

What can we learn from the history of aging research?

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There is currently a massive movement advocating for the enhancement of biomedical research on aging, sometimes referred to as “longevity advocacy” or “longevity activism” [1]. The principal argument of the longevity advocacy movement is that the therapies developed by biomedical research of aging should enable us to directly intervene in the aging process and thus prevent multiple aging-related diseases, thereby extending healthy longevity. This argument is based on the fact that aging is the main risk factor or underlying cause of all chronic non-communicable aging-related diseases, as well as a crucial risk factor for communicable infectious diseases. Hence, a therapeutic intervention into aging should enable the improvement of population health by preventing multiple aging-related diseases (multimorbidity) and compound disabilities that have aging as their common determinative factor. According to the longevity advocates, this increase in the healthy longevity of the population would create vast humanitarian and economic benefits, including benefits for the healthcare and welfare systems, as it would save expenses in these systems by extending the healthy and productive period of life. These savings would consequently free additional resources for further human and economic development. Therefore, there is a need to promote the advancement and support of biomedical research on aging that would be able to supply such therapeutic and preventive means [2]. This is a compelling concept, and it helped explain the importance of aging research to many audiences worldwide, including decision-makers. Yet, the concept is still largely hypothetical and, despite the indications of feasibility, it is still unknown whether intervention into aging will actually help prevent diseases and extend healthy longevity of the population. The confirmation or falsification of this hypothesis is a task of the future.

Can the history of aging research inform and guide the pursuit of this task? How well did the hypothesis about disease prevention by intervention into aging prove itself in practice in the past? Can we extrapolate or learn from this experience? Was aging research actually able to provide preventive treatments against multiple aging-related diseases and for extending healthy lifespan, as it has aimed for? Arguably, by and large, it was not able to create such treatments [3]. If we consider the history of aging research, it furnishes rather few examples of producing powerful preventive or therapeutic means, and little evidence of enabling a significant healthy life extension. Yet, there has been no shortage of excessive promises by some of the “rejuvenators” about producing fantastic results. Consequently, the entire pursuit of rejuvenation, anti-aging and life extension has been often relegated to the realm of quackery. At the same time, perhaps as an attempt of some aging and longevity researchers to avoid suspicions of quackery, they have often exhibited a profound pessimism about the applicability of aging studies to improve aging-related ill health. Many researchers have promised nothing and have not practically committed to bringing new therapies to the world. Many researchers have often expressed the hope that new therapies may eventually emerge thanks to “further research” – with more published papers, conference talks and grant awards, yet with practical outcomes uncertainly looming in the horizon. This attitude may create an impression of research of aging as a branch of mere academic curiosity.

As a result of the above opposing tendencies of no promise at all vs. too much promise, the search for practical anti-aging and life-extending means has been often perceived, alternatively, either as a purely academic, impractical occupation, or as an unorthodox

medical enterprise, bordering of charlatanry, in both cases with little or no practical consequences. Yet, historically, the truth may have been somewhere in the middle. Historically, the studies of aging, explicitly aiming to prolong human life and mitigate and even reverse the aging processes, though generally coming short of the original goals, often constituted a strong, though hardly ever acknowledged, motivation for medical research and practice. At least several modern biomedical fields have originated directly from rejuvenation and life extension studies [4]. These included hormone replacement therapies that were born in Charles-Edouard Brown-Sequard’s rejuvenation experiments with animal sex gland extracts (initially announced in 1889). Probiotic diets originated in Elie Metchnikoff’s dynamic theories of aging and correct living or “orthobiosis” (c. 1900). The development of clinical endocrinology owed much to “endocrine rejuvenation” operations, such as vasoligation, performed by Eugen Steinach and others (c. 1910s–1920s). Tissue transplantations in humans (allografts and xenografts) were first widely implemented in Serge Voronoff’s experiments with “rejuvenation by grafting” of sex gland tissues (c. 1910s–1920s). Cell culture and tissue engineering were pioneered in the work of Alexis Carrel and colleagues on cell and tissue immortalization (c. 1900–1920). Cell therapy, and particularly human embryonic cell therapy, was first widely conducted by Paul Niehans and others for the purposes of rejuvenation as early as the 1930s. Thus, the pursuit of life extension and aging postponement, and even attempts at aging reversal, have been integral and influential constituents in the history of medicine, giving rise to practical medical applications. Notably, the common principle of these studies was the proactive maintenance of stability of the entire organism [4].

Yet, despite these positive examples, we may still reflect on the relatively little practical progress that gerontological science has made since its inception about 120 years ago by Elie Metchnikoff who coined the term “gerontology” in the early 1900s [5]. Sometimes studies of aging are compared to the development of aviation since the early 1900s (since the first successful flight of the Wright brothers), as both fields encourage us to dream of new human capabilities that had not been believed to be possible before. Yet, compare the practical advancement made by aviation during this time (the ability of people to fly) vs. the advancement of gerontology (the ability to prevent aging-related diseases). Arguably, the large increases in life expectancy during this time have mainly resulted from developments in other medical fields (hygiene, vaccination, antibiotics, resuscitation technologies) that were mostly unaffected by gerontological studies. Indeed, in this period, in the study of aging, many observational and computational techniques, experimental models and theories of aging have been created. Yet we should also pause to think how little practical gerontological medical solutions have actually reached the general public to address the urgent challenges of the aging society. Now, over 120 years since the beginning of gerontology as a formal scientific discipline, and after perhaps centuries and millennia that humans have been interested in aging and longevity, no verifiable medical means exist to extend either the lifespan or the healthspan in humans. Neither the species-specific human lifespan nor the relative human healthspan are increasing. And even the general life expectancy – whose increase was a strong source of confidence in the progress of medical science in the past century – in the recent years of the COVID-19 crisis, was declining or stagnating around the world [6]. Arguably, the recent decline and stagnation in life expectancy are in a large extent due to the little ability to ameliorate aging-related

ill-health as the main risk factor also for COVID-19. Only a few biomedical interventions into aging are barely beginning to enter human trials. Some of the most notable of these interventions, such as metformin and rapamycin, have been known for many decades. There is still no agreed clinically applicable definition of aging or aging-related ill health, nor agreed evidence-based measures or evaluation criteria to assess the effectiveness of interventions against these conditions [7, 8]. The specific clinical requirements and regimens for older people are barely examined and addressed, even for traditional lifestyle interventions that have been known for centuries (such as balanced and moderate nutrition, exercise, rest and sleep), and even those known interventions are often disregarded.

This pause to think is needed not for any kind of schadenfreude or despair about the primary human search for longer, healthier and more productive life. It is needed in order to facilitate this pursuit. We need to think what factors have caused the relative lack of productivity of the aging research field that hindered the emergence and dissemination of valuable preventive and therapeutic measures, and attempt to improve these factors. Many methodological problems in the aging research field need to be recognized and addressed. There is a need to develop agreed and evidence-based definitions and evaluation criteria of aging [7], with a more rigorous theoretical mathematical apparatus [9]. There is a need to integrate diverse types of knowledge to comprehend the complexity of aging in a sufficient measure to enable effective and safe interventions. The types of knowledge that should be integrated include not only life-sciences, but should also encompass many other diverse and interdisciplinary domains and branches of science, from physics to environmental to social sciences [10]. A greater integration of history and philosophy is also required. For example, the implications of reductionist vs. holistic thinking in the history of aging research must be more fully understood [11, 12]. The common reluctance of people even to think about aging and seek aging-ameliorating and life-extending interventions, as a psychological coping mechanism, must be recognized and addressed. The development of new aging-ameliorating therapies should not be expected if there is an unwillingness even to recognize degenerative aging as a medical challenge that has to be proactively tackled [13]. We should also consider possible perverse economic and academic incentives and inefficient regulations that weigh against the development of practicable aging-ameliorating therapies. All these and perhaps many other considerations call for a thorough discussion by the academia and the public, to help find solutions and eliminate bottlenecks for the development of therapies. In any case, the primary motivation for these considerations and discussions should be the very human desire to prevent aging-related diseases and extend healthy life that should become a strong public and academic priority. The urgent need to extend healthy longevity, the promise of emerging biomedical technologies, as well as the realization of the little practical solutions achieved so far, may give us all a triple motivation to advance and support aging research, to implement it in practice, so it could live up to its promise and necessity. Let us hope that no more time will be lost, and urgent research and practical actions will be undertaken, so we and our loved ones, and the entire global population, will enjoy verified extended healthy longevity.

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Competing interests

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