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Evolutionary Orthodoxy: How and Why the Evolutionary Theory of Aging Went Astray

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Abstract: Prevailing ideas of how aging evolved are a poor fit with the picture of aging that is developing from genetics labs and breeding experiments. Nevertheless, the community of theorists is reluctant to consider alternate approaches because the differences are profound, calling into question much of the standard methodology of Population Genetics. (At stake is not the legacy of Darwin, but the particular model of Darwinian selection that has dominated the field of research since the middle of the 20th Century). This model may be a historic artifact, arising from a time before computers, when a premium was placed on equations that could be solved analytically. The standard Population Genetic model gained credibility through agreement with laboratory experiments that were designed to realize the assumptions of the model, rather than to mirror conditions in the natural world. Models of evolution based on pure individual selection or inclusive fitness cannot explain the basic phenomenology of aging. Aging is not the only area of conflict, however. Other areas which present difficulties for the standard model include the origin of sex, the maintenance of diversity, the basis of evolvability (including hierarchical structure of the genome), occasional persistence of eusociality without close relatedness, and many examples of strong altruism. From many corners of the field, creative and visionary biologists are calling for a re-thinking of the fundamental mechanisms of natural selection.

Keywords: Aging, evolution, group selection, neo-Darwinism, senescence.

INTRODUCTION

A liquid may be gently heated until its temperature is a few degrees above the boiling point, and yet it remains liquid until suddenly it may explode, triggered by a foreign particle or the smallest vibration. Thomas Kuhn [1] taught us that a theory may retain its stature in the scientific community long after a critical mass of experimental contradictions has falsified its foundation.

The evolutionary theories of aging that have become standard in the past half century have outlived their usefulness in explaining the phenomenology and genetics of aging, and yet the community of gerontologists and evolutionary theorists have been slow to assemble the puzzle pieces and realize that the picture they form does not conform to broad theoretical expectations. The situation is ripe for a paradigm shift.

The old paradigm has survived in part by shape-shifting. There are four acceptable theories, and when an experiment directly contradicts one, it is frequently interpreted as if it were evidence in favor of another. In fact, deep experimental contradictions plague all four theories. None of them are viable as a general explanation of the broad phenomenology of aging.

How did we arrive at this place? The root of the problem is traceable to a particular quantitative realization of Darwin's theory of natural selection that was codified principally by R. A. Fisher nearly a century ago. During the middle third of the 20th Century, Fisher's paradigm became the Standard Model for the operation of natural selection. While the theory was developing, mathematical evolutionists were working in a separate scientific world from naturalists and field biologists, with little interaction between the two. Then, during the period 1965-1975, the two fields came together. But instead of field biologists imposing the discipline of empiricism on a science that had developed too long as mathematical abstraction, the opposite occurred. The mathematical wing of evolutionary science convinced the naturalists that their theory was correct because it was logical and rigorous.

Any theory that has lost its empirical foundations is a troubled science. But in this case, laboratory experiments substituted for observations of nature to validate the mathematical theory. Experiments in artificial selection were set up to realize the conditions of the Standard Model, and the agreement between lab experiments and Fisher's theory was mistakenly regarded as validation that the theory indeed described the operation of adaptation and selection *in the natural world*.

There are now several areas in which evolutionary theory has become a poor fit with genetics and with observations of nature. Aging is the subject of the present essay, but other failures of the Standard Model include evolution of sex, maintenance of diversity, horizontal gene transfer, epigenetics, endosymbiosis, Lamarckian inheritance, and the structure of the genome, which shows the imprint of being optimized for evolvability. Aging is best understood as a cooperative adaptation, and analysis of all such altruistic behav-

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iors has been distorted by the narrow lens of inclusive fitness and the "selfish gene".

DARWIN IN A STRAITJACKET

R. A. Fisher (Fig. **1**) is a towering figure in 20th Century science. His ideas laid the foundation for the modern practice of statistics, which he developed along the way to the science of evolutionary genetics. His book on *The Genetical Theory of Natural Selection* [2] is the foundation on which quantitative evolutionary science has been built. His legacy was enriched and expanded through the 20th Century by such mathematical luminaries as Dobzhansky, Haldane, Hamilton and Maynard Smith. The approach begins with a gene-centric view of evolution and regards genes as independent agents, to a first approximation. In the standard paradigm that is called variously "Population Genetics" or "neo-Darwinism", or simply the "New Synthesis", a population of individuals exists within a static ecosystem, and various genotypes gradually grow more or less common, from generation to generation, within a fixed total population size. Epistasis, conspecific interactions, and ecosystem feedback are all handled as perturbations, as though they were secondary effects. The model is invalid on its face when any of these perturbations becomes a dominant influence. This alone is not reason to dismiss the model, for many models in science turn out to agree with experiment even when the assumptions of the model are explicitly violated (examples include the ideal gas law and the Schroedinger solutions for single electron orbitals of hydrogen, from which the chemistry of all elements is elaborated). But when we observe disagreement with predictions of the Standard Model, we should feel free to explore the consequences of more realistic assumptions at a fundamental level.

Fig. (1). Ronald A Fisher, father of modern population genetic theory.

Fisher's model was designed to be convenient for calculation, and tractable with the analytic methods available thirty years before digital computers. Curiously, the model was also motivated by the eugenics movement, and Fisher's passion to preserve the human race (and British aristocracy in particular) from a perilous dilution of their gene pool. The second half of *The Genetical Theory* is, in fact, an embarrassment that is ignored by modern readers of the first half; it is a political screed tinged with racism and discredited assumptions about race, class and the relationship between intelligence and financial success[1].

It was never believed that the assumptions underlying Fisher's model were literally true, but over a period of decades, Fisher argued convincingly that his methods captured the essential core mechanism of biological evolution. Fisher argued that the world is a large place, that evolutionary times are long, and variations in the environment that shape the fate of a particular allele will average out in the large. When Fisher debated this point (most famously with Sewell Wright in the 1940s), the questions were resolved by rhetoric and verbal logic; for us today, it may seem obvious to approach these questions with experiments and numerical simulations.

Wright painted verbal pictures of divided populations that could support his Shifting Balance model [3, 4]. Wade and Goodnight [5] demonstrated the mechanism in one of very few experiments in laboratory evolution that was *not* structured so as to realize Fisher's paradigm. David Wilson [6] proposed a picture based on the mathematical schema of George Price [7, 8] in which forces of natural selection operate on different levels simultaneously. And Michael Gilpin [9] pioneered the use of digital simulation to demonstrate that population dynamics is an evolutionary force to rival individual selection for fertility. Together, these ideas might have been taken as a cogent alternative to the monolithic precepts of Fisher; but historically they were lost in the current of science which, at the time, was under the spell of the Selfish Gene.

Another factor that worked in favor of Fisher's paradigm was the success of 19th century methodologies in using reductionist analysis to turn physics into a precise, quantitative discipline that made theoretical predictions. Biologists were naturally eager to emulate their methods, and the adoption of rigorous mathematical forms was considered a step in that direction. Of course, deriving quantitative predictions from a model was only half the making of a science; the other half was to validate these predictions against experiment.

[1] "We must face the paradox that the biologically successful members of our society are to be found principally among its social failures, and equally that classes of persons who are prosperous and socially successful are, on the whole, the biological failures, the unfit of the struggle for existence, doomed more or less speedily, according to their social distinction, to be eradicated from the human stock...In societies so constituted, we have evidence of the absolute failure of the economic system to reconcile the practice of individual reproduction with the permanent existence of a population fit, by their mutual services, for existence in society." 2. Fisher RA. The genetical theory of natural selection. Oxford,: The Clarendon Press; 1930. xiv, 272 pp.

Through the 20th Century, the quantitative theories of population genetics were indeed quite successful in explaining laboratory results in artificial selection. This led to the broad perception that there was a predictive, mathematical theory of evolution that had been thoroughly tested against reality, and was unassailable. This, however, was an illusion. The lab experiments were designed around the theory. Frequently, they studied one trait at a time, and selection for each trait was arranged within a static population in a constant environment, as assumed in the theory. The fact that the theory works well under these conditions tells us nothing, however, about whether such conditions prevail in the natural world, or whether principal modes of evolution in the natural world are well captured by the same model. There was a subtle circularity to the relationship between theory and experiment.

In fact, populations in natural ecosystems are not static. They are not even slowly-varying compared to the generation time of the participant species. Local population sizes typically vary by a factor of two or more over a single generation [10], and it is not uncommon for a population to collapse to extinction within a few generations [11, 12]. This is the basis for a radical form of "group selection", a concept that has been vigorously opposed by evolutionary theorists based only on the mathematical paradigm that has become standard in their discipline, ignoring field studies of the natural world and computer simulations [9]. Far from being naturally static, populations in realistic dynamic models tend to evolve toward dynamic chaos as individual selection pushes individual reproductive fitness ever higher [10]. The relative stability of ecosystems found in nature is evidence of ecosystem-level adaptations that preserve homeostasis. Demographic homeostasis is, in fact, an important target of natural selection, balancing against individual selection for ever faster growth and reproduction [13].

The categorical rejection of "group selection" has held Darwin's theory in a straitjacket these last fifty years. For aging theory, the point is that a great deal of the phenomenology and genetics of aging may be aptly regarded as functional adaptations for the sake of the community; but all considerations of group benefit have been dismissed because they violate the prevailing paradigm of neo-Darwinism, a.k.a. The Selfish Gene.

Indeed, there is a common genetic basis for aging, conserved and refined over a billion years of evolution. Aging is built into the life history, into the population dynamics of the ecosystem, into the individual genome at a deep level. But aging genes are not "selfish genes", and cannot be explained within the Standard Model. If we are to understand the evolutionary origins of aging, the conversation must be broadened to include ecosystem dynamics and selective pressures that act at a higher level than the selfish gene.

THE PRESENT PARADIGM: FOUR "ACCEPTABLE" THEORIES, AND THE FAILURES OF EACH

0. Wear and tear, stochasticity, and "damage" theories of aging (Fig. 2)

The idea that things degrade over time, that nothing lasts forever, has ancient roots. It was only in the 19th Century that this concept was formalized (by Rudolf Clausius [14]) as the Second Law of Thermodynamics.

> *In any closed physical system, the entropy will increase, until it attains its maximum value. The state of the system in which entropy realizes its maximum value is called 'equilibrium'.*

Only then did it become clear that the principle applied only to *closed systems*, isolated from the rest of the world. Living systems are not closed. This is no mere loophole in the Second Law, but the essential thermodynamic difference between living and non-living matter. By definition, a living thing taps free energy from its environment and uses it to grow, to reproduce, and to perform metabolic tasks. Entropy is excreted with the body's chemical waste. If living organisms were closed systems, subject to the Second Law, growth and reproduction would be impossible.

This was first realized by August Weismann [15], who first proposed that aging must command an evolutionary explanation, and attempted himself to put forth the first such.

Fig. (2). The misconception that bodies "wear out" in the same way as machines was discredited already in the 19th Century.

Weismann's theory was not yet clear, as he himself was the first to realize [16]; but the idea that aging must be explained from evolution and not simply from physics has been accepted by all who think deeply about the topic for more than a century.

Nevertheless, metabolic theories of aging have great currency still among gerontologists (though not, of course, among evolutionary biologists). This is because much about aging *appears* very much akin to damage. Oxidative damage is obvious at the cellular level, and "free radical theories of aging" have been ever-popular since first proposed by Denham Harman [17, 18]. For many years, it was thought that anti-oxidants would delay or even prevent aging, but in epidemiologic studies [19] and lab experiments [20], anti-oxidant therapies have failed [21]. If the problem is oxidation, why do anti-oxidants seem to make the problem worse [19]? Why do anti-oxidants in the body decline with age? More fundamentally, the question that cries out for explanation is why the body should permit damage to accumulate, when it is perfectly capable not only of repair but of *correcting* and *strengthening*, to build itself toward a condition ever larger, stronger, more robust [22]. Indeed, this is the substance of developmental biology.

If animals were "wearing out" with age, we would expect exercise to shorten life span. The opposite is true. We would expect that the bat, with its high activity and fast metabolism, should burn itself out faster than the mouse. But mice live about two years and bats about thirty.

Hormesis [23, 24] is a concept that was controversial for years, because it flies in the face of wear-and-tear theories of aging. It is no longer deniable that many stressors, including toxins in low doses, heat, cold, low-dose ionizing radiation, and infections all can lengthen life span. The better-known effects of exercise and caloric restriction for lengthening life span are now understood in terms of hormesis [25, 26].

Even osteo-arthritis, which was formerly understood as a cumulative effect of abrasion on cartilage, is now described as an effect of excessive inflammation, not essentially different from rheumatoid arthritis [27].

Thus wear-and-tear theories of aging are both theoretically unfounded and experimentally unsupported. They continue to have great currency because much of the decline that our bodies suffer with age appears in the form of damage, and because many researchers (and even more medical practitioners) do not ask the deeper question, why the body permits itself to suffer damage that it is perfectly capable of avoiding.

1. The Declining Force of Natural Selection: Mutation Accumulation and the Genetic Load

The idea derives from Peter Medawar, and his 1952 book, *An Unsolved Problem of Biology* [28]. If fitness is measured by the Malthusian Parameter ***r***, then the effect of vitality and fertility on ***r*** decline with age for two reasons: first, offspring that are produced early contribute more effectively to the exponential rate of expansion in a gene's prevalence; and second, incidental mortality (predation, disease, starvation) thins the population over time, so that even without aging, fewer individuals will remain alive at greater ages. It follows that the force of natural selection declines with age. Medawar imagined a hypothetical gene that acted only at late ages in life, and deduced that selective pressure on that gene would be small compared to a corresponding gene that had the same function earlier in life. Random, detrimental mutations in such a gene would take a long while for natural selection to clear. Could it be that "genetic load" in itself could explain the fundamental origin of aging? This became known as the Mutation Accumulation theory, after the theory was articulated in this form by Edney and Gill [29] (Fig. **3**).

Fig. (3). Mutation Accumulation theories are based on the idea of "genetic load". Mutations occur randomly in the genome all the time, and those that affect fitness only late in life may last a long while before selection weeds them out.

The Mutation Accumulation theory predicts that mutations that cause aging should be random, they should be of recent origin, and they should be different in different species. In the 1990s, the genetics of aging was studied for the first time, and it was discovered that there is an ancient genetic basis for aging, indeed that genes regulating aging have been preserved since the dawn of eukaryotic life [30, 31]. This is a fundamental feature of aging in the natural world, utterly incompatible with the Mutation Accumulation theory.

There exists a more direct refutation of the Mutation Accumulation hypothesis. Fisher's Fundamental Theorem tells us that the additive genetic variance of a trait is a measure of the strength of natural selection for that trait. If aging can be defined as an increase in mortality risk with age, then the test of whether it is an adaptation shaped by selection can be answered by measuring the variance in the mortality rate late in life, and the behavior of that variance as a function of age. Common sense tells us that mortality becomes increasingly certain at advanced age, and that the variance in mortality must therefore be very low late in life. But we need not rely on common sense; the measurement was actually performed [32, 33] by a team of researchers who understood the subtleties of measuring mortality as a population statistic. They used 65,000 flies subdivided into 256 genetically homogene-

ous populations. Their result was that the variation in mortality rate is small at late ages, and declines steeply. The significance of the result is that aging cannot be attributed to random mutations.

2. Genetic Tradeoffs over time: Antagonistic Pleiotropy

Some genetic traits might have benefits early in life, but cause harm at late ages. For example, fertility hormones might be expressed at high levels that increase early fertility, but have a corrosive effect on tissue, and cause damage that gradually accumulates. Williams [34] pointed out that the balance of natural selection will be to favor retention of such genes (because of the declining force of natural selection, as articulated by Medawar), and the theory that he articulated was provided with the catchy moniker "Antagonistic Pleiotropy" by Rose [35].

According to the theory known as Antagonistic Pleiotropy, all genes that cause aging should have benefits to individual fitness that outweigh their costs (Fig. **4**). It is curious, then, that for most genes that cause life span to shorten, no known benefit has yet been identified, and for exactly none of them has a quantitative comparison been made, demonstrating that the benefit outweighs the cost. As early as 1992, Stearns [36] catalogued such genes, and found that pleiotropic benefits were known for only half of the genes that were known to shorten life span. Since that time, the catalog of such genes has expanded widely, and benefits have been discovered for just a fraction of these. Nowadays, it is considered a triumph when *any* cost can be attributed to a gene that shortens life span. To actually compute the balance of the tradeoff for a particular gene has never been attempted.

A deeper problem for the theory is its assumption about timing. In 1957 when Williams proposed the idea, genetic science was new, and it was reasonable to suppose that once a gene was in the genome, an organism was stuck with it for life. Williams imagined that genes could outlive their usefulness and cause harm in old age. Fifty years after Williams, there are still prominent theorists who imagine a kind of inertia in expression of genes that are important for development, but whose ongoing expression later in life causes all the harm of aging [37, 38].

Now we know that more than 25% of the genome is associated with regulation and timing of gene transcription, while less than 2% is transcribed as proteins. Clearly the 25% has been subject to evolutionary pressure every bit as strong as the 2%. Timing of gene expression during development is exquisitely regulated, and there is no reason to suppose that a gene useful in early life would be constrained to persist in late life in the face of selective pressure to the contrary.

Thus, the theory would be hard-pressed to explain why genes continue to be expressed at ages when they are no longer beneficial; but the situation is actually worse than this. Gene expression late in life is different from earlier in ways that actually accelerate aging. For example, the antioxidants ubiquinone, melatonin, and glutathione are all present at *lower levels* in aging humans, despite the fact that there is more need for them with age. Conversely, NFkB, TGF-beta, LH and FSH are all expressed at *higher* levels as we age, even though they are contributing to inflammation that is becoming an important mortality risk.

There are direct contradictions to Antagonistic Pleiotropy as well. In marathon breeding experiments with fruit flies extending over 30 years, Rose [39] has been able to increase fertility and longevity simultaneously. In a recent study, the INDY gene, long known to increase life span in flies, was found to increase fertility as well [40].

3. Metabolic Tradeoffs and the 'Disposable Soma'

Kirkwood [41] proposed that aging is caused by the necessity for metabolic compromise. The body cannot simultaneously do every task well, and so there must be a tradeoff between resources devoted to the necessary immediate tasks (including reproduction) and to the repair and maintenance functions that assure the individual's ongoing viability into the future. Why does performing one task well imply that another task must be done less well? Kirkwood correctly surmised that the currency of the metabolism is energy, and that it is the limited availability of food energy that enforces the necessity for rationing and

Fig. (4). Pleiotropic theories of aging are based on the idea that there are tradeoffs implicit in the choices that natural selection has made, and that trading early vitality for senescence late in life provides a net benefit to fitness.

the necessity for rationing and compromise. Although this theory seems on its face to comport with the way we know that the world works, in fact, the theory runs aground when its predictions are compared to nature. The Disposable Soma predicts that males should live longer than females (since they expend less energy on reproduction). The opposite is true [42, 43]. The Disposable Soma predicts that bearing more children should be a major risk factor for mortality and a shorter life expectancy. No such correlation has been detected in animals [44], and in human demography, there is a slight *positive* correlation between fertility and life span [45-48].

There is also an insurmountable contradiction with the phenomena of life extension through caloric restriction. If the deep cause of aging were really the limited availability of food energy, then the ingestion of more food energy should resolve the conflict, enabling the body simultaneously to do a better job with all its functions, including repair/maintenance. The fact that animals generally live longer when they are fed less falsifies the Disposable Soma absolutely (Fig. **5**).

The only attempt to reconcile the Disposable Soma with caloric restriction was published by Kirkwood and his student, Daryl Shanley [49]. It is narrowly based on the energy metabolism of lactating mice, and even under the most favorable assumptions considered by these authors, finds only a very small range of CR parameters in which fewer calories can lead to longer life. Of course, most experiments in CR are conducted with non-breeding animals, and in any case the energy model used by Shanley/Kirkwood does not apply to males. A full refutation of the Shanley/Kirkwood model was published the following year by Mitteldorf [50].

To reconcile the basic reasonableness of Disposable Soma logic with the caloric restriction phenomenology, many gerontologists imagine that there are other scarce resources, other reasons that compel the body to choose between doing a good job of repair and reproducing in the present. No such scarce resource has ever been proposed, however, and I know of no publication in which this variant form of the Disposable Soma has been described in sufficient detail that it might be evaluated.

LIMITING THE DEBATE TO FAILED THEORIES

Until the latter part of the 20th Century, aging was regarded as an Unsolved Problem of Biology. Both Medawar's [28] book and Williams's [34] paper were written as tentative, if ambitious, partial resolutions of some of the conundrums of aging. These were excellent scientists, formulating hypotheses that were most consistent with prevailing understanding at the time. They clearly stated proposed mechanisms of selection, and made testable predictions. It takes nothing away from their achievement to note that the evidence amassed over the ensuing decades were deeply at variance with those predictions. It was the later scientists who failed to take the next step, and re-evaluate the old theories in light of new evidence. Instead, too many regarded the theories of Williams and Medawar as though they were a logical necessity, and wove a Baroque tapestry of exceptions rather than consider a fundamentally new theory.

It was only after the entire field of evolutionary biology became sclerotic in the 1970s and 80s that authorities in the field could assemble the hodge-podge of ideas that had been contributed and propose that, collectively, they might be regarded as the final explanation for the near-universal phenomenon of aging-unto-death that seems, on its face, to defy the fundamental Darwinian notion of maximized individual fitness. In an extraordinary paper [51], French demographer Eric LeBourg proposed closing the auction to further bids, and limiting consideration for all future time to the theories presently on the table. His Abstract reads (in full):

> *This article reviews some studies testing evolutionary theories of aging and shows that they are not always confirmed. Nevertheless, many gerontologists consider now that these theories provide a general explanation of the aging process. In such conditions, we may wonder whether time has come to provisionally accept these theories in order to redirect the research efforts of gerontologists towards other directions, such as the search for new means to modulate the aging process.*

This passage is striking not so much for its arrogance as for the deep rejection of scientific methodology that it implies. No matter what present contradictions exist, no matter what surprises may turn up in future lab results, we will limit our consideration to these sanctioned, pre-approved theories. This is proposed for the sake of efficiency.

Implicit is the idea that science can be pursued as a managed, linear process. Missing is the realization (attributed to Einstein) that "If we knew what we were doing, it wouldn't be called research."

Fig. (5). The Disposable Soma theory is based on allocation of the body's food energy budget. The theory is inconsistent on its face with the well-known phenomenon of life extension from caloric restriction.

And yet, LeBourg's Abstract describes well the state of affairs in aging science today. This has been my personal experience in seeking publication venues for many articles and an academic book. It is also an experience commonly related to me, both by interlopers in the field, and also by some well-respected bench scientists with international reputations and prominent, high-profile publications. Too frequently, framing a manuscript in terms of programmed aging is grounds not just for rejection, but for refusal to advance the submission in the peer review process.

> "The way evolution works makes it impossible for us to possess genes that are specifically designed to cause physiological decline with age or to control how long we live."[52].

Ironically, one of the authors of these words was, in his youth, responsible for falsifying a theory that had held sway for 50 years [53]. This statement is correct about two things: First, that within the limits of standard population genetic theory, the ways in which aging may be understood are severely limited. It is probably true that the existing evolutionary theories have exhausted the possibilities that are available without breaking out of the box. And second, the acceptance of senescence as a group-selected adaptation will necessitate a deep re-thinking of evolutionary theory, with consequences that extend far beyond the science of aging.

"ADAPTIVE AGING" A.K.A. "PROGRAMMED AGING"

The alternative paradigm that evolutionists have categorically rejected on theoretical grounds is based on multilevel selection. Life spans have evolved as a compromise between what is optimal for the individual (unlimited life span, perpetual growth and constantly increasing fertility [22]) and what is optimal for the community (a programmed life span that assures turnover to maintain diversity, and holds down population growth during times when overpopulation poses a potential threat to the ecosystem). I have promoted a Demographic Theory for the origin of aging. The reason that programmed, individual life spans are flexible, and extended particularly in times of hardship has everything to do with stabilizing population dynamics. Without flexibly-programmed death rates, there is reason to believe that stable ecosystems would not be possible [13, 54, 55] (Fig. **6**).

THE LEGACY OF CARL WOESE

The late Carl Woese [56] bequeathed to us a vision of the Road Not Taken [57] in 20th Century biology, and his plea for a more holistic approach in the 21st. Though his essay does not mention aging, his vision and his wisdom are directly relevant, because they speak to the mind-set that has caused biologists to cling to explanations for aging that don't work, and to resist the broadening of accepted evolutionary mechanisms.

I quote from Woese at length, as but a poor substitute for your reading the essay in its entirety.

> [T]he colorless, reductionist world of 19th century classical physics [has] strongly affected the outlook of western society in general. The living world did not exist in any fundamental sense for classical physics: reality lay only in atoms, their interactions, and certain forces that acted at a distance. The living world, in all its complexity and beauty, was merely a secondary, highly derived and complicated manifestation of atomic reality and, like everything else in our direct experience, could (in principle) be completely explained (away) in terms of the ever-jostling sea of tiny atomic particles [53]. The intuitive disparity between atomic reality and the "biological reality" inherent in direct experience became the dialectic that underlay the development of 20th century biology.
>
> ...molecular biology would prove a mixed blessing. On the positive side, those problems (or portions thereof) that were amenable to a reductionist approach would benefit from the fresh, no-nonsense outlook and experimental power of molecular biology. In addition, biology as a whole would benefit from the physicist's general modus operandi, *i.e.*, from the well-honed understanding of what science is and how it should be done: the crisp framing of problems, the clear understanding of what is and what isn't established truth, the importance of hypothesis testing, and the physicist's disinterested approach in general. On the negative side, biology's holistic problems, which were not commensurate with the new molecular perspective, would remain relatively or completely undeveloped. The result was a distorted growth of biology in the 20th century. The most pernicious aspect of the new molecular biology was it reductionist perspective, which came to permeate biology, completely changing its concept of living systems and leading then to a change in society's concept thereof...

Fig. (6). Surprising indications have been discovered in recent decades that the process of aging seems to be controlled by gene expression, on a flexible schedule in response to environmental cues.

> Fundamentalist reductionism (the reductionism of 19th century classical physics)... is *ipso facto* a statement about the nature of the world: living systems (like all else) can be completely understood in terms of the properties of their constituent parts. This is a view that flies in the face of what classically trained biologists tended to take for granted, the notion of emergent properties. Whereas emergence seems to be required to explain numerous biological phenomena, fundamentalist reductionism flatly denies its existence: in all cases the whole is no more than the sum of its parts. Thus, biology of the 20th century was in the strange position of having to contort itself to conform to a world view (fundamentalist reductionism) that 20th century physics was simultaneously in the process of rejecting…

The most transformative message of quantum mechanics is not uncertainty or wave/particle duality or discrete quanta of energy; the deepest and most revolutionary change inherent in 20th Century physics is precisely the repudiation of reductionism. This is "quantum entanglement", and it is pervasive, universal. We know now that the single-particle wave function is only an approximation, that an electron is not a particle unto itself but a piece of "electron stuff" that pervades the universe. Proper treatment of the dynamics of any one electron takes explicit account of the exchange symmetry that connects this electron to all electrons everywhere.

Woese is fascinated with the irony that 20th Century biology set out to emulate physics, but the physics it chose to emulate was the reductionist physics of the 19th Century. While 20th Century biology busied itself understanding the living organism as a biochemical machine, 20th Century physics was trying to understand and assimilate the message of holism thrust upon it by quantum mechanics, and by the remarkable coincidences in the "six numbers" that make possible the rich complexity of the universe we know [58, 59].

> I think the 20th century molecular era will come to be seen as a necessary and unavoidable transition stage in the overall course of biology: necessary because only by adopting a heavily reductionist orientation and the technology of classical physics could certain biological problems be brought to fruition and transitional because a biology viewed through the eyes of fundamentalist reductionism is an incomplete biology. Knowing the parts of isolated entities is not enough. A musical metaphor expresses it best: molecular biology could read notes in the score, but it couldn't hear the music. The molecular cup is now empty. The time has come to replace the purely reductionist "eyes-down" molecular perspective with a new and genuinely holistic, "eyes-up," view of the living world, one whose primary focus is on evolution, emergence, and biology's innate complexity…
>
> A heavy price was paid for molecular biology's obsession with metaphysical reductionism. It stripped the organism from its environment; separated it from its history, from the evolutionary flow; and shredded it into parts to the extent that a sense of the whole—the whole cell, the whole multicellular organism, the biosphere—was effectively gone. Darwin saw biology as a "tangled bank", with all its aspects interconnected. Our task now is to resynthesize biology; put the organism back into its environment; connect it again to its evolutionary past; and let us feel that complex flow that is organism, evolution, and environment united. The time has come for biology to enter the nonlinear world…
>
> [T]he entry of chemistry and physics into biology was inevitable. The technology that these sciences would introduce was not only welcome but very much needed... But the physics ... was a Trojan horse, something that would ultimately conquer biology from within and remake it in its own image. Biology would be totally fissioned, and its holistic side would be quashed. Biology would quickly become a science of lesser importance, for it had nothing fundamental to tell us about the world. Physics provided the ultimate explanations. Biology, as no more than complicated chemistry, was at the end of the line, merely providing baroque ornamentation on the great edifice of understanding that was physics—the hierarchy physics → chemistry → biology is burned into the thinking of all scientists, a pecking order that has done much to foster in society the (mistaken) notion that biology is only an applied science...
>
> Thus, biology...must choose (to) break free of reductionist hegemony, reintegrate itself, and press forward once more as a fundamental science. The latter course means an emphasis on holistic, "nonlinear," emergent biology—with understanding evolution and the nature of biological form as the primary, defining goals of a new biology...
>
> *One would be hard put to explain evolution and the problem of biological form in reductionist terms alone.*

CONCLUSION

As the mainstream of evolutionary science continues with business as usual, adapting the theory they know to try to understand the experiments at hand, there are three undercurrents pulling at the foundations of the field. First are those who look at aging with a wide-angle lens, and note that the big picture is not what the theory predicted. There is far too much genetic consistency to explain aging in terms of stochastic damage or random mutations [30, 31, 60-62]. And against the trade-off theories, there are counter-examples to each constraint that have been proposed to compel the evolution of aging [63]. Second, there is the school of multi-level selection, collecting examples of ways in which evolution has produced adaptations that are good for the broader community, often at steep cost to the fitness of the individual [64]. There is also a well-developed theory of multi-level selection, both from analytic equations [8, 65] and from computational models [66-68]. And third, there are creative and visionary biologists calling for a re-thinking of the fundamental operation of natural selection, based on mechanisms that Darwin never dreamed of [56, 69-72]. These three currents are pulling

together toward a "New New Synthesis" that will carry evolutionary theory into a new century, and will precipitate a re-visioning of aging along the way.

CONFLICT OF INTEREST

The author conforms that this article content has no conflict of interest.

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PATIENT'S CONSENT

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