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Life extension: a biomedical goal?

Scientific prospects, ethical concerns

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Summary

The potential for development of biomedical technologies capable of extending the human lifespan raises at least two kinds of question that it is important both to distinguish and to connect with one another: scientific, factual questions regarding the feasibility of life extension interventions; and questions concerning the ethical issues related to the extension of life- and healthspans. This paper provides an account of some life extension interventions considered to be amongst the most promising, and presents the ethical questions raised by the prospect of their pursuit. It is suggested that problems concerning the effects of these technologies on health care resources and on intergenerational relationships will be the most difficult to tackle.

Key words: *anti-aging; human enhancement; life extension*

Introduction: human longevity and lifespan extension

The average human lifespan has dramatically increased in the course of human history [1]. A comparison between early estimates of human longevity and data on wealthy countries today shows that life expectancy at birth has nearly tripled. Much of this increase took place in the past 150 years, after the industrial era, and was due to advances in nutrition, sanitation and medicine which brought about a significant reduction in juvenile mortality. This phenomenon is commonly known as the "epidemiological transition" [2]: increasingly, acute infectious diseases declined and mortality risks shifted to older ages, in conjunction with the rise of chronic degenerative diseases.

During the second half of the 20th century a crucial turning point has been reached in the increase of human life expectancy in industrialised countries: "from an earlier era dominated by the decline of acute infectious disease among juveniles, to a more recent era involving the decline of chronic degenerative disease among the elderly" [1]. Since 1970 or thereabouts a more rapid decline in death rates at higher ages is taking place: life expectancy is now driven by the extension of life at more advanced ages [3]. Data collected within national populations show that among the most significant factors affecting this trend is the reduction of mortality rates due to cardiovascular disease and cancer [1].

Biodemographic and epidemiological studies indicate that a significant proportion of the decline in death rates among the elderly in recent decades might be ascribed to medical progress [4]. It is likely that achievements in medical interventions on several age-related ailments, as well as the development of geriatric medicine, directed towards both prevention and treatment, have contributed to this trend. However, this hypothesis is not enough to form reliable predictions on future trends in average life extension. Hitherto the available demographic and epidemiological evidence can only suggest that the hypothesis of a further reduction in mortality at more advanced ages due to medical progress is highly plausible, yet this prospect is not ineluctable. The increase in life expectancy and the constant decline in death rates among the elderly in developed countries results from a complex interplay of environmental, genetic and medical factors [4], and predictions of future trends in average lifespan should be treated with caution. We should not forget that these forecasts are used to determine governmental policies on future health care and other social needs, and could inform public decisions on the financing of pensions and of programmes to support the elderly population [5, 6].

When discussing projections on future trends in life expectancy, researchers in the field of the biology, demography and epidemiology of human aging and longevity disagree on how long a future increase in the human lifespan might be. A survey of over 60 demographers, gerontologists and aging researchers asked to estimate life expectancy for a

person born in 2100 shows that opinions differ widely, with a half of forecasts not exceeding 100 years and a minority of the most optimistic predictions ranging from 500 to 5000 years [7]. These hazardous estimates are not surprising if one considers that interviewees who suggested them are researchers in the field of life extension. They include Michael Fossel, a researcher in the field of telomerase activation as a treatment for cellular senescence and an advocate of strategies to reverse the aging process; Roy Walford, a pioneer in the field of caloric restriction as a means to extend the human lifespan and a member of the crew of the Biosphere 2 project; and biogerontologist Aubrey de Grey, one of the most vigourous proponents of life extension research and editor in chief of the journal *Rejuvenation Research,* who argued that a newborn in the year 2100 would live 5000 years.

Aging as a target for biomedical intervention

This survey corroborates the lack of consensus among scientists about whether research on age-related diseases and on the mechanisms of senescence might lead to the extension of the human lifespan [8]. On the one hand, optimistic proponents of life-extension claim that there are "broken limits" to life expectancy, and that existing knowledge of human aging provides a basis for the manipulation of the aging process itself, which will eventually enhance human longevity [9]. On the other hand, more cautious scientists believe that there are insurmountable "biological limits" to the human lifespan, and that aging is a complex and multifaceted process which cannot be easily manipulated and controlled [10].

Life extension research is part of a larger biomedical field commonly known as anti-aging medicine. Emerging in the 1990s as a pioneering speciality in medical practice, anti-aging medicine has gained increasing consideration in the scientific as well in the public discourse [11]. The goal of anti-aging medicine is to prolong both a healthy lifespan and life expectancy by means of a combination of various techniques, such as advanced biomedical interventions, dietary regimes, physical training and aesthetic procedures [12]. A recent study of the Swiss National Centre for Technology Assessment (TA-SWISS) provides a comprehensive review of the vast array of interventions covered by anti-aging medicine [13].

Proponents of anti-aging medicine have made a number of predictions as to how far life- and healthspans would be extended through a multi-modal medical approach [11]. These predictions, as we have seen, are varied, and one of the reasons for this variation is the difference in opinions as to whether or not anti-aging medicine can be expected to delay the onset of the aging process, or to arrest or even reverse it, thus restoring vitality and function to the aging organism [14]. In addition, all anti-aging scientists agree that aging is a target for biomedical intervention [11]. Indeed, the basic assumption underlying life extension research is that biological aging, or "senescence", is a pathological phenomenon that can be prevented or reversed [15]. This assumption has been partially fuelled by progress in research on the biological mechanisms of senescence and by the florescence of new theories of ageing, which have definitively abandoned the naïve idea of the existence of a "biological clock" that measures the length of human life and activates a destructive process. These more complex views on the mechanisms of senescence – such as the hypothesis that aging results from the accumulation of unrepaired damage in cells, tissues and organs [16, 17] – are much more consistent with the hypothesis that an extension of the human lifespan could be achieved through medical intervention, thus overcoming the present limits to human longevity [18].

This view is explicitly opposed to much of the work that has been done in the field of gerontology to overcome the pathological model of old age developed by the medical profession in the 19th century [19]. This disease-oriented approach to aging was progressively abandoned during the 20th century: aging was gradually distinguished from disease, and the complex relationship between aging and disease began to be untangled. Nowadays, several attempts have been made in gerontology to define the general characteristics of aging, aiming to separate aging from other time-related processes and to clear the relationship between aging and age-related diseases. According to this view, age-related diseases should be distinguished from the aging process, which is not a disease as such, and should not be considered as a pathological phenomenon liable to manipulation [20, 21]. As the anthropologist Courtney E. Mykytyn points out, "anti-aging proponents seek to nullify this rhetoric by speaking instead of aging as the underlying factor so that osteoporosis and the like become a *symptom* of aging itself" [11].

Anti-aging medicine aims to promote research on biomedical technologies that have the potential to counteract or halt the degenerative process we habitually call "normal" or "natural" human aging [12]. Their way of thinking is supported by the bioethicist Arthur L. Caplan, who claims that the very same "naturalness" of aging, i.e., the idea that aging is part of human nature, is at issue [22]. Caplan grounds his argument on the evolutionary theory of aging, according to which senescence is simply a by-product of selective forces and has no particular function [23, 24]. If aging is not a "natural", intrinsic component of evolution, it may be manipulated exactly like any other process deemed as unnatural or pathological [22].

The proliferation of anti-aging practitioners and the increasing relevance attributed to life extension research in mainstream journals and books is partly due to the piloting force of the American Academy of Anti-Aging Medicine (A4M), whose primary goal is to have anti-aging medicine acknowledged as a medical speciality and a field of scientific research [11]. Founded in 1992, the A4M numbers 22 000-plus members representing over 105 nations (http://www.worldhealth.net). The vast majority of them are not gerontologists or geriatricians but rather medical doctors from different specialities such as cardiology, endocrinology, rehabilitation, and sports medicine, not to mention nutritionists, chiropractors and even psychotherapists [11]. The Academy supports national and international conferences, accredits anti-aging practitioners, seeks to attract funding for research in life extension strategies and

lobbies against mainstream gerontology, which accuses anti-aging proponents of being "snake oilers" [11].

The strategy adopted by anti-aging advocates is to put forward optimistic predictions on the feasibility and effectiveness of a range of interventions to prolong healthy lifespan and extend human longevity. A brief overview of some life extension interventions, in particular those that are deemed to be amongst the most promising, may help to clarify their feasibility and provide a basis for further discussion on the ethical implications of life extension as a biomedical goal.

Lifespan extension strategies: foreseeable interventions?

A significant lengthening of lifespan in a variety of species (e.g., yeast, worms, fish, rats and mice) can be induced by caloric restriction [25]. The caloric restriction protocol differs from starvation in that it consists of a lower caloric intake (by 30–70%) associated with wholly adequate amounts of proteins, vitamins and minerals, fatty acids and other nutrients. Basically this experimental intervention increases longevity patterns through the extension of healthy lifespan and the delay in the onset of senescence [26]. To understand whether caloric restriction may have the same beneficial impact on human aging, and how long it should last to produce beneficial effects on humans, studies on the effects of a 30% dietary restriction in rhesus monkeys were initiated. Preliminary results demonstrated that caloric restriction may slow or reduce some age-related physiological changes [27–30]. Findings of a 20-year longitudinal study in rhesus monkeys have recently been published, showing that moderate caloric restriction reduces the incidence of aging-related deaths and delays the onset of age-related pathologies such as diabetes, cancer, cardiovascular disease, and brain atrophy [31]. A few observational studies suggest that caloric restriction has beneficial effects on human health and aging [32]. These include natural experiments such as that conducted by a Spanish nursing home where patients who underwent a 35% reduction in caloric intake over 3 years reported fewer visits to the infirmary and a slight decrease in death rate [33]. Data from a pilot caloric restriction experiment using human subjects (e.g., the Biosphere 2 project) also suggest that the caloric restriction regimen improves several physiological functions in humans [34]. More recently, a review of information gathered in research on caloric restriction in humans shows that risk factors for cardiovascular diseases and diabetes are reduced in people on long-term caloric restriction [35]. These observations are highly encouraging and strongly suggest that caloric restriction may increase longevity and is likely to improve general health and well-being in aged humans. However, some studies have investigated the quality of life and potential "pitfalls" of long-term caloric restriction in humans [36, 37]. Although not clearly addressed in the literature, potential negative side effects may include hypotension, infertility, bone thinning and osteoporosis, and psychological conditions such as depression and irritability. Thus, the caloric restriction regimen used experimentally may not be feasible for most humans. It has been suggested that the development of interventions mimicking the effect of caloric restriction might provide the same health benefits and slowing of the aging process as a rigorous caloric restriction regimen, while avoiding the need to reduce food and caloric intake [37–39].

Besides caloric restriction, several hormone supply or replacement strategies are deemed to contrast the functional decline associated with aging [40]. Hormone treatments may include growth hormone (GH), dehydroepiandrosterone (DHEA), melatonin, testosterone, progesterone and oestrogen. Amongst these, the "anti-aging" action of GH has been widely extolled. In 1990 a noted study reported the effect on body composition of administering human GH for six months to 12 older men [41]. This study unleashed a spate of publications extolling the benefits of growth hormone in reversing or preventing aging [42]. Beyond these claims for GH's miraculous effects, research on GH continues to be promising. Release of GH from the pituitary gland declines with age and reduced levels of GH almost certainly contribute to age-related loss of muscle mass, increase in adiposity and loss of bone mineral [41, 43]. These changes resemble those observed in adult GH deficiency and may be reduced or reversed by GH therapy. However, there is no evidence for effects of GH therapy on life expectancy. It was claimed that, although GH supplementation has been shown to improve some of the physiological changes associated with aging, GH therapy did not prove to be life extending [44]. Indeed, it was suggested that the "anti-aging" action of GH refers to its effects on body composition and functioning in elderly individuals rather than to its role in determining longer lifespan [45, 46]. Still, further uncertainty remains concerning the goals of foreseeable treatments based on GH [47]. Indeed, it is questionable whether they should include preserving ability to work, preserving independence, avoiding need for care, boosting vitality, or simply reducing morbidity. Finally, scientific knowledge of the possible individual risks or unwanted effects for GH-treated patients is still scant and warrants further research. In fact, it is not known whether long-term administration of growth hormone in the elderly is potentially harmful, particularly with regard to the risk of cancer [42, 47].

Research on interventions aimed at prolonging healthy lifespan and delaying the aging process includes reduction of oxidative damage and telome-rase activation. Recent studies have demonstrated that oxidative stress is a major determinant of lifespan in worms and flies, and that it can be counteracted by pharmacological intervention or genetic engineering techniques [48–52]. These studies have proved that strategies designed to counteract oxidative damage postpone the onset of senescence in invertebrate model organisms and significantly extend their lifespan. However, these strategies did not induce a similar extension of the lifespan in mammals, where a more complex control system working via the aging process probably needs more specific and elaborate interventions [26]. As reviewed by Harman, more sophisticated measures to reduce oxidative damage may include, among others, caloric restriction, antioxidant enzymes, superoxide dismutase (SOD) mimics, and dietary antioxidants [53]. At present, however, there is still scant evidence from human studies that interventions

aimed at reducing oxidative stress damage might lead to a reduction in the rate of aging.

There is growing evidence that telomere shortening limits the regenerative potential of organ cells during aging and chronic disease [52]. Telomeres are stretches of noncoding DNA located at the ends of each linear chromosome, which play an important role in cellular senescence due to cell replication. Each cell division results in ever-shorter telomeres and altered telomere structure. It was observed that activation of the telomerase enzyme regenerates telomeres, prevents replicative senescence and immortalises human primary cell cultures [54, 55]. The requirement of telomerase for human cell immortality, together with the observation that telomeres shorten with age, led to the hypothesis that telomere length may regulate cell replicative lifespan in vivo and eventually contribute to aging. The possibility of using telomerase activation to extend the regenerative potential of cells during aging and chronic disease depends on the effects of telomerase activity on tumour formation [52, 56]. Indeed, studies from telomerase-deficient mice suggest a dual role of telomere shortening and telomerase activation during cancer initiation and progression.

Life extension as a morally questionable biomedical goal

None of the potential life extension interventions reviewed in the previous paragraph seems to provide conclusive evidence for future applications in humans. Although anti-aging predictions are much less reliable than their proponents claim, they have a tremendous impact on our understanding of aging and of the scope of biomedical research [11, 57]. Predictions of the feasibility and effectiveness of life extension interventions are tied to the belief that senescence should be considered a painful pathological phenomenon that has to be treated. Such predictions maintain that the surge in population aging might contribute to socioeconomic stagnation or regression, and represents a collective and individual risk that should be counteracted through public health policies aimed at promoting anti-aging interventions [57]. In fact, life extension advocates picture aging as a "global dilemma" and anti-aging medicine as the sole viable solution to the mounting public expenditure on the elderly populations in developed countries [12]. Hence it is not surprising that the voluminous A4M website is named "worldhealth.net".

Although overoptimistic and hazardous, these predictions contribute to the construction of life extension as a biomedical goal, moored to a moral obligation to halt the aging process for the sake of the global population [11]. The pursuit of this goal promises to bring previously unimaginable benefits to mankind, but generates significant worries as well. Of all the arguments that have been put forward against these scientific developments, concerns about distributive justice offer the best prospects for a critical stance on anti-aging medicine and research. Even if life extension interventions should reduce the health care needs of the elderly population, problems may nonetheless arise for other basic resources, such as water or food. In fact it can be predicted that one of the consequences of an increase in the lifespan would be the increase in the population; if this is so, it seems likely that the scientific success of life-extending technologies would impose an unbearable burden on the environment and its resources.

In any case, even if population is equal, the unbalance between the young and old may pose problems of intergenerational justice [58]. The most evident is tied to pensions: the more the ratio between the generations favours the older ones, the more the younger will need to contribute to guarantee the social security of the former. Of course, the younger will eventually be repaid for their sacrifices by a longer life, and the increase in the lifespan should also determine a prolongation of active and working life for the elderly; however, prolonging the working life of people with increased lifespans may not be beneficial for them, and may itself pose further problems of justice. Large numbers of still working, much older people might create serious problems for the new generations striving for success or acknowledgment of their capacities.

Another ethical worry is that, in all probability, life-extending technologies would be implemented for a relatively long time only in the more affluent countries that already have a high life expectancy; this would further widen the gap between resources and opportunities among sections of the world population [59]. Some object to this consideration, noting that all scientific developments have first been implemented in some small areas of the world and have achieved widespread dissemination only with time; life extension techniques would simply follow along the same path [60]. A possible rejoinder is that, unlike other cases, what is at issue is a qualitatively altogether new benefit, to be conferred on some, while a large part of the world population still lacks the resources even to attain the condition that would be "cured" by the new technologies. It is not that we have found a therapy for some disease that previously went uncured, but that we have decided to cure something that previously was not considered a disease; and it could be argued that, as a matter of international justice, uncontroversial diseases with lost standing should take precedence, in the health care agenda, over new and controversial objects of care.

It can also be argued that the prospect of increasing the lifespan of only a part of humankind is morally objectionable because it would create a sort of new, "posthuman" or "more-than-human" race, living alongside the unmodified one. To this it has been answered that such a situation would not be so new and morally objectionable, since it is simply inevitable: it is a fact that, nowadays, there are dramatic differences in the life expectancy of people from different countries, and in fact we could say that parallel populations with very different life opportunities already inhabit our earth [61]. While unpleasant this fact is not unjust, because the fact that we cannot confer a benefit on everyone does not justify or mandate that we confer it on no one, but only that we try to extend it to everyone in due course. As a matter of fact, it is only the spread of certain technologies in the richest areas of the world that may lead to their benefits being extended to the less fortunate areas. Moreover, the advantages conferred by life extension techniques are not positional, that is, they are not inherently dependent on the fact that others are not enjoying them; there-

fore, fairness cannot dictate that we stop seeking them for ourselves, but only that we work to eventually attain universal provision.

A possible rejoinder is that past injustices do not justify new ones; it is true that analogous inequities have been justified in the past, since they were not considered relevant moral failings. However, it must be borne in mind that in those days the world was in no way thought of as a global community, and the injustice of differences in life circumstances among different regions could easily be underrated. The situation is far different today, when we have a much clearer consciousness of the globalised world's interdependency, and a similar attitude may in fact not be justified [62].

Conclusions

Optimistic predictions of the feasibility and effectiveness of life extension should be critically reviewed in the light of their ethical and social implications. Some anti-aging scientists claim that arguments against anti-aging medicine will simply be dismissed by research outcomes [63]. We would claim that the problem is not with the availability of results, but with defining the nature of what we consider "results".

The idea that life extension research will necessarily translate into what some judges interpret as a result (i.e. the cure of aging) is problematic, because the translational process from potential life extension interventions into reality is not only a matter of science. Suppose we have laboratory advances that are promising for the future translation of laboratory work to the clinic. This result would matter scientifically, but would not solve the ethical and social questions of life-extending interventions. Even if we should succeed in the laboratory, the problems of equitable access to such interventions, the impacts of the future implementation of life extension on health care systems, the risk of pressure to make use of life extension techniques – all these issues will still be with us. Here, more than ever, it must be stressed that the "nature" of what we consider "results" matters not only scientifically, but also ethically and socially [64]. Ethical and social debate on these issues is therefore much needed, along with scientific research and discussion.

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