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A Science-Based Review of the World's Best-Selling Book on Aging

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Dear Editor

Herodatus, the father of ancient Greek history, recorded lore about a what has been termed a fountain of youth 2500 years ago. Innumerable adventurers searched for the legendary waters and countless hucksters sold the dream and/or known false promises to enrich themselves. While age reversal is an old grift, the latest version has reached new heights of feigned legitimacy and hype.

Lifespan: Why We Age and Why We Don't Have To, written by Harvard scientist David A. Sinclair with assistance of journalist Matthew D. LaPlante (Sinclair and LaPlante, 2019), proposes two counterfactual questions on the back cover: "what if aging is a disease—and that disease is treatable."

The second counterfactual attempts to neutralize the first in the sense that if there were a gene or a pill that could treat aging, one could be convinced that we don't have to age. In such a world, people could choose to receive longevity medicine to reverse the disease called aging. There are similar rhetorical setups in Dr. Sinclair's public presentations: what if you could keep your grandparents alive and healthy for another hundred years so that they could meet your great grandchildren? These dreamy counterfactuals transport people away from three basic facts about aging that are not addressed in the bestseller.

First, all vertebrate animal species have a distribution of natural lifespans that are limited by their gene sets—human longevity appears top out at about 120 years (Gavrilova and Gavrilov, 2020).

Second, animal gene sets evolved to allow individuals to acquire food, avoid predation, find mates and successfully reproduce. Long-lived species like humans also provide a substantial investment in caretaking of offspring until they can obtain food, avoid predation and reproduce for themselves. The advantages conferred to youth by parents mean that genetic selections for parental health are extant in caretaking species. Such genetic selections for post-reproductive health are not extant in non-caretaking species (Brenner, 2022a).

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Third, for animals that can mate multiple times, longevity is an emergent property of the ability to continue to do all the things required to reproduce and promote the success of offspring. Animal gene sets have been subject to genetic selections for guile, strength and famine-resistance but haven't been directly selected for longevity because, as a rule, animals are able to successfully reproduce when they are relatively young (Rose, 1994).

Think of it this way: if foxes can reproduce at 6 months, what genetic selections are present for them to live for six years? The ones that live for 6 years might reasonably produce 6 times as many offspring as those who perish in a year but those who die in a year would still contribute to the gene pool so long as they are successful at reproducing. Indeed, experiments done in flies that were selected for the ability to reproduce late in life suggest that hundreds or thousands of genes, not single dominantly acting genes, are modified to allow every organ system to function better over time in the resulting long-lived flies (Burke et al., 2010). However, animals in the wild are under little to no direct genetic selection for longevity beyond that to produce reproductive success.

A more fanciful science of aging is presented in *Lifespan*. According to the book, Sinclair discovered genes called sirtuins that extend lifespan in organisms from yeasts to humans and he found sirtuin activators in red wine and elsewhere. Why do we age? Sinclair's theory is poor information transmission that can be fixed by greater sirtuin function. Why we don't have to age? He says that we can take sirtuin activators every morning and soon, we'll take chemicals that will safely reprogram our genes to restore youthful vigor. Readers can also sign up to measure their age (there will be a subscription for that) and join the author's community of age-hackers who will reverse aging together.

With the book having been translated into dozens of languages, expanded into a podcast, social media outlets, a newsletter, and a tease of sequels, it is high time to examine the book's claims.

Is aging a disease? Age is clearly a risk factor for a wide variety of diseases but aging is not itself a disease. The most powerful mutations ever identified—from worms to rodents—that can extend lifespan inactivate genes controlling growth (Bartke, 2021). Worms and mice with disruptions in these genes are small, infertile, and very long lived, thereby establishing the connection between growth and development and the process of aging. Indeed, Sinclair has voiced support for the idea that aging begins shortly after the fertilization of eggs. Thus, to say that aging is a disease is to pathologize life itself.

Is aging treatable? In the sense that the rate of aging can be modified by genes and the environment, yes. However, aging is easy to accelerate, *i.e.* by smoking, overweight, infectious diseases and other factors, and much harder to slow. Caloric restriction extends animal lifespan when compared to caged animals with constant access to food. However, it is more accurate to say that unrestricted access to food is a life-shortening condition that is unlike conditions in the wild to which animals are adapted (Sohal and Forster, 2014). To be sure, lifestyle changes that improve fitness improve people's health trajectory such that a person can go from an aging-worse lifestyle to an aging-better lifestyle. Getting healthier isn't age reversal though.

Do sirtuins extend lifespan in yeast, invertebrates and vertebrates? Has Sinclair discovered sirtuin activators? Based on 25 years of work by academic and industrial investigators, the clear answer to both questions is no (Brenner, 2022b).

Whereas *Lifespan* claims that sirtuins are dominantly acting longevity genes from yeast to humans (Sinclair and LaPlante, 2019), analysis of the work reveals that in yeast, sirtuin genes help 1 in 5 million cells live longer in one model of aging whereas they shorten lifespan for the entire culture (Brenner, 2022b). Early reports of sirtuins extending lifespan in invertebrates could not be independently replicated. In 2011, researchers from 7 institutions published together that sirtuin genes do not extend lifespan in worms or flies (Burnett et al., 2011). We learned in 2016 that, just as it does in yeast, the fly sirtuin gene antagonizes lifespan extension in conditions of dietary restriction (Slade and Staveley, 2016). While all the positive results made global headlines and are described in *Lifespan*, the negative results have not been amplified by mass media.

Resveratrol is the molecule found in red wine that Sinclair claims as a sirtuin activator. There is a global consensus that resveratrol disturbs the assay used to measure sirtuin activity and generates a false signal (Brenner, 2022b).

Sinclair's theories were *au courant* for two decades. Indeed, sirtuins and resveratrol have been subjects of hundreds of stories in the mass media. A 2008 *New York Times* article reported that sirtuin activators would be developed as diabetes medications that, as a side effect, would extend lifespan (Wade, 2008). The global interest in sirtuins and sirtuin activators was such that companies—most notably GSK—spent many billions of dollars trying to get a positive result and could not because the so-called sirtuin activators don't activate sirtuins and because sirtuins are not longevity genes. *Lifespan* therefore represents a pivot in which a person central to the failure of the largest longevity medicine program in pharmaceutical history turns to the general public to retell his story. In the retelling, sirtuins are longevity genes and sirtuin activators are real.

The tech and cryptocurrency bubbles of 2020–2021 pushed a great deal of private funding into companies in the longevity space. From afar, it may seem like breakthroughs are on the horizon. For example, *Lifespan* tells us that one can rejuvenate mice by partial reprogramming with Yamanaka factors that are used to convert cells from a grown person into stem cells (Sinclair and LaPlante, 2019). *Lifespan* does not tell us that when these treatments are performed on cells in the laboratory, one gets tumors and teratomas (Friedmann-Morvinski and Verma, 2014) and that there is no published study in which even 20 mice have been examined carefully for safety after trying these types of techniques.

Moreover, while the general public is now relatively aware of CRISPR technologies and may think that it will be simple to modify our genome to increase our lifespan, they do not understand that there are no known dominantly acting mammalian longevity genes (and in fact Sinclair's book implies sirtuins are just such genes despite the fact that they don't extend lifespan).

As the premise of the book is that we don't have to age, it is no surprise that the book includes Sinclair's daily regimen, which includes 1 gram of type 2 diabetes drug metformin

in addition to aspirin, resveratrol and three vitamins. While Sinclair tells people these are not recommendations for others, he advertises the page number on social media in response to being asked what to take for longevity. Indeed, there is clear evidence from social media that there are huge numbers of followers that believe that Sinclair is providing them with an inside track to extend healthy aging. The regimen is potentially damaging for individuals without type 2 diabetes as there is strong evidence that metformin use blunts the beneficial effects of physical activity (Konopka et al., 2019). As maintenance of high degrees of physical (Lee and Paffenbarger, 2000) and mental activity (Valenzuela and Sachdev, 2009) are clearly geroprotective and polypharmacy is associated with greater mortality when controlled for comorbidity and age (Chang et al., 2020), the most highly reproduced page from Sinclair's book may be contributing to significant health risks.

In the accompanying *Lifespan* podcast, Sinclair makes innumerable non-evidence based statements about benefits of time-restricted eating, statements about age-reversal as evidenced only by changing biomarkers (Fahy et al., 2019), and even potential immortality by repeatable drug treatments. The latter statements were particularly shocking because one of the drugs used to lower biomarkers of aging was growth hormone, which is clearly defined by genetics as a pro-aging molecule (Bartke, 2021).

For decades, the "worried well" were typically middle-aged people with a high health preoccupation (Miller et al., 1988). Today, at least on social media, longevity followers appear to include a significant proportion of young adults, suggesting that anti-aging fad diets, drugs and practices are being adopted in ways that could add many years of exposure to drugs that lack an evidentiary basis for their off-label adoption.

Sinclair's attempts to commercialize scientific discoveries have an abysmal track record—these include the multibillion dollar investment of GSK in his sirtuin story (Schmidt, 2010) and Ovascience, whose work in female fertility could not be replicated (Powell, 2006; Weintraub, 2016). For scientific discoveries to be developed they need to be real but for books to sell, the stories just have to be good. The reach of *Lifespan* is a problem for the world precisely because a Harvard scientist is telling fictitious stories about aging that go nowhere other than continuing hype as legendary as anything in Herodotus.

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- Members of the general public and investment community have caught the longevity bug and appear to believe that major breakthroughs have been made in extending human lifespan
- Lifespan, a book by Harvard scientist David Sinclair, has become an influential source of misinformation on longevity, featuring counterfactual claims about longevity genes being conserved between yeast and humans, the existence of supposed activators of these genes, and claimed successful age reversal in mice based on partial reprogramming
- The book has popularized a stack of drugs and supplements with significant potential to harm the general public
- The reviewer suggests that scientists and physicians emphasize to the general public that aging is known to be a highly polygenic developmental process and that the most important things that people can do to age better are to maintain high physical and mental activity