies, and in mice, with details of the implementation varying substantially across taxa.

CLK-1 is a gene originally discovered in worms [26], inactivation of which increases life span via a mechanism independent of the IGF pathway. The homologous gene in mice is MCLK1, and its deletion also leads to enhanced life span [27].

Other, less well-known conserved genes for aging have been catalogued by Budovsky et al. [28], who conducted a widely-targeted, computer-based search for networks of genes that regulate aging across disparate taxa.

Apoptosis [29] and cellular senescence (telomeric aging) [30] are two ancient mechanisms of programmed death at the cellular level. It has been known for decades that these mechanisms remain active in multicellular organisms, including humans; but it has always been assumed that their presence can be explained by an adaptive benefit for the individual. Apoptosis is important for ridding the body of diseased or defective cells, including malignancies. Telomeric aging provides last-ditch protection against tumors, imposing a limit on runaway reproduction. But recent experiments suggest that both mechanisms also play an active role in an organismal aging program.

Short telomeres have been associated with increased mortality and shorter life spans in humans [31, 32] as well as other mammals [33, 34] and birds [35, 36]. This is surprising because telomerase is available in the genome to extend telomeres as needed. Thus it would appear that the body has a simple, cost-free pathway to longer life span simply by expressing an available enzyme. The older, more traditional understanding of the role of telomerase rationing in mammals is that it is a defense against runaway cell proliferation in cancer [37]. Why, then, should we expect telomerase to increase life span in flatworms, which are not subject to cancer [38]? And why would the replication counter have evolved in protists, hundreds of millions of years before there was cancer?

Apoptosis has been documented in yeast cells as an altruistic adaptation during periods of food scarcity [39]. There are biochemical parallels between apoptosis at the cellular level and aging at the organismic level, an indication that aging in multicellular organisms has evolved, at least in part, from the ancient program for cell death in protists [40, 41]. Apoptosis is triggered by mitochondria in a cascade with H_2O_2 as intercellular mediator [42]. This phenomenon in human neurons may be associated with Alzheimer's disease [43, 44].

There is one more article of direct evidence contradicting the *MA* theory and all theories of aging based on low selection pressure. The proper measure of selection pressure (first defined by Fisher [1] is called *additive genetic variance*. This quantity has been measured in fruitflies [45, 46] with respect to late mortality as the target trait. The result is that additive genetic variance for mortality is low, and decreasing late in life. This is the signature of an adaptation, and is difficult to reconcile with the idea that aging is caused by random mutations.

3. Theories of Tradeoffs: Antagonistic Pleiotropy and the Disposable Soma

Theories based on evolutionary tradeoffs posit that the deep evolutionary cause of aging is an inescapable tradeoff between preservation of the soma and other tasks essential to fitness, such as metabolism and reproduction. These theories offer a way to explain aging within the context of standard population genetic theory (based on individual fitness). But only if tradeoffs are truly inescapable are the pleiotropic theories tenable. There is a great deal of empirical support for the existence of pleiotropy that affects aging, but no support for the thesis that the tradeoffs are inescapable. On the contrary, for many aging genes discovered in wild-type animals, no substantial benefit has yet been identified.

Tradeoffs may be genetic or they may be metabolic. Williams [47], first proposed direct genetic tradeoffs: genes that have benefits for reproduction or robustness in early life, but which cause deterioration leading to death at late ages. The idea of metabolic tradeoffs was the basis of the Disposable Soma theory of Kirkwood [3]; he proposed that a limited budget of food energy forces the body to compromise among reproduction, metabolism, and somatic repair.

3.1 Classic Pleiotropy: Genetic Tradeoffs

In proposing this theory in 1957, Williams [47] assumed that, since aging affects a core component of individual fitness, it must be tied to an equally essential, positive advantage. It was natural to imagine that aging derived from unavoidable side-effects of fertility genes.

In the intervening years, many examples of pleiotropic tradeoffs have been documented. Breeding for longevity often has deleterious consequences for other aspects of fitness. Many genes for aging have been discovered that have a balancing, beneficial effect. But in two respects, Williams's vision has not been borne out: (1) Beneficial side-effects don't seem to be universal, casting doubt on the premise that it is the individual benefits that are responsible for the evolution of aging; and (2) the benefits often seem to be peripheral to the core fitness functions of survival and reproduction.

At the back of Stephen Stearns's textbook [48] on life history evolution is a table of experiments that were designed to look for evidence of trade-offs between fertility and longevity in diverse animal species. About half the studies find some relationship and half find none. (Taking into account publication bias – that negative results frequently go unreported – the true proportion may be well under half.) This situation has been taken [49] as qualified confirmation of the pleiotropic theory of senescence, given the uncertainty and complexity in all biological experiments. However, the theory depends crucially on the premise that pleiotropy is unavoidable, and that longevity cannot be attained without a sacrifice in fertility, or some other important fitness component. The experiments on their face do not support pleiotropic theory, but indicate instead that trade-offs between fertility and longevity are secondary modifiers of aging genes – not their *raison d'être*.

A large-scale, direct effort to look for a tradeoff between fertility and longevity has been ongoing in the laboratory of Michael Rose since the 1980s[50]. Fruit flies are bred for longevity by collecting eggs from the longest-lived individuals in each generation. Rose expected that he would see a decline in fertility as the longevity of the flies was extended by artificial selection. [51] But after a brief initial downturn, the fertility of the test strain has increased steadily in comparison with the controls. After twelve years of laboratory evolution, the test strain lived longer (mean 74 vs 41 days) *and* laid more eggs than the controls (63 vs 52 eggs in a 24-hour period). This result baldly contradicted the prediction of pleiotropic theory. Rose, however, has remained loyal to the theory in which he was trained, and dismisses his own results as a laboratory artifact [50].

Although the deep, compulsory link between fertility and longevity was not found, the flies bred in this fashion were not super-competitors in the sense that they had other crippling defects that explain why this variety has not evolved in the wild. Other breeding regimens (with the waterflea *Daphnia pulex*) *have* produced such super-competitors: apparently superior in strength, size, survival, longevity, and fertility to the wild type [52]. Evolutionary theorists have scrambled to explain why this strain has not appeared in the wild [53].

Much of the experimental work on the genetics of life span have been conducted with the roundworm *C. elegans*. The UCSF laboratory of Cynthia Kenyon, in particular, has conducted an intensive search for examples of mutations that extend life span without identifiable cost to other aspects of the worm's fitness. These are most impressive when they are gene deletions, indicating that the identified gene has evolved in the wild type despite the fact that it has no other effect than to curtail life span. Several examples of such genes have been identified. The *AGE-1* mutant [26], and several of the many *DAF* mutant worms [54] exhibit normal fertility, and no cost of extended life span has been identified. Similarly, in fruitflies that are engineered to overexpress a gene dubbed *dFOXO* seem to extend life span without a cost to fertility [55]. Some mutations in the gene called INDY (for "I'm not dead yet") similarly seem to offer cost-free life extension [56].

The actions of the *daf-2* gene with respect to fertility and longevity are separable according to the timing of the gene's expression. Using RNA interference, it is has been demonstrated [57] that if the mutant gene is masked during development, and then expressed in maturity, then it has no effect on fertility, but offers full life extension, about a factor of two. Differential expression of genes through a lifetime is a universal feature in higher life forms; so why has selection not arranged this *daf-2* variant to be expressed only after maturity?

3.2 Tradeoffs in Resource Allocation: The Disposable Soma Theory

According to the *Disposable Soma* (*DS*) theory [3], there are competing metabolic demands for energy: reproduction, immune defense against parasites, locomotion, nervous system, etc. As the body's essential molecules become chemically damaged, repair and maintenance becomes one demand for energy among many. The body is forced to optimize its overall energy use, compromising each of these demands. This is a logical proof that repair and maintenance cannot be perfect, and that damage will inevitably accumulate.

As an abstract theory, it is appealing to think that senescence results from a failure to allocate sufficient energy for repair and maintenance. But the behavior of diverse animals under caloric restriction clashes profoundly with predictions of the DS theory. Animals that are fed less live longer. If it were true that the calorie budget was the root cause of aging, we must expect that caloric restriction should cause *shortening* of life span [58]. When *less* food energy is available, each of the demands on that energy must share the burden, making do with a reduced share of the smaller total.

For many species, reproduction requires a substantial energy investment. It is a logical possibility that reproduction may be constrained to be either 'on' or 'off', with no in-between state. Then there will be a point in the caloric restriction curve when reproduction is abruptly shut down, and more energy becomes available on the far side of that line, before the decline in available energy inevitably continues. Shanley and Kirkwood attempted a *DS* model of aging in mice based on this effect, and reported [59] the limited success of their model in an optimistic light. But in most versions of their model, there was no energy dividend for repair and maintenance, and in the one version showing a dividend, it appeared over a narrow range of caloric restriction, for lactating female mice only. In contrast, the CR data show that life span is extended linearly as calories are reduced over a broad range, and the experiments are generally performed comparing non-reproducing mice with other non-reproducing mice, male and female [58]. Absent the energy of lactation, Shanley's model predicts clearly that the CR mice should have curtailed life spans.

A direct and general test applicable to any of the theories of metabolic tradeoff was conducted by Ricklefs and Cadena [60]. They cross-tabulated fertility and longevity for captive birds and mammals in zoos, and found a slight *positive* correlation. Similarly, many demographers have sought for evidence of a "cost of reproduction" in humans, and have found no relationship [61, 62] or a small *positive* association [63, 64] between fertility and longevity. One well-publicized study claimed to discern a cost of reproduction in a historic database of British nobility [65], but its methodology was compromised by use of an obscure and inappropriate statistical test [66]. Standard linear correlation on the same database reveals a positive correlation [66].

3.3 Adaptive Pleiotropy: an Alternate Theory

Genetic tradeoffs affecting life span appear to be a common feature across taxa, but not a precondition or physical necessity. If we accept at face value evidence that aging itself is an adaptation, then it must be a group-level adaptation, as senescence offers only costs, not benefits to the individual. The question then arises: how is individual selection prevented from undoing senescence? My own hypothesis is that pleiotropy itself is an adaptation, selected for its effect of suppressing individual competition for longer reproductive life spans. The conservation of aging genetics suggests that aging has been an important target of natural selection over the ions; in this view, pleiotropy is one instrument by which the genetic basis for aging has been protected from the contravening force of individual selection. The conventional view is that antagonistic pleiotropy is an unavoidable physical property of some genes, but empirical data indicates that pleiotropy is neither unavoidable nor universal. The alternative view which I propose is that pleiotropy is a "design feature." Without it, aging would be lost to rapid individual selection, and with it, aging is preserved, creating population-scale benefits to which short-term selection is blind.

4. Adaptive Theories of Aging

Several of the phenomena cited above as evidence against one of the three other theories may also be interpreted as affirmative evidence for an adaptive origin of aging:

Programmed death in protists: There are two forms of programmed death in protists. These are apoptosis [39] and cellular senescence (via telomeres) [30]. No other theory has yet been proposed than that these are independent adaptations based on benefits to the

microbial community. What is more, both these mechanisms remain active in higher organisms, and have been implicated in human aging [67]. If programmed death could evolve half a billion years ago in microbes, this undercuts the theoretical proposition that it is not possible for aging to evolve in more complex life forms.

Conserved families of aging genes: Genes that control aging go back half a billion years, and remain closely related in widely separated taxa (Guarente and Kenyon 2000; Kenyon 2001; Budovsky, Abramovich et al. 2007). All other such conserved genes relate to core aspects of cellular metabolism. This constitutes evidence that natural selection has treated aging as a core process.

Low additive genetic variance: Additive genetic variance is the technical measure of the variation in natural genotypes upon which selection is acting. High AGV is indicative of random mutations or genetic drift; low AGV is the signature of an adaptation. AGV of late mortality has been found to be low [45, 46], declining with advancing age.

Caloric Restriction and other forms of hormesis: Most animal species that have been studied in laboratory experiments evince a capacity to extend life span when deprived of food. This implies that fully fed animals are not living as long as they are capable.

The CR response is but one example of a more general phenomenon known as *hormesis* [68]. Modest environmental challenges in many other forms also lead to enhanced longevity: Aerobic exercise, low doses of toxins [69–71] or ionizing radiation [72], electric shocks [73], infection, physical injury, heat [74, 75], and cold [73, 76]. Human as well as animal evidence concerning radiation hormesis is reviewed by Luckey [77].

Hormetic phenomena suggest that life span is plastic under genetic control, that it can be increased without cost or side-effects in response to a more challenging and competitive environment. Forbes [78] reviews a wide range of hormetic phenomena, and concludes that fitness hormesis is surprising in the context of evolutionary theory based on individual selection. Why is the life extension program not implemented in less challenging times?

Here are two additional lines of evidence for aging as an adaptation, selected for its own sake:

4.1 Programmed Death in Semelparous Plants and Animals

Semelparous organisms are animals and plants whose life histories are organized around a single burst of reproduction. Almost without exception, they die promptly on the completion of reproduction, and they die in ways that appear to be manifestly programmed. Annual plants, the octopus [79], and Pacific salmon [80] are examples.

Many ecologists accept as a matter of course that "genetically programmed, irreversible degeneration subsequent to breeding" is a group-level adaptation [80]. Demonstration of programmed death in semelparous organisms detracts from the plausibility of arguments that programmed senescence in iteroparous organisms is theoretically excluded.

4.2 Aging Can Be Accelerated by Nervous Signaling

Ablating the chemical sensor of the worm *C. elegans* causes an increase in life span [81]. Fruitfly life span is attenuated not just by abundant food supply, but merely by the odor of food [82]. And experiments with mosaic worms indicates that genes affecting life span act through the nervous system, rather than through reproductive or endocrine tissue [83]. These results indicate that life span is controlled in response to chemical and nervous signals – consistent with a flexible genetic program, but not consistent with maximization.

4.3 How Might Senescence Have Evolved As an Adaptation?

Early theories of senescence as an adaptation were based on two ideas that have been discredited for good reason. The first is that damage to the soma inevitably accumulates with age, and that death is programmed in order to rid the population of old, damaged individuals so that they can be replaced with younger, more perfect ones. The second is that aging offers benefits for adaptability in a population, and enhances the rate of evolution.

The idea that somatic damage must inevitably accumulate, and that programmed death was nature's way to rid the population of these imperfect specimens, was Weismann's [5] original theory for evolution of aging. He abandoned his theory, because he realized there is no necessity for damage to accumulate, and that it is almost always metabolically cheaper to repair somatic damage than to cast aside the soma and create a new one from seed. This objection is

sound, but the idea remains appealing, and variations have continued to be published in the modern literature: Kirchner & Roy [84] present a numerical model in which infections may cause sterility but not death, and the aging evolves to rid the community of sterile individuals. Travis and Dytham [85, 86] model a mechanism for the evolution of programmed death as an adaptation, given that individual fecundity declines with age. These models escape Weismann's dilemma, but in doing so introduce assumptions that are likely to limit their general applicability.

The idea that aging evolves as an adaptation to accelerate the pace of adaptive change in a population also has a long history. The premise is qualitatively sound, but it is difficult to imagine quantitative models in which the mechanism can work. It is true that if a population is able to evolve more rapidly, it will eventually overtake another population that evolves more slowly, and so enjoys a decisive advantage in the very long run. But the long run is very long indeed, for the benefit appears only on an evolutionary time scale. Meanwhile, the costs of aging are being borne directly by the individual in a single lifetime. Even generous assumptions about relatedness and isolation of groups fail to make the game worth the candle.

These arguments were well-appreciated by the community of evolutionary theorists [87, 88] when the subject of group selection was hotly debated in the 1970's; in fact, they were decisive in establishing a consensus that aging could not evolve as an adaptation in its own right.

4.4 The Demographic Theory

More than thirty years ago, Gilpin [89] demonstrated that ecological interactions can fundamentally alter the balance between selection for individual fitness and for group cooperation. Before Gilpin, it was assumed by theorists that processes leading to extinction were characteristically slow, requiring many individual lifetimes. Gilpin showed how predator-prey dynamics drastically change the time scale. Groups of predators that over-exploit their prey are punished swiftly, usually within a single generation.

The Demographic Theory of Senescence [90] posits that there is no inherent reason why ecosystems should be stable. To the extent that we have demographic homeostasis, it is an evolved adaptation. Since every species depends on other species for its viability, ecological homeostasis becomes a major target of natural selection, rivaling the imperative to maximize individual reproductive output in its strength, and tempering individual fitness in its effect. Population cycles can be rapid and lethal, wiping out entire communities in a single generation. (This is in contrast to benefits of diversity or evolvability, which act slowly because they affect the rate of change of fitness, but not fitness itself.)

Individual selection for increased reproductive success naturally leads to overexploitation of prey, and puts populations on a collision course with unstable population dynamics [90]. (This is the original "tragedy of the commons" [91]) Local extinctions then proceed swiftly, and group selection can operate very efficiently under such conditions. Competition among demes drives population dynamics back from the brink of chaos.

Senescence tempers individual reproductive output in a way that offers particular advantages for demographic homeostasis. The problem of volatility may be described as a tendency for a population to grow too rapidly when conditions are favorable, and to collapse too precipitously when resources are scarce. The effects of aging on a population in its growing phase are to limit life span, to diminish the number of offspring per individual lifetime, and thus to suppress the rate of population growth. But when the same population is in collapse, most animals are dying of starvation. Few live long enough for old age to contribute to their demise. Thus aging exacts its greatest toll when the population is freely expanding, but does not add appreciably to the rate of decline when the population is collapsing. The CR adaptation further enhances the effectiveness of senescence for modulating unstable dynamics, since it pushes the death rate from senescence even lower under the conditions of starvation that attend the contracting phase of the population cycle [90].

Besides predator-prey dynamics, a second population dynamic effect may also be important in the evolution of aging. Populations that are too crowded and too homogeneous are vulnerable to microbial epidemics. Aging helps to regulate population density and to enhance diversity. Epidemics constitute another force of group selection that is rapid and efficient.

In fact, the effect of epidemics is widely accepted as a mechanism, not for evolution of aging, but evolution of sex. This is the "Red Queen Hypothesis" [92] and the same arguments for its potency

carry over when the explanation is applied to evolution of aging [66]

Starvation and epidemics are the two most lethal threats to an overcrowded, homogeneous population. Population dynamics may provide the toehold that enables senescence to evolve "uphill," in opposition to individual selection. In the long run, the benefits for population diversity and rate of adaptation may play a crucial role in establishing senescence as a core, conserved process.

CONCLUSION

The phenomenology of senescence creates a sharp challenge to classical evolutionary theory. If evidence is accepted on its face that aging is an evolved genetic program, then the axioms of population genetic theory will have to be rewritten.

There is a great deal of mathematical theory based on these axioms, and also a great deal of corroborating experimental research. But the empirical support comes only from the laboratory, not from nature. Field experiments in natural selection are, for the most part, impractical for scientists who wish to see results in a human lifetime. Hence it has become standard practice in evolutionary science to test theory against laboratory experiments in artificial selection. Laboratory corroboration gives the illusion that population genetic theory is on a firm empirical foundation, but in reality a crucial step in the reasoning remains untested: is nature's selection criterion the same as the one used in the laboratory?

Population genetic theory postulates that fitness is an individual trait computed from a schedule of reproduction. Competition and selection are presumed on theoretical grounds to take place at the level of individual-vs-individual, rather than at the level of communities, populations or entire ecoystems.

If programmed aging is accepted as an evolved adaptation, it follows that natural selection must be routinely operating not only to optimize individual reproductive fitness, but also to sculpt stable ecosystems.

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