ISSN 0006-2979, Biochemistry (Moscow), 2012, Vol. 77, No. 7, pp. 716-725. © Pleiades Publishing, Ltd., 2012.
Published in Russian in Biokhimiya, 2012, Vol. 77, No. 7, pp. 858-870.

REVIEW

Adaptive Aging in the Context of Evolutionary Theory

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Received March 28, 2012

Abstract—Compelling evidence for an adaptive origin of aging has clashed with traditional evolutionary theory based on exclusively individual selection. The consensus view has been to try to understand aging in the context of a narrow, restrictive evolutionary paradigm, called the Modern Synthesis, or neo-Darwinism. But neo-Darwinism has shown itself to be inadequate in other ways, failing to account for stable ecosystems, for the evolution of sex and the maintenance of diversity and the architecture of the genome, which appears to be optimized for evolvability. Thus aging is not the only reason to consider overhauling the standard theoretical framework. Selection for stable ecosystems is rapid and efficient, and so it is the easiest modification of the neo-Darwinian paradigm to understand and to model. Aging may be understood in this context. More profound and more mysterious are the ways in which the process of evolution itself has been transformed in a bootstrapping process of selection for evolvability. Evolving organisms have learned to channel their variation in ways that are likely to enhance their long-term prospects. This is an expanded notion of fitness. Only in this context can the full spectrum of sophisticated adaptations be understood, including aging, sex, diversity, ecological interdependence, and the structure of the genome.

DOI: 10.1134/S0006297912070036

Key words: evolvability, aging, sex, evolutionary capacitance, canalization

EVOLUTION OF AGING: WHEN DATA AND THEORY COLLIDE

Diverse and robust experimental evidence points to an adaptive origin for aging [1, 2]. For example:

- Genes have been discovered that increase life span when inactivated [3, 4]; many of these genes have been conserved over a wide stretch of evolutionary history [5, 6]; and some have no known pleiotropic benefit [7].
- Two ancient mechanisms of programmed death are found in some primitive, single-celled eukaryotes: cellular senescence and apoptosis [8, 9];
- and both mechanisms remain part of the aging program in vertebrates today [10-12].
- The body is able to moderate aging, but chooses not to do so when resources are most abundant and it is free of other stresses [13, 14].

Yet standard thinking about evolutionary theory unequivocally rules out the idea that aging could be adaptive [15, 16]. Should we examine the experiments more carefully and look for other ways to interpret their results, or does the situation indicate the need for a re-thinking of evolutionary theory? I have argued for amending the current evolutionary theory of aging, and expanding the recognized mechanisms of natural selection to accommodate the evidence that aging has been selected as an adaptation [2, 17, 18]. (For the opposite perspective, I recommend a thoughtful discussion including commentary by several leading aging scientists, led by George Martin [19].)

Experience counsels that we should not lightly abandon theories that have enjoyed success in explaining a broad range of phenomena. Why not simply patch existing evolutionary theory, or expand it minimally to accommodate data on aging? If the theory were well-grounded and agreed with a broad range of observations, this would be the indicated course. But standard evolutionary theory ("neo-Darwinism") may be uniquely vulnerable, precisely because aging is not the only area in which it has failed. Neo-Darwinism cannot accommodate the ubiquity of sexual reproduction (especially when the twofold cost of carrying males is considered) [20, 21]; neo-Darwinism cannot explain the hierarchical structure of the eukaryotic genome, with command-and-control functions that dictate the expression of many lower-level genes [22]; neo-Darwinism takes genetic diversity as a given, but cannot account for the persistence of diversity [23]; neo-Darwinism explicitly rules out horizontal gene transfer and genome-merging phenomena that have been important at crucial turning points in evolutionary history [24, 25]; even some common examples of co-evolution between species are poorly-treated by neo-Darwinism [26].

The neo-Darwinian paradigm has done well in framing the results of experiments in laboratory evolution; but this may be because laboratory experiments are designed around accumulation of genes that already exist as polymorphisms within the laboratory's breeding population. In other words, lab experiments rarely depend on creation of evolutionary novelty, and never require the multiple independent new structures that are most difficult for evolutionary theory to account for. Furthermore, artificial selection in laboratory models is frequently designed with intention to replicate the neo-Darwinian assumption about how natural selection is supposed to work. Hence laboratory evolution offers no independent test of whether these assumptions are applicable in nature [27].

In fact, the science of neo-Darwinism is uniquely "top-heavy" with theory, and it lacks a solid foundation of observational support. From its origins in the 1920s, the theory was derived from axioms by mathematical scientists, and not pieced together from the bottom up by field biologists [28]. Many evolutionary biologists have been educated to believe that the neo-Darwinian paradigm is "how evolution works". It is the framework within which they think, and no conceivable observation could falsify that belief. New findings in genetics and even medicine are interpreted within the context of neo-Darwinian theory. For the science of aging in particular, this has been a consistent distortion of the underlying data, thwarting understanding.

In recent years, there has been an uprising of dissent against neo-Darwinism, but there is as yet no consensus on what theory might replace it. There is, however, an emergent theme common to many of the criticisms: that is the evolution of evolvability. The process of evolution has itself been the target of natural selection [29, 30], and some broad features of the biosphere are explainable not from the imperative to survive and reproduce, but rather from the imperative to adapt in a changing world [23, 24]. This is a framework in which aging may find a natural explanation [31, 32].

FROM DARWIN TO NEO-DARWIN

Today, the dominant school of evolutionary thinking is called *population genetics* or the *modern synthesis* or (the word I shall use) *neo-Darwinism*. It has its roots in the first half of the XX century, when mathematical biologists – notably J. B. S. Haldane [33], Sewell Wright [34], and R. A. Fisher [35] – sought to re-cast Darwin's Theory of Evolution as a quantitative science.

Neo-Darwinism is not the same thing as Darwinian evolution [36]. Darwin was a consummate observer of nature. His thinking was (appropriately, I think) vague and even modestly self-contradictory at times as he described the various ways that natural selection can work. Neo-Darwinism was a movement to make Darwinian theory more quantitative and rigorous. Influence of the successful methods of XIX century physics is manifest throughout, as is the fashion for eugenics, which inspired and distorted the work of Fisher. Fisher was the most mathematically adept of the three, and the least concerned with biological examples. Of the three founders of neo-Darwinism, it was Fisher's paradigm that has predominated historically. His model describes pure competition among different alleles of a gene, against an unchanging background of other genes, in an unchanging physical and ecological environment. As an axiomatic discipline, neo-Darwinism is straightforward and logically compelling. But the picture of the world which it paints is a simplistic caricature of real-life evolution. There are many cases for which the theory works well, but we should not be surprised that there are other cases for which the theory is inadequate.

Neo-Darwinism is a model for the process of selection, which requires a diverse population in which to work. But where does diversity come from and what maintains it? In particular, how is genetic variation channeled into modes that have a non-negligible probability of being useful enhancements to fitness? These may be much more critical questions for the workings of evolution than the issue of selection [23].

Neo-Darwinism's answer to the question of the origin of variation is blind, random mutation. This was not Darwin's answer. Darwin did not know where genetic variation came from, and he clearly *knew* that he did not know. Based on experience with breeding of domestic animals, he intuited the existence of Lamarckian inheritance; and he regarded "spontaneous" variation as a mystery: "There can be little doubt that use in our domestic animals strengthens and enlarges certain parts, and disuse diminishes them; and that such modifications are inherited" [37], and again: "This has been effected chiefly through the natural selection of numerous successive, slight, favorable variations; aided in an important manner by the inherited effects of the use and disuse of parts; and in an unimportant manner, that is in relation to adaptive structures, whether past or present, by the direct action of external conditions, and by variations which seem to us in our ignorance to arise spontaneously. It appears that I formerly underrated the frequency and value of these latter forms of variation, as leading to permanent modifications of structure independently of natural selection" [37].

Darwin never used the word "fitness", and spoke variously of the qualities that are acted upon by natural selection in different circumstances. Fisher sought to cast "fitness" as the defined target of natural selection, and sought a precise, mathematical definition. In asexual species, fitness can be associated with an individual, and an individual's selective success is measured by the speed with which it copies itself. For sexual species, Fisher faced the complication that no two individuals are identi-

cal, and he resolved this issue by associating fitness with genes rather than with whole organisms (hence the popularized notion of a "selfish gene"). The fitness of a gene is a grand average of the contribution that it makes to reproductive success, averaged over all genetic combinations in which it appears, in all different environments. Thus, the theory works well for situations where single genes have unique effects (e.g. eye color), and also when many genes combine additively to determine a single trait (e.g. body length). But it runs into trouble with complex traits controlled by many genes whose effects are interdependent in intricate ways: body shapes, complex behaviors, and, of course, aging.

Early in the history of neo-Darwinism, the single selective mechanism, which Dawkins [38] later dubbed the s*elfish gene*, came to be regarded as the unique standard of theoretical legitimacy. Missing are many other mechanisms conceived by Darwin, including the role of ecological context, which was the very etymology of the word "fit". Too many biologists seek to understand evolution one-species-at-a-time, or (worse) one-trait-at-a-time, as if the ecological context were fixed and unchanging. Neglected also is the interaction among genes – the common condition that genes work together – and that the effect of any particular gene depends critically on the combination of other genes with which it is associated. The interaction among genes is termed *epistasis*, and in neo-Darwinism, it is taken to be a small effect that modifies but does not essentially alter the action of natural selection. For traits that involve many parts acting together, this is a poor approximation. There is evidence (unknown in Fisher's time) that the evolutionary process is highly optimized. For example, genes that function together are linked on the same chromosome, so that they are likely to be passed on as a unit [39, 40], and mutation rates are low where they are likely to break features of the core metabolism, higher in selected areas where prospects for change are more auspicious [41]. Perhaps it is a small extension of neo-Darwinian thinking to substitute for selfish genes selfish *groups* of interdependent genes; but what is far more difficult to understand: how did the genome come to be structured and optimized in a way that benefits the *rate of increase* of fitness, but not fitness itself [29]?

Some Biological Phenomena that Are not Well-Explained by the Neo-Darwinian Mechanism

Sex. This is the most widely-recognized failing of the selfish-gene theory. Recombination and gene sharing are nearly universal in the biosphere. Sex was an invention that greatly enhanced the rate of evolvability, but this is a long-term investment in the community. It fits poorly with the neo-Darwinian emphasis on offspring count and immediate benefit. In these terms, sexual reproduction is usually implemented at enormous individual cost: for higher organisms, the price is a factor of two in conventional measures of fitness, the "cost of males". This in itself may be considered a one-line disproof of the thesis that short-term reproductive success is the primary target of natural selection.

Sex maintains and enhances population variation, assuring that many more combinations of traits are tried out than could possibly be tested if mutation were the only source of population diversity. Sex also binds communities together, tying the fate of individuals to the fate of the deme. Thus sex helps to elevate the level at which selection operates from the individual to the breeding community; and, of course, sex could not have evolved based on individual selection. This is an example of the claim (below) that evolution of evolvability is a bootstrapping process that has operated recursively, on an exponentially accelerating scale.

Genotype-phenotype mapping. The particular language by which the genotype determines phenotypic traits does not contribute directly to individual fitness; it has an enormous impact, however, on the rate at which evolution can occur. Most obvious and straightforward genetic languages for specifying phenotypes would evolve so slowly as to make biological evolution impossible within the lifetime of our universe. We must imagine that mechanisms of inheritance were not fixed once as a lucky accident that has prevailed because of its evolvability, but rather that mechanisms of inheritance are themselves the target of ongoing natural selection for evolvability.

***Hox* genes.** The most striking feature of the genotype/phenotype map is its hierarchical structure with *hox* genes controlling the development of entire organs and systems. From *hox* genes to chromosomes, down to the individual exons that are cut and spliced in various combinations to make genes, the entire genome has been organized in modules. This is a global adaptation that must have taken eons to develop, and yet it yields no fitness benefit, only a second order benefit in the *rate of change* of fitness. Hence, it is difficult to reconcile with neo-Darwinist models.

Consider an analogy with computer programs: If genomes were built one mutation at a time, you would expect that they would look like what used to be called "spaghetti code" in the archaic world of Fortran. The genome would be full of quirks and kluges, and things that happen to work in this particular case, though not in general. There is some of this; but remarkably, we find that the genome is hierarchically ordered. There are master switches – *hox* genes – that can turn on whole genetic programs, with many hundreds of genes, all ordered in just the right way.

The benefits of this kind of structuring of the genome are wholly long-term. Unlike the case of sex, it is hard to estimate the cost of a structured genome. But, like sex, the benefits of the structured genome with *hox* genes do

not accrue to the individual in the current generation, or even in a small number of generations. The benefit manifests only over evolutionary time, after thousands or tens of thousands of generations.

Phenotypic plasticity. In adapting to any particular environment, it is enormously easier to come up with a targeted solution that narrowly addresses the particular situation. And yet, living things are plastic, adapting on the fly to individual variations in their microenvironments. To the extent that the range of microenvironments could never have been experienced in the lifetime of one individual, phenotypic plasticity represents a multi-generational adaptation. Phenotypic plasticity must have evolved as a long-term response to unpredictable change in the environment. This is "lineage selection" on a grand scale.

Remarkably, it has been discovered in recent years that phenotypic plasticity can have a trans-generational component. This has been called "epigenetic inheritance", and its mechanism falls outside the model of neo-Darwinism.

Epigenetic inheritance. Can traits that are acquired during an individual's life experience be passed on to offspring? In the XVIII century, this was the primary mechanism of evolution as proposed by Jean-Baptiste Lamarck. Darwin proposed a limited role for Lamarckian inheritance, which he called "use and disuse" of body parts. In the generation following Darwin, August Weismann [42] reported results from one careful but limited experiment that discredited the idea of Lamarckian inheritance for generations to come. What he measured was not Darwin's "use and disuse", but the effect of cutting off a mouse's tail on the tail length of its offspring. (Weismann found there was none.)

Today, Lamarckian inheritance has no place in neo-Darwinist evolutionary theory. However, experiments in recent years have uncovered intriguing examples in which the life experience of an individual affects its offsprings' phenotype for two and three generations to come [36]. This has been named "epigenetic inheritance", but it is not well-understood. Adaptations can be passed epigenetically from the father [43] as well as the mother. The best available hypothesis is that biochemical signaling can affect the histones and methylation that control gene expression, and that the chromosome's environment is somehow replicated along with the DNA.

It has been argued that heritable histone modifications are just the beginning, that Lamarckian inheritance is a much broader phenomenon, and that it entails permanent changes to the genome as well as temporary changes in gene expression [24, 36].

Co-evolution. Some instances of co-evolution find a natural explanation within the framework of neo-Darwinism. For example, the symbiosis within the components of a lichen is easy to understand, because lichens comprise two individual organisms that are interdependent. What each one does to benefit its partner reflects back in a direct effect on the self. But there are other examples of co-evolution that do not fit well within the neo-Darwinian paradigm. Consider, for example, the nectar, which flowers provide to bees in exchange for pollination. In the short term, bees are attracted to flowers by their sweet smell and bright colors; but in the long term, bees continue to visit flowers because the flowers provide nectar, which is carried back to the hive for food. Neo-Darwinian logic predicts an opportunity for "cheater" flowers to undermine this system: a mutant plant may invest more in scent and appearance, but less in nectar itself. Then bees would be more likely to visit the flower and carry its pollen, though they might find out too late that there was no nectar to be harvested [44]. The reason that this sort of co-evolution is problematic in the neo-Darwinian paradigm is that the cost of a co-evolved trait is borne by the individual, but the benefit passes to many of the commensal partners, and by the time it is reflected back, the benefit falls broadly on those that have the trait and those that do not.

Diversity. Darwin already recognized the maintenance of diversity as a puzzle. He had no knowledge of Mendelian inheritance, and believed that the attributes of an offspring were blended or averaged from the attributes of the parents. With this mode of inheritance, diversity would rapidly collapse. With the neo-Darwinian synthesis, combining Mendelian inheritance with Darwinian selection, the problem of diversity became less severe and attracted less attention. Still, it remains a weakness of neo-Darwinian theory. It is the experience of every neophyte in evolutionary computer simulation that, in simple models (based on standard population genetics) a single genotype evolves quickly to fixation. Evolution proceeds to a fitness maximum, and stops. The models are telling us something about the way biological evolution works: it cannot be a straightforward race to produce the most replicates. Such a simple contest produces permanent winners and eliminates losers far too quickly, and a great deal of information is thereby lost.

In fact, diversity in itself has been a major target of natural selection, a component of fitness at the group level. Some selection for diversity can be explained by conventional models of frequency-dependent selection [45]; but such mechanisms only apply to the maintenance of diversity itself, and not to the creation of second-order mechanisms (like sex and aging) that seem to exist for the purpose of enhancing diversity. In practice, one of the greatest advantages of maintaining diversity is that a trait that was useful in the evolutionary past may be useful again in the future, as environments continue to change and sometimes cycle back to recapitulate features of the past. There is a long-term evolutionary advantage to be had by silently preserving traits that were useful in the past, so they do not have to be evolved anew should they become useful again in the future.

Reversion, or *evolutionary capacitance*. Darwin noted that traits may be lost from the phenotype but not the genotype in the course of evolution. What he observed was that it is much easier to re-evolve a trait that was recently lost than it would be to create the same trait for the first time. But in the transition to neo-Darwinism, the idea that a trait might be stored in the genome for later use seemed untenable. This principle was formalized by Louis Dollo [46], and for many decades, it was widely quoted as Dollo's Law: "An organism is unable to return, even partially, to a previous stage already realized in the ranks of its ancestors".

But in our present understanding of molecular genetics, we say that genes remain hidden in the genome, but their expression is suppressed, so that they may easily be recovered. This phenomenon has been re-discovered in the last decade, and named "evolutionary capacitance", by analogy with the ability of an electric capacitor to store charge within [47, 48]. Evolutionary capacitance represents another way in which variation is not blind, suppressing random destruction and favoring adaptive change. This in itself is an exception to neo-Darwinian orthodoxy; but the larger challenge is this: How did the phenomenon of evolutionary capacitance come to be? Like aging and sex and *hox* genes, it is an adaptation, which has value only for the *pace* of evolution, and not for the fitness of the individual or its immediate progeny [29].

Horizontal gene transfer (HGT). Bacteria freely exchange genetic information in the form of plasmids. They are promiscuous, picking up DNA that derived from others very different from themselves. HGT in higher organisms is mediated by viruses, and is far less common, but perhaps crucially important at critical junctures. HGT seems to have been responsible for some of the great transitions in evolutionary history. Every organism alive today can trace different parts of its genome to diverse lineages, very different from its direct ancestors. Carl Woese [49] has noted that Darwin's tree of life is, in fact, better characterized as a web of life.

Predatory restraint. Many field biologists are convinced by their experience that predator species space themselves out and control their populations to avoid unsustainable expansion. But neo-Darwinist theory denies the possibility that such restraint could evolve. Debates about whether coordinated behaviors of restraint could be found in nature played a key role in the scientific history of the neo-Darwinian model.

History of the Group Selection Controversy

The ascendance of the "selfish gene" model was accomplished in the 1960s and 70s, in the course of a debate over the question whether an animal community might cooperate to regulate its population density. This is a key question, and the fact that evolutionary theorists triumphed over observers of nature has led to fundamental and wide-ranging misunderstandings through the last 40 years.

V. C. Wynne-Edwards was an exemplary practitioner of the old school of naturalism. In 1962, he published a book [50] that culminated a life's work on biological communities. He described, citing diverse examples, the ways in which animal populations restrain their reproduction to avoid overpopulation and safeguard the ecological resources on which they collectively depend. A few years later, a smart young biologist named George Williams published his rejoinder [15], in which he took Wynne-Edwards to task for wanting rigor in his theoretical reasoning. Wynne-Edwards was implicitly invoking "group selection", and Williams doubted that this process played a role in Darwinian evolution. It was not theoretically possible, Williams wrote, that natural selection could operate in the way that Wynne-Edwards claimed.

A debate ensued over the following decade, unfolding in pages of evolutionary journals that had once been filled with observations and descriptions but now tended increasingly toward sophisticated mathematics. The debate was disconcertingly abstract, and framed in simplistic terms. "Individual selection" describes the (neo-Darwinian) process whereby one version of a gene comes to replace another, by demonstrating a superior ability to copy itself into succeeding generations. "Group selection" is the process by which communities or entire ecosystems compete and replace one another *en masse*. A cooperating community may achieve a collective viability that is higher than is possible in a similar community lacking cooperation. Cooperation frequently requires individuals to sacrifice some of their own fitness for the sake of the community; so that a cooperative community may out-compete an un-cooperative community despite the fact that the cooperating individuals are individually less fit than the non-cooperators.

Wynne-Edwards, George Price [51, 52], and D. S. Wilson [53, 54] argued that group selection and individual selection were competing forces that contributed to complexity in the workings of evolution. Williams and John Maynard Smith [55], among others, argued that individual selection was so much quicker and more effective than group selection, that whenever the two processes came into conflict, individual selection was overwhelmingly likely to prevail. The contribution to this debate of W. D. Hamilton [56, 57] was to carve out an exception where the individual's sacrifice benefits close relatives. Hamilton provided a mathematical foundation for understanding "kin selection", in which a gene may cause individuals to behave in a way that may be detrimental to the individual bearing the gene, but which is more than compensated by benefits to others who, by virtue of their genetic relatedness to the focal individual, have a high probability of carrying the same gene. Kin

selection is the only basis for evolution of cooperation recognized within neo-Darwinism.

The neo-Darwinists prevailed in this debate, and "group selection" became a tag of derision. Cooperation was declared to be an illusion, and any adaptation that appeared to be beneficial to the community must have an alternative explanation from the perspective of kin selection. A wave of theoretical research followed, in which an author would cite an instance of apparent altruism, and propose a mechanism by which it *might* have (implicitly *must* have) evolved through the "selfish gene". The literature of aging has been especially vulnerable to this dynamic.

Special Status of the Population Regulation Problem

In fact, the phenomenon that Wynne-Edwards described is central to understanding how it is that evolution has managed to transcend the crude race for maximal reproduction, which naive theorists have postulated as the sum and substance of natural selection. Many of the mechanisms described above as affecting only evolvability and not fitness (e.g. sex, *hox* genes, diversity, capacitors) are truly difficult to understand, because the fitness costs are so immediate, while the benefits accrue over long periods of evolutionary history. Group selection must be imagined to operate over an extended evolutionary timescale, all the while pushing uphill against individual selection, which is more efficient and tends to wipe out its progress. Cooperative communities are easily invaded by individuals who benefit from the behaviors of all around them, but do not participate in those behaviors or share the costs. (This is commonly called the "cheater problem" [58].)

But one form of group selection is easy to understand (as first pointed out by Gilpin [59]), and that is cooperation to protect fragile ecosystems and prevent overpopulation. The canonical example is a predator population grown too large for the prey upon which it feeds. Population growth can be rapid, and the line between sustainability and starvation is thin. Within a single generation, a population of predators can wipe out the food source on which its children depend, and trigger a local extinction. Other populations that are genetically programmed for more effective ecosystem preservation can then move in and supplant the one that is too profligate. This is the fastest-acting, and thus the most powerful form of group selection.

Predatory restraint, though strongly altruistic, is easily understood in terms of simple and modest extensions of the neo-Darwinian model. Although individual fitness costs are substantial, shifts in population dynamics can be swift and lethal, wiping out entire communities in a generation or two. This is true both in theoretical models [59, 60] and also observations in nature [61, 62]. The pace of group selection in this case easily rivals the pace of individual selection, and the substantial influence of group selection ought to be perfectly clear.

How Aging Might Have Evolved as an Adaptation: Two Mechanisms

The reasoning that tells us aging has evolved as an adaptation is silent about how or why aging evolved, or what fitness advantage it confers. All theories of aging as an adaptive program fall into just two classes: The Demographic Theory is based on stability of ecosystems, and the dangers of population overshoot; the Evolvability Theory is based on the fact that a population with aging turns over more rapidly, and so is more flexible in response to environmental change[1]. These two theories fit into the larger narrative about the need for a broader understanding of evolutionary mechanisms, beyond neo-Darwinism.

The Demographic Theory. All animals depend on other "producer species" for the energy they need to live. As selection for faster reproduction pushes fertility ever higher, there is a danger that animal populations will outgrow the producer species that support them, and suffer population collapse as a consequence [17, 65]. Though it is beneficial for the individuals to reproduce as fast as possible, it is counterproductive (and sometimes catastrophic) for the community when reproduction outpaces the producer species in their ecosystem. Rapid, exponential population growth can lead to overshoot, population crashes, and extinctions. Adaptive aging is an effective response to this problem. Not only is the overall population growth rate tempered, but the death rate is brought partially under genetic control, and deaths from aging follow a complementary pattern: highest when deaths from starvation, epidemics, and overcrowding are at their minimum [66]. The mechanism by which aging might be selected is easy to understand and to model, because population cycles are a rapid and efficient mode of group selection.

Further evidence for the evolutionary connection between population dynamics and aging is provided by the Caloric Restriction (CR) effect. Quite generally, animals live longer when their diet is reduced to near-starvation levels. From a physiological perspective, it is difficult to understand why the stress of starvation should induce a protective effect. But as a population-level adaptation, the CR effect is clearly useful. When the community is threat-

[1] There are also benefits based on purging the population of individuals who have been damaged with age, or who have become infertile with age. Such theories are only relevant if we admit the inevitability that damage must accrue with age. But this damage is itself an aspect of aging, so the theories have a kind of circular logic, as pointed out by Medawar [63, 64].

ened by starvation, individuals become more robust in other respects. The death rate from aging recedes as the death rate from starvation increases, so that the net result is to stabilize populations in times of abundance and times of scarcity. If the evolutionary purpose of the CR effect is to stabilize population dynamics and help avoid extinctions, this adds credibility to the theory that aging in general has evolved for the promotion of demographic homeostasis.

A weakness of the Demographic Theory is that the same group-level problem can be solved without aging, simply by lowering the individual rate of predation, or by maturing later, or by lowering individual fertility. Why would nature need self-destruction of perfectly sound organisms when similar population regulation could be achieved simply by moderating reproduction rate in response to population density? In answer, there is some evidence that aging (especially in the form of fertility loss) is able to stabilize population cycles at a lower cost to individual fitness than these other life history adaptations [67].

The Evolvability Theory. In a population at its carrying capacity, the rate at which new, young organisms can grow up is limited by the rate at which adults vacate their space in the niche. A population that ages creates more opportunity than a hypothetical non-aging population; thus the population turnover rate is higher, and evolution can proceed more rapidly [31, 32]. Aging also promotes diversity, by limiting the extent to which offspring of just a few super-fit individuals might come to dominate a population, and diversity, in turn, benefits the pace of evolution [68]. A population with aging can adapt more quickly when the environment changes, and in an evolutionary race, the aging population will eventually overtake a population that turns over less rapidly because its members do not age. The problems with this theory are quantitative: the costs of aging are immediate and have substantial consequence for individual fitness, while the benefits take many generations to accrue. Numerical models of the process only succeed in evolving aging when the rate of environmental change is set artificially high, and made to proceed consistently in a single direction. The theory has a severe problem with cheaters, because the group benefits of aging are not confined to conspecifics that share the aging gene, but are spread over everyone that shares an ecological niche – potentially including even other species. The mechanism of the Demographic Theory is fast, and easy to understand and to model. The Evolvability Theory works qualitatively, but is difficult to model, and easily undermined by cheaters. So is the Demographic Theory to be preferred? Maybe not.

Evolvability Adaptations and the Evolution of Evolution

In the above list of major evolutionary features that neo-Darwinism cannot explain, seven of the nine are adaptations that favor the rate of evolution. Some of these do so at substantial cost to present fitness (ranging up to a factor of two for diecious species (separate sexes)), while for others the cost is difficult to account. These adaptations are deep, affecting the architecture of the genome, constraints on reproduction, and the structure of life itself. There are complex features of life that clearly required a substantial time to evolve, and more time to bear fruit as actualized fitness, and which were opposed all during this time by selection at the individual level.

All these features defy present-day evolutionary understanding. Naive, algebraic theory says they are not ESS (evolutionarily-stable strategies) and should not be able even to persist once established, let alone to climb uphill against individual selection during the millions of years that must have been required to create them. Computer models also cannot begin to capture the complexity of the processes by which these features evolved, (though they may be able to account for organization of the genome in ways favorable to evolvability, assuming that there is no cost [39]).

The conclusion must be that adaptations for the rate of evolution have become incorporated far more effectively than we can account for with *any* quantitative evolutionary theory (not limited to neo-Darwinism). It follows from this that the plausibility of the Evolvability Theory for the evolution of aging should not be discounted just because we cannot yet understand or model it. As an evolvability adaptation, the phenomenon of aging is in excellent company, along with other diversity adaptations like sex, and with the genotype/phenotype map, with epigenetic inheritance mechanisms, and the enormous range of adaptations for phenotypic plasticity.

A Bootstrapping Process

I regard the evolution of evolvability as a great unsolved (and to some extent unacknowledged) mystery. There is no question that evolvability adaptations offer a long-term advantage, but "long-term" in this case means thousands of generations, while short-term selection for the more direct and salient aspects of fitness – survival and reproduction – should have swamped the advantages of evolvability very early in the process.

One hint about how the evolution of evolvability might have proceeded is that it is a bootstrapping process; that is to say, evolvability adaptations make possible the selection of more evolvability adaptations. In order for evolvability adaptations to make headway, paths that offer short-term advantage must be effectively blocked off, inaccessible to the emerging variation that is the feedstock of evolution. The more dead ends are avoided, the easier it is to select adaptations with long-term advantages. Here are four examples of such a "roadblock" process, promoting long-term adaptations by cutting off short-term temptation.

1) Protists like *paramecium* exchange genes via sexual conjugation, but they reproduce by mitosis; thus the process of gene exchange is uncoupled from the process of reproduction. Conjugation has short-term costs to the individual and long-term advantages for the community. A successful cell has everything to lose and nothing to gain by sharing its genes with a random partner, because recombination disrupts combinations of genes that have proven successful. Nevertheless, occasional conjugation in protist colonies is vital to the genetic health of the community. Individual cells may replicate hundreds of times between conjugation events. What keeps conjugation behaviors from being lost to short-term selection? The answer is that cellular senescence – the shortening of telomeres – serves to enforce the imperative to share genes. Telomeres shorten with each replication event, and though telomerase is available in the genome, it is not expressed but held back. It is in the process of conjugation that telomeres are restored with telomerase, giving the cell a new lease on reproductive life for several hundred generations to come. This whole mechanism of generation-counting and telomere shortening may be an adaptation for the purpose of locking sex in place, assuring that protists are not tempted to revert away from gene-sharing functions [69].

2) In most multicellular life, sex is firmly tied to the function of reproduction so that there is no reproduction without sex. This is an arrangement that must have required many evolutionary steps, and is also easily lost [17]. Its only purpose is to make sex obligatory, preventing reversion to a life style that is more efficient for reproduction but has less evolutionary potential.

3) In hermaphrodites, there are always mechanical barriers to self-fertilization. In flowers with seed and pollen, the seed is structurally protected from the pollen that is closest. Earthworms have both sex organs, but their anatomy makes it difficult to self-fertilize. And in lizards that are able to change sex, the male and female roles are separated temporally [70].

Inbreeding depression (or "hybrid vigor") has no explanation from genetic fundamentals, and I speculate that it may be a widespread adaptation to discourage self-fertilization.

4) The greatest part of the burden of the fitness cost of sex is due not to the mechanics of sex but to the separation into two sexual forms, the "cost of males". In theory, hermaphrodites have a twofold advantage in fitness as measured by reproductive potential (although this difference is not observed when hermaphroditic species are compared side-by-side with diecious cousins [17]). The only advantage of separate sexes is that it makes much more difficult and improbable the reversion to self-fertilization or parthenogenesis.

These are all examples of evolutionary dead ends that have become obstructed. Every time a pathway with short-term advantages is made inaccessible to evolution, the viability of long-term adaptations is enhanced – including adaptations that offer further benefits for evolvability. This is the bootstrap.

All the mysteries of evolution are about ways in which complex adaptations have come about, involving many pieces that seem to have no adaptive value until assembled. Evolution appears like a conjurer: adaptation gives the appearance of being able to look into the future, though we know that it has had only the past to work on. Like the old carnival fortune-teller with her crystal ball, she has a lot of experience under her belt, and has become so good at gathering clues in the present that she creates a powerful illusion of being able to anticipate the future. We may not yet understand the details of how evolution is able to perform this trick, but perhaps it is a useful framework to think of evolution as a self-modifying process, a system of variation and selection that includes the ability to mold and reshape the directions of variation, if not the criteria for selection[2].

MECHANISMS OF EVOLUTION AND THE CHANGING MEANING OF "FITNESS" – THE BIG PICTURE

Fitness is the ability to thrive and expand in the biosphere. This has very different meanings on different scales of time and space. When we look at what has evolved, it is clear that the neo-Darwinian view of fitness that focuses exclusively on the individual and looks just one generation into the future is but a small part of nature's criteria for selection.

The history of life has been described as a progression to ever wider levels of organization, based on competition of larger entities. We presume that evolution began with molecules and proceeded to chromosomes, to cells, to multi-cellular entities, and then to communities. It is likely that at the beginning of this process there was only competition for survival and reproduction, the crudest and most immediate measures of fitness. In that era, the postulates of neo-Darwinism held strictly true. But evolution has been a self-modifying process, as organisms have learned not just how to reproduce faster, but also how to evolve more efficiency, to channel variation in directions likely to be adaptive, and to avoid evolutionary dead ends. In the beginning was only individual selection (and perhaps the "individual" was but a molecule); but over time the contest for ever higher rates of reproduction was gradually transformed to a sophisticated game including com-

[2] James Shapiro has been writing for years about "natural genetic engineering". He cites examples of ways in which microbes are able to modify their own genome in a targeted way in response to stress, and direct their own evolution. We may yet discover that multi-celled eukaryotes and even vertebrates are just as smart as bacteria in this regard [22].

petition and cooperation at ever higher levels. In the present, the nature of the competition is highly complex, and can be understood in terms of many levels of selection operating simultaneously.

The benefits of cooperation provide the imperative for forming new, more inclusive evolutionary units. Increments in fitness are traded among levels of selection through the evolution of behaviors that are costly to individuals yet beneficial to groups. Cooperation is necessary for the emergence of new units of selection precisely because it trades fitness at the lower level (the costs of cooperation) for increased fitness at the group level (its benefits). In this way, cooperation can create new levels of fitness and individuality. This trade, if sustained through group selection, kin selection, and conflict mediation, results in an increase in the heritability of fitness and individuality at the higher level. In this way, new, higher levels of selection may emerge in the evolutionary process [71].

In the changing, self-modifying game of evolution, a crucial first step was the emergence of ecological webs of dependency. It became unprofitable (and sometimes disastrous) to reproduce more rapidly than the producers at the base of the ecosystem could sustain. Thus the first group-level adaptations were about cooperation to moderate growth and conserve renewable resources, as described by Wynne-Edwards [50]. But once the straight jacket of competition for ever-faster reproduction was off, the nature of the game changed forever. The door was open for more sophisticated strategies that would bear fruit only over longer periods of time. Programmed life spans were among the first cooperative strategies to emerge, because aging offers immediate benefits for demographic homeostasis and stabilization of ecosystems. But as the necessity for unthrottled reproduction was tempered, the most important strategies to emerge were those that affected evolvability and the pace of evolutionary change, because such adaptations act recursively in an exponentially-accelerating progression.

The remarkable thing about aging is that it has evolved despite substantial individual cost, and despite the fact that its advantage (for evolvability, for diversity, and for stability of population dynamics) is very diffuse, indirect, and weak. If the target of natural selection is evolvability, then aging must be considered part of the fine-tuning. Still, aging has been fiercely defended in the face of substantial selection pressure for longer life span; and aging has become sophisticated and plastic in its implementation. Aging must be understood in the context of an evolutionary process that is itself efficient, complex, and highly evolved.

REFERENCES

1. Mitteldorf, J. (2004) *Evol. Ecol. Res.*, **6**, 1-17.
2. Mitteldorf, J. (2010) *Evolutionary Origins of Aging*, in *Approaches to the Control of Aging: Building a Pathway to Human Life Extension* (Fahy, G. M., West, M. D., Coles, L. S., and Harris, S. B., eds.) Springer, New York.
3. Migliaccio, E., Giorgio, M., Mele, S., Pelicci, G., Reboldi, P., Pandolfi, P. P., Lanfrancone, L., and Pelicci, P. G. (1999) *Nature*, **402**, 309-313.
4. Ayyadevara, S., Alla, R., Thaden, J. J., and Shmookler Reis, R. J. (2008) *Aging Cell*, **7**, 13-22.
5. Guarente, L., and Kenyon, C. (2000) *Nature*, **408**, 255-262.
6. Kenyon, C. (2001) *Cell*, **105**, 165-168.
7. Kenyon, C. (2005) *Cell*, **120**, 449-460.
8. Clark, W. R. (2004) *Advances in Gerontology (Moscow)*, **14**, 7-20.
9. Fabrizio, P., Battistella, L., Vardavas, R., Gattazzo, C., Liou, L. L., Diaspro, A., Dossen, J. W., Gralla, E. B., and Longo, V. D. (2004) *J. Cell Boil.*, **166**, 1055-1067.
10. Cawthon, R. M., Smith, K. R., O'Brien, E., Sivatchenko, A., and Kerber, R. A. (2003) *Lancet*, **361**, 393-395.
11. Marzetti, E., and Leeuwenburgh, C. (2006) *Exp. Gerontol.*, **41**, 1234-1238.
12. Pistilli, E. E., Jackson, J. R., and Alway, S. E. (2006) *Apoptosis*, **11**, 2115-2126.
13. Forbes, V. (2000) *Funct. Ecol.*, **14**, 12-24.
14. Masoro, E. J. (2007) *Interdiscip. Topics Gerontol.*, **35**, 1-17.
15. Williams, G. (1966) *Adaptation and Natural Selection*, Princeton University Press, Princeton.
16. Olshansky, S., Hayflick, L., and Carnes, B. (2002) *Sci. Am.*, **286**, 92-95.
17. Mitteldorf, J. (2006) *Evol. Ecol. Res.*, **8**, 561-574.
18. Mitteldorf, J., and Pepper, J. (2009) *J. Theor. Biol.*, **260**, 186-195.
19. Martin, G. M. (2005) *American Aging Assoc. Newsletter*, 1-15.
20. Bell, G. (1982) *The Masterpiece of Nature: The Evolution and Genetics of Sexuality*, University of California Press, Berkeley.
21. Burt, A. (2000) *Evol. Int. J. Org. Evol.*, **54**, 337-351.
22. Ruddle, F. H., Bartels, J. L., Bentley, K. L., Kappen, C., Murtha, M. T., and Pendleton, J. W. (1994) *Ann. Rev. Genet.*, **28**, 423-442.
23. Kirschner, M., and Gerhart, J. (2006) *The Plausibility of Life*, Yale University Press, New Haven, CT.
24. Shapiro, J. A. (2011) *Evolution: A View from the 21st Century*, FT Press.
25. Margulis, L., and Sagan, D. (2002) *Acquiring Genomes*, Basic Books.
26. Thompson, J. N. (1994) *The Coevolutionary Process*, University of Chicago Press, Chicago.
27. Endler, J. A. (1985) *Natural Selection in the Wild*, Princeton University Press, Princeton, NJ.
28. Sober, E. (1980) *Philosophy Sci.*, **47**, 350-380.
29. Layzer, D. (1980) *Am. Nat.*, **115**, 809-826.
30. Wagner, G. P., and Altenberg, L. (1996) *Evolution*, **50**, 967-976.
31. Martins, A. C. (2011) *PLOS One*, **6**, e24328.
32. Libertini, G. (1988) *J. Theor. Biol.*, **132**, 145-162.
33. Haldane, J. B. S. (1924) *Trans Cambridge Phil. Soc.*, **23**, 19-41.
34. Wright, S. (1931) *Genetics*, **16**, 97-159.
35. Fisher, R. A. (1930) *The Genetical Theory of Natural Selection*, The Clarendon Press, Oxford.
36. Cabej, N. R. (2012) *Epigenetic Principles of Evolution*, Elsevier, Boston, MA.

37. Darwin, C. (1872) *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*, John Murray, London.
38. Dawkins, R. (1976) *The Selfish Gene*, Oxford University Press, Oxford.
39. Pepper, J. W. (2003) *Biosystems*, **69**, 115-126.
40. Hughes, A. L. (2000) *Adaptive Evolution of Genes and Genomes*, Oxford University Press, Oxford, UK.
41. Bejerano, G., Pheasant, M., Makunin, I., Stephen, S., Kent, W. J., Mattick, J. S., and Haussler, D. (2004) *Science*, **304**, 1321-1325.
42. Weismann, A., Poulton, E. B., Schonland, S., and Shipley, A. E. (1891) *Essays upon Heredity and Kindred Biological Problems*, Clarendon Press, Oxford.
43. Pembrey, M. E. (2002) *Eur. J. Hum. Genet.*, **10**, 669-671.
44. Wright, G. A., Choudhary, A. F., and Bentley, M. A. (2009) *Proc. Biol. Sci.*, **276**, 2597-2604.
45. Takahata, N., and Nei, M. (1990) *Genetics*, **124**, 967-978.
46. Dollo, L. (1893) *Bull. Soc. Belg. Geol. Pal. Hydr.*, **VII**, 164-166.
47. Masel, J. (2005) *Genetics*, **170**, 1359-1371.
48. Bergman, A., and Siegal, M. L. (2003) *Nature*, **424**, 549-552.
49. Woese, C. R. (2000) *Proc. Natl. Acad. Sci. USA*, **97**, 8392-8396.
50. Wynne-Edwards, V. (1962) *Animal Dispersion in Relation to Social Behavior*, Oliver & Boyd, Edinburgh.
51. Price, G. R. (1970) *Nature*, **227**, 520-521.
52. Price, G. R. (1972) *Ann. Hum. Genet.*, **35**, 485-490.
53. Wilson, D. S. (1975) *Proc. Natl. Acad. Sci. USA*, **72**, 143-146.
54. Wilson, D. S. (1980) *The Natural Selection of Populations and Communities*, Benjamin Cummings, Menlo Park, CA.
55. Maynard Smith, J. (1976) *Q. Rev. Biol.*, **51**, 277-283.
56. Hamilton, W. D. (1964) *J. Theor. Biol.*, **7**, 1-16.
57. Hamilton, W. D. (1964) *J. Theor. Biol.*, **7**, 17-52.
58. Sober, E., and Wilson, D. S. (1998) *Unto Others: The Evolution and Psychology of Unselfish Behavior*, Harvard University Press, Cambridge, MA.
59. Gilpin, M. E. (1975) *Group Selection in Predator-Prey Communities*, Princeton University Press, Princeton.
60. Pepper, J., and Smuts, B. B. (2000) in *Dynamics in Human and Primate Societies: Agent-Based Modeling of Social and Spatial Processes* (Kohler, T. A., and Gumerman, G. J., eds.) Oxford University Press, Oxford, pp. 45-76.
61. Klein, D. R. (1968) *J. Wildlife Manag.*, **32**, 350-367.
62. Lockwood, J. A., and Debrey, L. D. (1990) *Environ. Entomol.*, **19**, 1194-1205.
63. Travis, J. M. (2004) *J. Gerontol.*, **59**, 301-305.
64. Medawar, P. B. (1952) *An Unsolved Problem of Biology*, Published for the college by H. K. Lewis, London.
65. Trubitsyn, A. (2006) *Advances in Gerontology (Moscow)*, **19**, 13-24.
66. Mitteldorf, J., and Pepper, J. (2007) *Theory Biosci.*, **126**, 3-8.
67. Mitteldorf, J., and Goodnight, C. (2012) *Oikos*, in press; DOI: 10.1111/j.1600-0706.2012.19995.x
68. Bowles, J. T. (1998) *Med. Hypoth.*, **51**, 179-221.
69. Clark, W. R. (1998) *Sex and the Origins of Death*, Oxford University Press, Oxford.
70. Policansky, D. (1982) *Ann. Rev. Ecol. Syst.*, **13**, 471-495.
71. Michod, R. E. (1999) in *Levels of Selection in Evolution* (Keller, L., ed.) Princeton University Press, Princeton, NJ.