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How Evolutionary Thinking Affects People's Ideas About Aging Interventions

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ABSTRACT

Evolutionary theory has guided the development of antiaging interventions in some conscious and some unconscious ways. It is a standard assumption that the body's health has been optimized by natural selection, and that the most benign and promising medical strategies should support the body's efforts to maintain itself. The very concept of natural healing is a reflection of evolutionary thinking about health. Meanwhile, a developing body of experimental evidence points to the startling hypothesis that aging is a metabolic program, under genetic control we are programmed for death. Evolution has provided that the aging program can be abated in times of stress, e.g., caloric restriction. CR mimetics are already recognized as a promising avenue for antiaging research. Beyond this, there are two ancient mechanisms of programmed death in protists that have survived half a billion years of evolution, and still figure in the aging of vertebrates today. These are apoptosis and replicative senescence via telomere truncation. Most researchers have been wary of modifying these mechanisms because they are known to play a stopgap role in cancer prevention. But intriguing evidence suggests that, despite some counter-carcinogenic function, the net result of both these mechanisms may be to shorten lifespan. Thus, interventions that suppress apoptosis and that preserve telomeres may be promising avenues for life extension research. A third element of the body's self-destruction program co-opts the inflammation response. Epidemiological evidence suggests that NSAIDs including aspirin protect against atherosclerosis, arthritis, and some forms of cancer. It may be that aging engages an autoimmune response that can be modified by drugs acting more narrowly on this same pathway. The existence of an evolutionary program that controls aging from the top down supports a new optimism concerning the types of antiaging interventions that are possible, and the likelihood that simple strategies may have dramatic results without dramatic side-effects.

INTRODUCTION

EXPLICITLY OR IMPLICITLY, evolutionary thinking shapes people's ideas of how to address disease and human aging. But evolutionary theory has collided with a body of recent experimental results, which suggests a surprising new picture for the evolutionary meaning of aging.

General principles of evolution have convinced people that human bodies are optimized for health and longevity. If people get sick, it is because something has gone wrong. The preferred approach is to support and strengthen the body's own defenses, so that a "natural" state of health can be restored. When that fails, people seek to repair the damage.

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However, research on the genetics of aging indicates that evolutionary theory has essentially misunderstood where aging comes from, and what is its root cause. These experiments point to programmed death: human bodies do not wear out, nor do they fail because they have been optimized under pleiotropic restrictions, trading longevity for fertility. Rather, human bodies have simply been designed to self-destruct with age.

This is a jarring thesis, opposed not only by individual-based evolutionary theory, but also by cultural values that glorify nature and teach that she has put her best work into humans. Scientists and laypeople alike find programmed death to be an unsettling proposition. But, for longevity medicine, the idea offers great promise: It will be far easier to thwart a metabolic function than to improve upon existing defenses that have already been optimized by millions of years of natural selection.

One must deconstruct the idea of "natural," which has become so embedded in current health values that people may forget from whence it derives. The original argument is that humans, like other living things, were shaped by natural selection and optimized for the conditions that prevailed during most of that time when their genes were evolving. Many of the diseases of modern life can be traced to the stress that has resulted from living and working under "un-natural" conditions (i.e., conditions that differ essentially from those under which humans evolved). It is this kind of thinking that ultimately justifies the idea that herbs should be preferred to manufactured medicines. The "paleo diet" explicitly invokes an evolutionary past in choosing appropriate nutrition. However, there are far more subtle ways in which evolutionary thinking affects research strategies and guides the search for promising interventions to extend healthy lifespan. The origins of aging are not fully understood, but people are certain that the function of medical interventions is to fix something that has gone wrong, or help or stimulate the body's natural repair mechanisms.

What is not considered is that aging may be a program controlled by a pathway of hormonal signals. The idea that all one has to do is jam some of those signaling processes to thwart the progression of aging is not taken seriously. Can it be that simple?

THE EVIDENCE

The idea that aging is a genetic program shaped over evolutionary time and selected for its own sake, is anathema to evolutionary theory. Nevertheless, the evidence for this hypothesis is strong, widespread, and diverse. It comes from recent experiments in genetics and breeding, but it is also implicit in the phenomenology of aging, much of which has been known for a long time. A more detailed recent account[1] of this evidence is summarized in the following.

Tradeoffs sought but not found

Genetic experiments specifically designed to look for pleiotropy have found only soft tradeoffs and inconsistent evidence. If pleiotropy were really the root cause of aging, these tradeoffs should jump out. Michael Rose[2] has been breeding fruit flies for longevity since 1980, fully expecting fertility to decline as longevity increased. He now has flies that live more than twice as long as their wild progenitors and they also lay more eggs every day of their lives than the wild type. At the back of Stearns' textbook[3] is a table of experiments that were designed to look for evidence of tradeoffs between fertility and longevity in diverse animal species. About half the studies find some relationship and half find none. On its face, this indicates that tradeoffs between fertility and longevity are secondary modifiers of aging genes rather than their *raison d'être*.

Caloric restriction and hormesis

The suppression of aging associated with caloric restriction is *prima facie* evidence for the plasticity (under genetic control) of those aging processes. This and other hormetic phenomena lend the impression that the metabolism could slow the aging process, were it only programmed to do so. Theorists[4] have sought refuge in the hypothesis that life extension in calorically restricted animals is mediated by

fertility suppression, but the correlation between increased lifespan and depressed fertility is inconsistent.[5]

Hormesis refers to a strengthening response in an organism exposed to toxins, radiation, or other environmental stress. Paradoxically, living things are broadly observed to live longer when stressed. This suggests that lifespan can be increased without cost or side-effects in response to a more challenging and competitive environment. Forbes[6] reviews a wide range of hormetic phenomena and concludes that fitness hormesis is surprising in the context of evolutionary theory based on individual selection. The essence of the paradox is this: Why is the life extension program not implemented in less challenging times? If genes are available for extending life and, thereby, enhancing fitness, then why is this program ever shut down? Why should animals that have plenty to eat, and are not poisoned, heat shocked, or compelled to exercise vigorously live shorter lives?

Single genes that extend lifespan

Genetic studies of *C. elegans* support the hypothesis that senescence is regulated by genes independently of fertility.[7] Several point mutations have been identified that extend lifespan in a way that suggests this is happening without countervailing cost. Some such genes have homologs that extend lifespan in species ranging from yeast to worms to flies to mammals.[8]

Replicative senescence and apoptosis

The oldest of all senescence mechanisms are replicative senescence and apoptosis. Both have been observed to limit the lifespan of protists, and parallel genetic mechanisms have been conserved over hundreds of millions of years. Telomeres and apoptosis have been observed to be active agents of senescence today, in organisms ranging from yeast to humans.

In higher organisms, it has been hypothesized that replicative senescence defends against the runaway reproduction characteristic of tumor growth. However, it may be that telomeric aging remains an effective senescence mechanism even in higher organisms. In a recent demographic study[9] telomere length was measured from archival samples of blood drawn from 60-year-old individuals. In the ensuing 15 years, people with the shortest telomeres in their blood cells were more than twice as likely to die as those with the longest telomeres.

Apoptosis, too, has long been thought to be a sacrifice of individual cells for the good of the soma as a whole, but recent studies by Longo[10] demonstrate that yeast cells undergo apoptosis when stressed by hunger, for the good of the colony. This is a direct demonstration that apoptosis can be an altruistic adaptation.

Semelparity

Some life histories are organized around a single burst of reproduction. Such organisms generally experience accelerated senescence and die promptly when reproduction is complete. This is one of nature's most dramatic demonstrations of programmed death. Pleiotropic theory insists that the burst of reproduction is responsible for the rapid aging and death that follow, but the evidence is otherwise.

Every gardener knows that flowering annuals wither and die shortly after their flowers go to seed. However, if the flowers are removed before they form pods, the plant can be induced to flower repeatedly over an extended time. If it were the burst of reproductive effort that killed the plant, one would not expect the plant to be capable of replacing its flowers so handily. It is more fitting to regard this phenomenon as a form of programmed death, triggered by the final stages of seeding.

After laying her eggs, the female octopus stops eating and starves to death.[11] Lest one doubt that this is an example of programmed death, the animal's behavior can be altered by surgical removal of the optic gland, which evidently asserts control over a genetic program. Without the optic gland, the animal resumes feeding and can survive to breed another season.

HOW COULD EVOLUTIONARY THEORY HAVE GONE ASTRAY?

This is a question for the history and sociology of science, to which the author can only

outline an answer. Darwin's was a qualitative theory, closely reasoned but with no mathematical content. At the turn of the 20th century, Mendelian genetics was rediscovered and integrated with evolutionary thinking. The earliest evolutionary theorists defined fitness in terms of gene frequency in a population: Fitness was identified with whatever qualities permitted a gene to leave more copies of itself (as a percentage of the population) in the succeeding generation. The Eukler-Lotka equation[12] defined a quantity called the "Malthusian parameter," denoted by ***r***, which was promoted by R.A. Fisher[13] as the mathematical definition of fitness. ***r*** is, in essence, a weighted average of the number of viable offspring created by an individual, with weights that reward fertility early in the life cycle, which leads to a fast rate of exponential increase within the population.

The science of *population genetics* developed over the ensuing decades. A great body of evolutionary theory grew from Fisher's schema and his identification of fitness with ***r***. Alongside the theory, an experimental science of laboratory evolution grew up, which has validated the findings of population genetic theory. This has created the impression among theorists and experimentalists alike that the theory of population genetics is well grounded and has a broad base of experimental support.

The weakness of this structure is that it is based entirely on laboratory studies, rather than field observations. If you ask an evolutionary biologist, he will tell you that field work is too difficult, and that real ecosystems are too messy. The real world seldom presents situations clean enough to test the predictions of population genetics unambiguously. Nevertheless, the great majority of laboratory studies in evolution are based on artificial selection, in which the most successful reproducers of the past generation are rewarded with increased representation in the next. In other words, the experiments have been designed to incorporate the selection criteria that population genetics theory says are the right ones. This is not independent validation, but circular reasoning.

In fact, the best evidence is that the Malthusian parameter is not what is maximized in nature's laboratory. Experiments have dramatically contradicted the predictions of the theory.[14] It is easy to evolve lines of insects or worms in the laboratory that appear to surpass their wild-type cousins in fertility, longevity, growth rate, and every other factor that goes into ***r***.

It is the author's belief that evolutionary theory has failed to take sustainability of ecosystems into account. Maximizing ***r*** generally leads to depletion of renewable resources. The organism that trashes its ecosystem faces prompt extinction. The author has developed this thesis elsewhere,[15] but the ideas herein are not dependent on this particular theoretic framework. The evidence that aging is an independent, regulated developmental program is solid, and new theory will be required account for this; but progress in medical science of aging need not wait on this theory.

IMPLICATIONS FOR MEDICINE

It is a robust prediction of population genetic theory that aging cannot be selected as an adaptation. Aging has only negative effects on individual fitness, and if it has arisen in diverse populations, it must have been as a side-effect, or epiphenomenon of evolution, and not through the explicit action of natural selection.

However, if the theory is wrong, then it may be that humans age simply because of aging genes. There are time bombs built into peoples' developmental clocks that destroy them on cue. It could be that lengthening the human lifespan could be as straightforward as defusing some of these bombs.

Implications for medical intervention are potentially very broad, and new ideas will come from people with an expertise that the author cannot claim. The following examples are listed in the hope of seeding this process.

There is evidence that three mechanisms that protect the body in other contexts turn against the body and (deliberately) destroy it in advanced age. These are:

- Telomeric aging
- Inflammation
- Apoptosis

Although all three systems have protective roles, there is cause to believe that simply downregulating them in old age may have life extension benefits.

Telomeres

There is evidence from historic blood samples that middle-aged people with long telomeres in their blood have greater life expectancies than people with shorter telomeres.[9] Genetically engineered worms with long telomeres live longer than controls.[16]

Inflammation

Aspirin and other nonsteroidal antiinflammatories are blunt instruments that merely damp the body's inflammation response, yet they appear to strengthen the aging human body against arterial disease and, possibly, cancer.

Apoptosis

It has been assumed that apoptosis is a programmed response in diseased cells, which sacrifices the cell to save the body; but there is evidence that apoptosis is on a hair trigger; that is, it is destroying healthy cells on a massive scale in aging mammals. In experiments with mice,[17] knocking out some apoptosis genes has the expected effect of slightly increasing the cancer rate, but the unexpected net effect is substantial extension of the lifespan.

CONCLUSION

An unfounded faith in Nature's benevolence has been steering antiaging research away from some straightforward approaches to antiaging medicine. In particular, several lines of experiment in the last decade suggest that broad systems of aging are controlled by a handful of genes. Expressions of these genes point to upstream controls that provide promising targets for medical intervention. Hormonal systems that trigger senescence may be indicating the royal road to longevity interventions.

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