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An Evolutionary and Genomic Approach to Challenges and Opportunities for Eliminating Aging

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Abstract: While solutions to major scientific and medical problems are never perfect or complete, it is still reasonable to delineate cases where both have been essentially solved. For example, Darwin's theory of natural selection provides a successful solution to the problem of biological adaptation, while the germ theory of infection solved the scientific problem of contagious disease. Likewise in the context of medicine, we have effectively solved the problem of contagious disease, reducing it to a minor cause of death and disability for almost everyone in countries with advanced medicine and adequate resources. Evolutionary biologists claim to have solved the scientific problem of aging: we explain it theoretically using Hamilton's forces of natural selection; in experimental evolution we readily manipulate the onset, rate, and eventual cessation of aging by manipulating these forces. In this article, we turn to the technological challenge of solving the medical problem of aging. While we feel that the broad outlines of such a solution are clear enough starting from the evolutionary solution to the scientific problem of aging, we do not claim that we can give a complete or exhaustive plan for medically solving the problem of aging. But we are confident that biology and medicine will effectively solve the problem of aging within the next 50 years, providing Hamiltonian lifestyle changes, tissue repair, and genomic technological opportunities are fully exploited in public health practices, in medical practice, and in medical research, respectively.

Keywords: Death spiral, evolutionary biology, experimental evolution, genomics, Hamilton's forces of natural selection, Medawar.

A SOLVED PROBLEM OF EVOLUTIONARY BIOLOGY BUT AN UNSOLVED PROBLEM OF MEDICINE

Though cell-molecular biologists have shown relatively little interest in the evolutionary genetics of aging, evolutionary biologists claim to have solved the problem of aging [1-3], in the sense originally posed by Medawar's [4] "An unsolved problem of biology." That is, like Mendelian genetics as a solution to the problem of heredity in animals and plants or Darwin's natural selection as a solution to the problem of adaptation, evolutionary geneticists claim that we have the kernel of a successful explanation for the phenomenon of aging. And not trivially, we claim that we can explain why there are species in which aging is absent [5, 6] and why there are cohorts where it comes to a stop at late ages [7]. We know of no other theory with comparable success where the scientific explanation, or systematic manipulation [8-11], of aging is concerned. We are far from working out all the details, especially with respect to the genomic, transcriptomic, and metabolic machinery involved, though we have made a useful start [12-13]. But that's not unusual in science.

Against this success, there is the unsolved medical problem of human aging, particularly the control or mitigation of human aging. Here the contrast is stark. We are far from having a reliable technology for mitigating the many adverse effects of human aging. Even caloric restriction will probably not have much effect on human aging [14], and it is an arduous intervention that is unlikely to be widely used.

Here we will sketch our rough plan for how to go about solving the medical problem of human aging over the course of the next 50 years. Our technological proposals are based on evolutionary biology and genomics, particularly what they have revealed with respect to the fundamental constraints on tinkering with human aging. But we will be bringing in technological possibilities from across the range of biology, as we are sure that the medical problem of aging is too difficult to be left to any one discipline within biology or, indeed, medicine.

THE CASE OF INFECTIOUS DISEASE: FROM SOLVED BIOLOGY TO SOLVED MEDICINE

It is important to bear in mind that industrialized countries have gone from basic biological insights to transformative medical solutions before. The paradigmatic case for us would be the germ theory of contagious disease. Louis Pasteur, his students, and his colleagues spear-headed the triumph of the microbial explanation of fermentation, infection, and decomposition against the competing "miasma" theory of disease in the late 19th Century. The notion that diseases such as bubonic plague, cholera, and malaria ("sick air") are caused by noxious polluting fumes or *miasma* of the air from filth and putrid decaying matter had lingered for centuries [15-17]. Miasmaticists like Commissioner of the Board of

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Health Sir William Chadwick and nurse-activist Florence Nightingale helped inspire important reforms in sanitation, so the impact of this idea was not entirely bad [17-19]. But even before Pasteur's work, there was dissent from the miasma theory. Dr. John Snow had already proposed that cholera was caused by drinking a contagion found in water [20]. In 1854, Italian scientist Filippo Pacini discovered the microorganism responsible for cholera, *Vibrio cholera*, which was re-discovered in the 1880s by Robert Koch [21, 22], the other figure who played a leading role in establishing the microbial theory of infectious disease. With the waning of the miasma theory, the microbial germ theory of contagious disease was accepted as a scientific solution as definitive as Darwin's solution to the problem of adaptation.

Microbial scientific research in turn eventually led to the widespread adoption of vaccination, sterilization, hygiene, water purification, and so on. We even got some doctors to wash their hands before and after they touched their patients. This range of medical and public health interventions has by now largely solved the problem of contagious disease. In poor areas of the world, infant infections, malaria, and tuberculosis still kill millions of people, as they did everywhere before 1900. But if sufficient resources were made available to such countries, they too could largely eliminate infectious diseases as major sources of mortality. Even the much-feared HIV epidemic has been largely neutralized in countries with advanced medicine, thanks to the use of antiviral medications. In effect, medicine has made infection a minor cause of death and disability for most of the populations of countries with advanced medical technology and ample resources. Contagious disease is thus now a *solved problem* of medicine, as well as science.

THE PHYSIOLOGICAL AND GENOMIC COMPLEXITY OF AGING

To be frank, we are struck by the extent to which some enthusiasts for solving the medical problem of aging resort to the assumption that aging is a simple unitary disease, apparently in order to foment further enthusiasm for the project of solving the medical problem that it poses. Whether those who take this position plump for a single mechanism of aging, such as free-radical damage [23], or a handful, such as the seven deadly sins of SENS [24], we believe that they vastly understate the difficulty of aging as a problem for medicine. Not accidentally, we suggest, such understatement is greatly abetted by overlooking or neglecting the reasoning and findings of evolutionary theory, evolutionary physiology, and evolutionary genomics.

Evolutionary biologists have long suggested that *whenever* there are Mendelian alleles which sacrifice later health, survival, and reproduction for early reproduction, then natural selection is likely to increase the frequency of such alleles [25]. The "whenever" in this sentence is intended to cover *any* allele affecting *any* organ, *any* bit of molecular physiology, and *any* problem of coordination among organ systems. For this reason, evolutionary biologists have been characteristically skeptical of *all* cell-molecular theories for aging that claim to be global and sufficient, including proposals that there are simple interventions which might lead to massive improvements in the human aging process. [But see below for an evolutionarily-based intervention proposal which is relatively simple].

A significant amount of research has been done on the evolutionary physiology of aging in *Drosophila melanogaster* populations that have had their aging slowed or postponed using evolutionary manipulation, some of it collected or reviewed in the book *Methuselah Flies* [26]. This research reveals some of the complexity underlying the physiology of aging in fruit flies, if only because it has proven so easy to find specific bits of physiological machinery that are altered in order to slow aging: slowed development [27], increased stress resistance [28, 29], increased flight endurance [30, 31], increased metabolic reserves [29], and so on. In our own laboratories, and no doubt in others as well, we have still more unpublished data which reveal other physiological machinery that selection alters in order to mitigate the impact of aging.

We are just now seeing useful genome-wide analyses of the molecular genetic foundations of aging. In *D. melanogaster,* genome-wide assays of gene expression have suggested that hundreds of genes have altered expression levels during the course of aging [32], in response to dietary restriction [32], and in response to selection on lifespan [33]. A surprisingly large proportion of the single-nucleotide polymorphisms (SNPs) studied by Teotonio *et al*. [34] proved to be involved in the response to forward and reverse selection on longevity, a result corroborated by Burke *et al*. [35] in their genome-wide, though only modestly-powered, study of the SNPs involved in the differentiation of two sets of populations with contrasting longevities. Again, we have still more unpublished genomic data which underscores these initial findings, supporting the early hypothesis that aging has vast genomic complexity [13, 36].

The ineluctable conclusion, for us at least, is that aging is not simple or easily delineated at the levels of physiology or genomics. However we are to make progress with the medical problem of aging, pretending that aging is mechanistically simple is not going to be productive.

STEP ONE: GETTING ON TO A BETTER AGING TRAJECTORY

Despite this complexity "under the hood," as evolutionists we nonetheless believe that the overarching control of aging by evolution is quite simple: aging arises from the decline in Hamilton's [1] forces of natural selection during the first part of adulthood. That is why we and others have found it easy to postpone aging using lab evolution in which the age at first reproduction is significantly postponed, and thus the decline in Hamilton's forces is delayed [3, 26]. But the idea of manipulating human evolution in this way is an unproductive non-starter; leaving aside the ethical issues, it would take many thousands of years -- far too long [37].

Recently we had another idea of some relevance for mitigating human aging based on evolutionary theory. This idea derives from a scenario in which a population undergoes a substantial change in diet or lifestyle in recent evolutionary time. The evidence we have from experimental evolution suggests rapid adaptation to a novel environment [38], particularly for early components of fitness such as develop-

mental speed and initial fecundity. But Hamilton's forces of natural selection fall with age in almost all cases, yielding weaker immediate adaptation at later ages [7]. Explicit simulations of this have the expected effect: lack of adaptation to the new environment at later ages (Phung *et al*., under review; See Fig. **1**), despite rapid adaptation at early ages. Furthermore, experimental tests of this idea in some of our *D. melanogaster* lab populations that have undergone dietary shifts corroborate this general Hamiltonian mechanism (Rutledge *et al*., in prep.; See Fig. **2**). So the idea works in explicit theory and in careful laboratory experiments.

The implication of this generally formulated bit of theory and its experimental corroboration is that *older* humans may gain significant health benefits, including mitigation of aging, by shifting to diets that resemble those of Paleolithic ancestors. We do *not* expect such benefits to arise at early ages reliably, say before 30-40 years of age. But our theoretical and model-organism tests of this idea, sketched in (Figs. **1** & **2**), suggest to us that a shift to historically accurate Paleolithic diets and exercise regimes might have substantial benefits with respect to the health and function of older people. This is no medical panacea, and it certainly

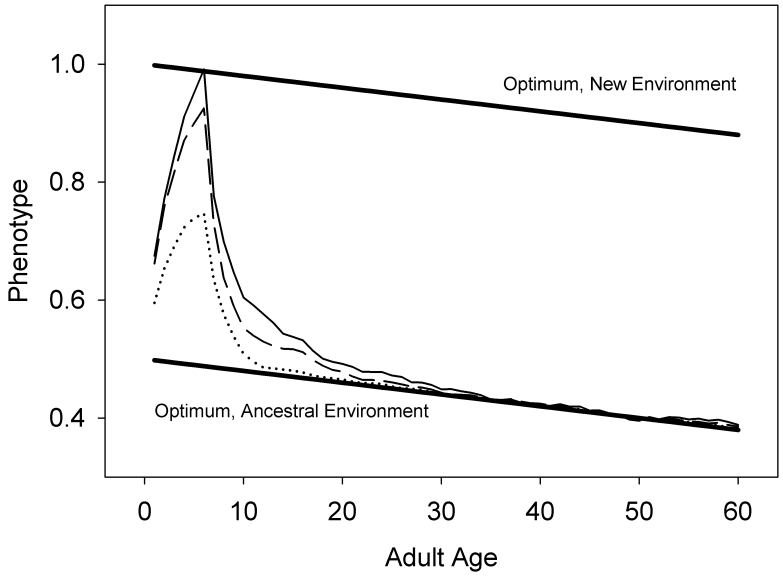

Fig. (1). The straight lines at the top and bottom show the optimum phenotype for new and the ancestral environments, respectively. When an evolving population shifts to a new environment in which the optimum age-specific phenotype is changed, natural selection will tend to move the population towards that new optimum at each age. But it is much faster at this early in adult life compared with later in adult life. The curves in between the two optimum lines show the intermediate steps of the evolving population's phenotype, with the dotted line giving the initial evolutionary response, the dashed line showing a later intermediate step, and the thin solid line showing the evolutionary outcome still later in the process of adaptation.

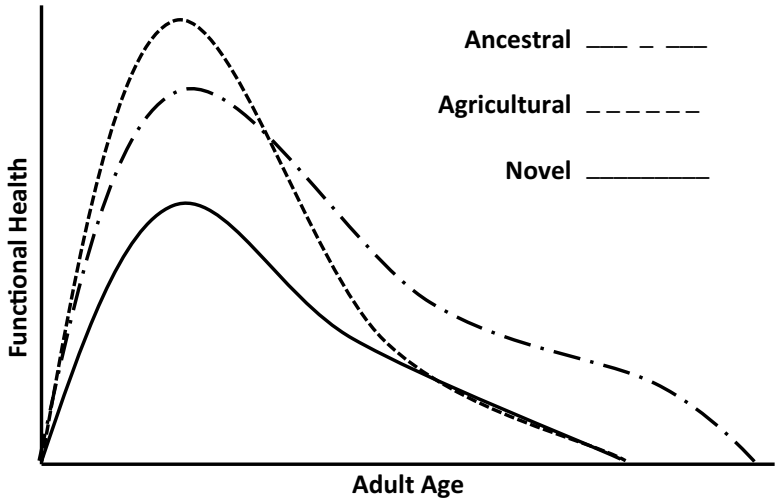

Fig. (2). The indicated functional health measure in our research is usually measured as the product of an individual's probability of survival to a specific adult age and fertility at that age, but other measures are conceivable. The graph schematically summarizes recent data of ours in which individuals fare as well or better on an evolutionarily recent "agricultural" diet as on their ancestral diet, but only at early ages. At later ages, the Hamiltonian diet hypothesis implies that older individuals should fare better on an ancestral diet, when Hamilton's forces of natural selection have weakened enough to have short-changed adaptation to agricultural food. Those given evolutionarily novel "industrial" foods fare considerably worse than those given ancestral foods at all ages.

won't cure or wholly eliminate medical diseases like heart disease or cancer. We are not suggesting that such lifestyle changes are an alternative to effective medical diagnosis or treatment. But this type of lifestyle change could buy some time and some health for older individuals now, when most of our available anti-aging technology is crude and ineffective.

STEP TWO: BETTER EXCISION AND AUTOLOGOUS TISSUE REPAIR

Modern medicine is getting steadily better at surgical excision and tissue repair. In the first respect, the tools for cutting out tissue are becoming steadily more precise, with the advent of better imaging technology and high-precision lasers. In the second respect, great progress is being made with the creation of "autologous" tissues that are derived from patients, particularly pluripotent stem cells, for use in their own repair. Sometimes autologous stem cells can be injected and then find their way to damaged tissues that need to be repaired, there to contribute to regenerative tissue growth. In other cases, local proliferation of cells can be elicited with appropriate signaling molecules. Finally, autologous patient cells can be grown on synthetic, donor, or animal protein scaffolds for subsequent implantation or in situ.

Thus the cut, repair, and replace technologies of medicine are getting significantly better. Such technologies will further enhance the capacity of older people to have their macroscopic damage repaired, from tissues lost to cancer excision to those lost to infarction.

STEP THREE: COMING BACK FROM DEATH SPIRALS

One of the surprising recent turns in our research has been the discovery of a detectable death spiral in *Drosophila*, in which individual flies that are about to die are distinguishably different well before death itself occurs [39-41]. This raises the possibility of discovering ways of reversing likely prospects of death by some specific intervention(s) in an experimental fruit fly context.

Our suspicion is that human patients too often enter death spirals long prior to the death event itself. The identification and aggressive treatment of such patients, particularly with a view to enabling them to escape from the physiological processes of dying, could be a transformative medical strategy contributing to extended lifespans. More modestly, just a postponement in the onset of the death-spiral would add to our productive lives and reduce end-of-life medical expenses.

STEP FOUR: GENOMICALLY-BASED MOLECULAR RE-TUNING

All the *Drosophila* genomic data available to us now seem to indicate that many of the loci that are both transcribed and translated are involved in the modulation of biological aging in fruit flies, as well as many other kinds of DNA sequences. Probably at least some of the latter come from the new class of transcribed but not translated loci concerning which there is much excitement in the research community.

Biology as a whole is far from being able to figure how all this abundant genetic variation controls aging, even in simple metazoan animals like fruit flies. And this is to say nothing of the far harder human case, for which we will never be able to achieve the kind of evolutionary genomic analysis that we have with fruit flies.

But there are some points of hope even in this challenging prospect. First, there is a great deal of orthology between fruit fly and human genomes. It has been estimated that about 77% of the known gene sequences associated with human disease have highly similar sequences in *Drosophila* [42, 43]. Further work has indicated that more than 50% of disease-associated genes across ~20 physiological systems and nearly 40% of other genes in humans have orthologs (not to mention paralogs and other similar sequences) in *Drosophila* [44]. Significantly, a high proportion of those loci identified from gene expression contrasts in *Drosophila* populations of different average longevities have orthologs present in the human genome, well over 80% [45]. This implies that knowledge derived from the genomics of aging in fruit flies might well be of value in parsing the genomics of aging in humans.

Second, the parsing and manipulation of complex networks of information is one of the central technologies of this, the internet era. Eventually, even the genomic complexity that underpins aging in fruit flies will yield to such network analysis. And then the task will be how to exploit our genomic deciphering of *Drosophila* or *Caenorhabiditis* or *Mus* aging in the human context.

Overall, we do not expect much progress on this front during this decade. But at the same time, we regard it as inevitable. And we expect that this hard-core genomic parsing will lead to medical products like effective pharmaceuticals that will better ameliorate, if not eliminate, chronic aging-associated diseases, like Alzheimer's. To revert to our parallel (and not analogy) with the medical impact of the microbial germ theory of infectious disease, it was sometime after Pasteur's chief contributions that effective antibiotics and antivirals were developed, more than 40 years. But developed they were, and with them progress against contagious disease accelerated still more.

CONCLUSION: ENDLESS BENIGN PLATEAUS OF MORTALITY THAT ARE LOWERED GRADUALLY

We are optimistic about the eventual defeat of aging on a scale comparable to our present-day triumph over contagious disease. There are several reasons for our long-term optimism. One of them is *not* that we think the physiology or the genomics of controlling aging are simple, as we have indicated. On the contrary, we think that they are very complex. But this challenge is now, in our minds, only one of sorting out details; the outlines of the task are fairly clear to us. In particular, there are central, scientifically well-established, and promising features of aging that lead us to believe that it can be largely mitigated. We will now list them in order:

1. ***Aging is well understood in evolutionary biology.*** Unlike the confusions and obscurities of much cell-molecular theorizing about aging, within evolutionary biology aging is commonly regarded as a well-understood and

scientifically resolved problem. While molecular reductionists continue to aspire to play the role of "aging theorists," their many failures and retractions do not need to concern those who wish to get on with addressing the medical problem of aging.

2. Aging comes to a stop on its own in many species under sufficiently good conditions. One of the surprising findings of the last two decades is the reasonably firm demonstration that aging eventually stops [46, 47]. This is a finding that evolutionary theory has now explained and studied experimentally [7]; it turns out to be a natural corollary of Hamilton's forces, which eventually plateau and thereby sometimes produce eventual plateaus in age-specific mortality, fecundity, and virility [11, 48, 49].

Human aging used to stop too, often in the early 90s [50]. Now it rarely stops or does so only at very late ages [51]. This we regard as the inevitable outcome of the deterioration in the quality of the human diet and the sedentary lifestyles of most contemporary industrial populations. Specifically, we expect a deterioration in human aging from the severe evolutionary novelty of a life in which vast quantities of junk food are consumed by people who sit in chairs, sofas, and car seats almost their entire waking lives.

Escaping this almost endless deterioration is as simple as improved "organic" diets and chronic activity. With pre-industrial diets and lifestyles, we can hope that people will regain the mortality plateaus that prevailed before the 1920s. With reversion to evolutionarily still earlier diets, such as an appropriate hunter-gatherer diet, and lifestyles later in adult life, it may be possible to arrest aging earlier than the age of 90 years, perhaps as early as 70 years of age. Moreover, if our theoretical work and our experimental findings with *Drosophila* are indeed relevant to the human case, then finely adjusted changes to diet and activity patterns may arrest aging when we are in much better condition.

Note, however, that this lifestyle change is not a complete solution to the medical aging problem, even on an optimistic scenario. Rather, we will need a better developed arsenal of tissue-level repair and genomically-improved pharmaceuticals to proceed to the next step: gradually lowering the levels of mortality, infertility, and debilitation associated with our best evolutionarily built-in aging plateaus. The parallel in medical history would be the difference between the immediate benefits of improved public sanitation, pasteurization of milk, antiseptic surgery, and diligent quarantine – first achieved in the immediate aftermath of Pasteur's work -- and the subsequent development of antibiotics, antivirals, and other more advanced antimicrobial technologies later in the 20th Century. In effect, useful "public health" measures involving aging can be taken now, but we have decades of genomic and cellular research to perform before we can largely obliterate aging as a cause of death.

In any case, it will be far less challenging to modulate a phenomenon that can come to an end on its own, as opposed to a process of deterioration that relentlessly accelerates until nearly everyone is dead [52, 53]. The latter is the demographic pattern of our aging when we subject ourselves to industrial lifestyles. The former was the pattern of aging revealed by human demography in the recent past, a pattern that lifestyle reversion should permit.

3. Experimental evolutionary genomics is a very powerful tool for cracking open complex genetics. We would be more uncertain about the eventual prospects for medically nailing the many network features of the human physiology of aging if we did not already know the extent to which biologists can probe the genomic differences underlying the experimental evolution of aging in fruit flies [13, 35], and potentially mice as well [54]. With enough replication and reasonably sustained selection, even genome-wide analysis of aging becomes remarkably penetrating, at least in model organisms. Further, the substantial orthology between fruit flies and humans provides a warrant for hoping that insights into the genomics of aging in *Drosophila* will prepare the way for effective penetration into the genomics of aging in humans as well [45].

4. Aging is a network and computational problem like many other such problems that 21st Century science is steadfastly focused on. Aging research is vastly underfunded, particularly compared to the practical problems that aging poses for most populations and their governments. And even that small amount of funding is usually wasted on cell-molecular theories of aging as cogent and useful as the miasma theory of contagious disease. But research on network-computation problems like which products one might want to buy, cyberwarfare, terrorist cells proliferating through social media, and economic dysfunction is massive, well-funded, and ongoing. Many of the tools that are being developed for those seemingly more pressing problems will prove to be usable in the deciphering and manipulation of the comparably complex networks of biological function and dysfunction that underlie aging.

While we frankly doubt that the senior authors of this article will live to be 100 years old, we are confident that our present graduate students are likely to, in part because of the technological possibilities that we have outlined here. Absent global war, we are confident that aging will be a solved medical problem well before this century is done, given that it is now a solved scientific problem.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT'S CONSENT

Declared None.

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