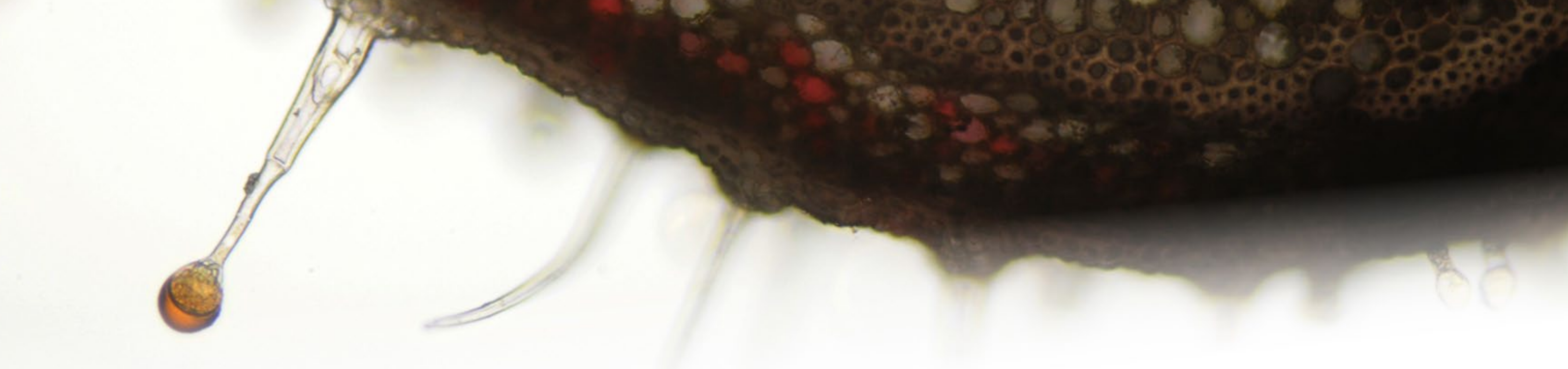

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HISTORY OF MEDICINE: PEER-REVIEWED ARTICLE

Lessons for Responsible Geroscience From the History of Longevity

Nicolai Wohns, MD and Daniel Promislow, DPhil

Abstract
Advances in public health, medicine, and technology since the mid-19th century have redefined what is considered "natural" for human beings. This article situates contemporary geroscience in that historical context. The development of gerotherapies must be guided by historical insight, ethical foresight, and a commitment to justice. Since extending lifespans has important societal consequences, how aging research will affect future generations should be prioritized. Equitable access to gerotherapies, as well as an emphasis on social responsibility and the influence of community on health and longevity, must remain central to any vision of the future of aging.

Transformation of Longevity

Aging and longevity have undergone a profound transformation over the centuries, driven by remarkable advances in science, technology, and public health. Once plagued by high rates of infant mortality and the ever-present threat of infectious diseases, the global population in the modern era has seen average lifespan nearly double in the past 2 centuries.[1] In this article, we explore the historical context of lifespan extension and then turn our attention to efforts by geroscientists to extend lifespan by tackling the underlying biological processes of aging itself. We highlight important lessons from the history of longevity, arguing that equitable access to gerotherapies, as well as an emphasis on social responsibility and the influence of community on health and longevity, must remain central to any vision of the future of aging.

Historical Gains in Lifespan

For most of human history prior to the modern era, life expectancy at birth was relatively constant.[2] As recently as 1860, a person born in the United States could expect to live 39 years.[3] Over the subsequent 100 years, however, life expectancy rose dramatically. More people were surviving birth and childhood, thanks to ambitious social, economic, and public health initiatives. Revolutions in sanitation and nutrition played integral roles.[4] Access to clean water and proper waste disposal reduced the spread of waterborne diseases like cholera and typhoid. Agricultural yields increased dramatically, leading to increased caloric intake and better nutritional states. Improved neonatal care reduced child mortality rates. Furthermore, the development and widespread use of vaccines reduced mortality from childhood infectious diseases like smallpox, polio, and measles.[4] The discovery of penicillin and other antibiotics dramatically decreased deaths from bacterial infections, which were leading causes of death for much of human history.[4] In addition to medical, sanitary, and nutritional improvements, economic and social development played a centrally important role in increasing longevity. Specifically, rising incomes, better housing, and higher levels of education led to better health literacy and healthier lifestyles.[4] These society-wide interventions were a success; by 1960, life expectancy at birth in the United States had increased to 70 years.[3]

As more people survived to old age, cancer, cardiovascular disease, and neurodegenerative diseases emerged as leading causes of mortality and, as a result, became targets for research and intervention.[5] Further gains have been made over subsequent years—average life expectancy at birth was 78.4 years in 2023[6]—in part due to improved treatments for cardiovascular disease and cancer that are both more widespread and more efficacious.[4]

Questioning "Natural" Human Lifespan

Given these dramatic historical changes in lifespan, how then should we conceive of a "natural human lifespan"? Even within a single population, quantitative genetics tells us that, at the individual level, differences in lifespan potential among people are shaped not only by the environmental factors discussed above, but by the genes they have inherited from their ancestors. But these heritable factors account for only 20% to 30% of the variation in human lifespan,[7] and only one or two genes are known to have large effects on life expectancy worldwide.[8,9,10] This fact underscores that the majority of the variation in lifespan among individuals within populations, as well as between populations, is shaped by environmental factors, many of which are modifiable.[11,12]

In this light, natural human lifespan might be conceived as the maximum lifespan, under optimal conditions, for a given genotype. Optimal conditions, to be clear, here refer to environmental features associated with prolonged longevity for a given population, including modifiable behaviors (eg, avoiding cigarette smoking, optimizing nutrition and exercise, sleeping well, maintaining an active social life, pursuing personally rewarding activities), minimizing pathological infectious diseases and risk of accidents, and so on.[11] Thus, "natural" becomes an expression of intrinsic longevity potential modified by extrinsic environmental interactions. Whether or not this view is ultimately correct, it is helpful in one clear way: it brings into focus the contemporary emphasis on aging as a fundamentally malleable and modifiable condition.[13]

But this contemporary emphasis is not entirely new. The idea that environmental factors and lifestyle choices can promote greater health and longevity resonates with similar claims from antiquity. Hippocrates, for example, spoke of the impact of climate, geography, and water quality on health and disease in his treatise, *Airs, Waters, and Places*, which dates from the 5th or 4th century BCE.[14] He also advocated a balanced diet, regular exercise, and moderation in habits as critical for maintaining health and longevity. Cicero, in his essay *De Senectute* from 44 BCE, similarly gives prudent advice regarding diet, exercise, and social interaction for the purposes of healthy aging—advice that would sound familiar to a contemporary reader.[15] Nevertheless, the unrivaled gains in lifespan over the last 2 centuries demonstrate that systemic societal and environmental changes (eg, sanitation, nutrition, workplace reforms) and scientific advances (eg, vaccines, antibiotics) were necessary to make significant progress.

Social and Systemic Dimensions of Lifespan Extension

Three important points emerge from these observations. First, many of the factors that, historically, have increased life expectancy (eg, sanitation, nutrition, workplace reforms, mass vaccinations) do so for everyone; these are societal benefits. The contrary is also true, however: fewer community resources and a relative lack of health infrastructure lead to worse health and shorter longevity.[4] Indeed, in addition to increasing life expectancy, the last 2 centuries saw increasing disparities in longevity between rich and poor countries.[4] Racial disparities in longevity and the socioeconomic inequity that contributes to them remain stark, with certain racial groups experiencing greater improvements in longevity than their racially marginalized counterparts.[16] Access to quality health care, education, and nutritious food often correlates with higher income levels—those with such privileges lead longer, healthier lives.[17,18] Thus, a second important point is that population-wide gains in longevity can mask within-population differences in longevity that reflect and perpetuate social divisions. The health and well-being of those around you—your community—and your community's infrastructure and resources are pivotal determinants of your own lifespan. These points underscore the collective dimension of health and longevity, highlighting that individual well-being is deeply intertwined with communal care.

The history of lifespan extension also teaches us that increasing population-wide life expectancy has deeply enmeshed systemic consequences, affecting family structures, social security systems, health care costs, and workforce dynamics.[19] Societal modernization and growing wealth accumulation and economic opportunities have led to delayed marriage and childbearing, as well as fewer offspring, all of which have reshaped traditional family planning and patterns of schooling.[20] At the same time, the retiree-to-labor force ratio has grown, leading to a rise in the number of years that social security benefits are paid out, which strains the financial viability of the program.[21] Additionally, extended lifespans have historically led to longer periods of managing chronic diseases.[22] Indeed, there is evidence that gains in lifespan have not been matched by proportionate gains in so-called health span.[23] These 3 points—that advances in public health extend life as a collective good yet can deepen social inequities and also drive broad social and economic change—are among the most important takeaways from the history of longevity.

Three Novel Features of Gerotherapy

Looking to current and future efforts, the difficulty in further increasing life expectancy should not be underestimated.[24] Childhood mortality in developed countries is now so low (roughly 5.6 per 1000 live births in the United States in 2023)[6] that further improvements in early-life survival, while of course worth pursuing, will have little impact on overall life expectancy. Furthermore, it has been estimated that even by eliminating all deaths from both cardiovascular disease and cancer, life expectancy at birth would still be less than 90 years.[25]

It is in this light that the emerging era of geroscience represents a fundamentally new approach and offers the potential for further increases in longevity. While there are no current gerotherapies proven to be effective in slowing, halting, or reversing biological aging in humans, numerous clinical trials are ongoing to study their effects.[26] These include studies of the effects of senolytics, which target and eliminate senescent cells that accumulate with age,[27] and of mTOR inhibitors, which appear to mimic the beneficial effects of caloric restriction by reducing inflammation, increasing fatty acid oxidation, inducing autophagy, and enhancing expression of key mitochondrial proteins.[28,29] In 2006, Shinya Yamanaka made the Nobel prize-winning discovery[30] that a set of 4 transcription factors can reprogram mature cells back to an embryonic-like "pluripotent" state; in recent years, geroscientists have suggested that the Yamanaka factors might also be able to turn back the clock on aging.[31]

There are many potential distinctions between traditional public health interventions and gerotherapeutic approaches. Here we discuss three. First, gerotherapy primarily targets mid-life and old age, instead of the conditions of early life. For example, senolytics, mTOR inhibitors, and Yamanaka factors are specifically designed to address and counteract the cumulative effects of aging processes that become more salient as we grow older.[28,31] Second, the *direct* impact of gerotherapeutics is novel, as traditional public health advances have primarily had an indirect impact. Important public health interventions increase lifespan by decreasing mortality from extrinsic sources through the manipulation of disease ecology. For instance, big public works projects like sewer systems, water chlorination, and mass vaccination campaigns all disrupt the transmission of pathogens, leading indirectly to benefits observed at the population level. In contrast, gerotherapeutics are designed to alter the intrinsic mechanisms of aging itself. Rather than mitigating extrinsic mortality risk, these interventions aim to modulate cellular and molecular mechanisms that constitute the very process of biological aging, with direct effects on individual risk of age-related disease. Finally, the era of gerotherapeutics embodies an *individualized* approach to longevity, which contrasts with the public health initiatives of the 19th and early 20th centuries. Senolytics and mTOR inhibitors are being developed as treatments for individuals,[28,31] similar to contemporary treatments for cardiovascular disease and cancer. Taken together, these 3 distinguishing features of gerotherapies mark a shift in strategy vis-à-vis longevity, one that makes it all the more vital to reflect on the historical trajectories that brought us here and the lessons they offer for guiding the future of aging science.

Lessons for Responsible Geroscience

The history of longevity holds several important lessons for thinking about the future. First, serious consideration must be given to how gerotherapeutic interventions could affect future generations. Although it is a matter of some debate whether or not advances in gerotherapy will lead to increased health spans, increased lifespans, or both,[32] we must nevertheless anticipate that if gerotherapies are successful, further shifts in a society's demographic profile will similarly provoke profound disruptions across the socioeconomic landscape. Addressing these diverse effects requires an interdisciplinary approach that draws on the expertise of economists, political scientists, sociologists, health systems specialists, and geriatricians, among others. Second, equity and justice must be taken into account, as the goal is to improve health and longevity for all.[33] If gerotherapies are only available to the privileged, then they will exacerbate inequalities and social divisions. This possibility is particularly important, given the individualized nature of gerotherapy. Third, we must continue to protect, maintain, and expand the population-wide, systemic initiatives that have enabled the great gains in longevity since the 19th century, some of which are under increasing threat. For example, progress in expanding access to proper sanitation facilities appears to be stagnating worldwide, with the absolute number of people without access continuing to rise.[34] Vaccine hesitancy, misinformation, and political polarization are decreasing immunization coverage.[35] And cuts to maternal and child health programs and limited access to reproductive health care in some regions threaten to undo progress in reducing maternal and infant mortality rates.[36] Moreover, we must advocate for these interventions for the health and well-being not only of others, but of ourselves. The health of one's community and environment plays a critical role in determining one's own lifespan. While geroscience represents a fundamentally novel approach to extending lifespans, its success must be complemented by preserving and strengthening foundational public health measures, thereby fostering a future in which longevity gains can be better shared across all segments of society.

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Nicolai Wohns, MD is a physician and doctoral candidate in philosophy at the University of Washington in Seattle. His dissertation research is on the philosophy of aging, with a particular focus on normative and epistemic questions about advances in geroscience.

Daniel Promislow, DPhil is a senior scientist at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston, Massachusetts. Among his honors, he is a fellow of the American Association for the Advancement of Science and of the Gerontological Society of America. He has worked on the biology of aging for over 3 decades, using a variety of approaches to study natural variation in aging in diverse species. As co-founder and director of the Dog Aging Project, Dr Promislow leads a

longitudinal study of tens of thousands of companion dogs from across the United States.

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