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Aging and the Inevitable Limit to Human Life Span

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Abstract

There is a long-lasting debate about a natural limit to human life span, and it has been argued that the maximum reported age at death, which has not increased for ca 25 years, fluctuates around 115 years, even if some persons live beyond this age. We argue that the close connection of species-specific longevity with life history strategies explains why human life span is limited and cannot reach the considerably longer life spans of several other species.

In recent centuries, humankind did manage to significantly postpone mortality from such causes as violence, famine, and infectious diseases, to such an extent that the main causes of death, at least in the developed world, are now age-related illnesses, such as cardiovascular diseases and cancer [e.g., 1]. Aging, which can be defined as the process that increases disease risk with age, reduces vitality and bodily functions, and eventually brings life to a close, is now the main reason human life expectancy can no longer increase at the same pace as in previous decades, from ca 25 years at birth 2 centuries ago [2] to ca 80 today in the most developed countries. This life span improvement has greatly increased interest in the study of biological aging – biogerontology – and in processes that could postpone death by delaying or preventing components of the aging process.

While there is some evidence for species showing negligible senescence, most notably *Hydra*, at least for 8 years [3] – with other species such as clams living for centuries [4] or even millennia, as coral reefs do [5] – aging appears to be universal in the animal kingdom. The foundation for that remains the theoretical work by such eminent scientists as Fisher, Haldane, Hamilton, Medawar, Williams, and Charlesworth [6]. Their work made it clear that, at least for sexually reproducing species, age-related deterioration and death is an inevitable outcome. While there have been multiple attempts to dispute this general principle, proffering arguments that vary from programmed aging to negative senescence, their case is not strong [7]. Indeed, as argued by Finch [8], we often lack the necessary life span data to conclude that a species does not age.

Most biologists accept the concept of species-specific life span, i.e., maximum life span of a species as determined by its genetic make-up, which in turn is shaped by evolution under a given set of environmental constraints. Hence, maximum life span is intricately interwoven with life history strategies and, in mammals, there is a continuum with short-lived species of small body size, early ma-

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turing with short gestation periods and giving birth at short intervals to numerous offspring (e.g., most rodents) and long-lived species (e.g., elephants, humans) with opposite life history parameters [9]. Thus, life span cannot evolve independently from other life history traits.

In animals, maximum life span is often defined as the mean life span of the longest-lived 10% of a given cohort of that species. Of note, maximum life span should be distinguished from average life span or life expectancy, which is strongly dependent on environmental conditions and life style factors. Maximum life span is much less dependent on the environment: people dying in their 80s about 2,000 years ago were rare but have been documented, and centenarians were observed 2 centuries ago when life expectancy at birth was still very low. However, the first super-centenarians, i.e., people reaching 110 years of age, were documented only some decades ago [10], undoubtedly because of the dramatic increase in the numbers of healthy elderly which only began quite recently. The same is true for animals. For example, mice in the wild rarely live beyond 10 months due to predation, famine or cold [11]. However, in the lab they can live for over 30 months, and it is commonly observed that feral species live longer in zoos than in the wild [12].

Maximum life span for most species remains unknown. For example, naked mole rats have become a favorite animal model for studying aging due to the fact that the life span of that species appears to be very long as compared to a mouse, i.e., at least 10 times longer [13], possibly because it is an eusocial species with only one breeding female, which is linked to a high longevity of the queen, like in monogynous ant species [14]. However, contrarily to ants, the breeding female is not morphologically different from other mole rats and can be replaced by any female. Yet, it is still unknown what the maximum life span of the naked mole rat is. But even for species that have been studied more extensively, such as mice, rats and certain primates, maximum life span can only be estimated. This is because not only have these species not been studied in very large numbers, but we also lack the necessary detailed information about optimal conditions to maintain animals of a specific species for the maximum possible time.

The Case of Human Beings

For humans, the situation was very similar to that of animals in the wild for most of their history. However, the last 2 centuries have seen a dramatic improvement in the human condition accompanied by an equally impressive increased knowledge of human pathology. Today, millions of people reach old age in good health, allowing more of them to become centenarians and a few even super-centenarians. This situation makes humans unique as a species in which we can for the first time test if there truly is a maximum life span. Indeed, the fact that human life expectancy at birth, which has increased from a mere 50 years in the most developed countries in 1900 to well over 80 in 2015, did not show any signs of plateauing off in recent decades has led some authors to conclude that also maximum life span is fluid and perhaps even malleable [15].

If maximum life span in humans is indeed fluid we may see a continuous increase of the maximum reported age at death (MRAD) over time, similar to what has thus far been observed for life expectancy at birth, ever since the human condition vastly improved since the late 18th century. Using data combined from the UK, USA, France, and Japan in the International Database on Longevity and the Gerontological Research Group database, it has recently been shown that while such an increase in MRAD did take place, at least since the 1960s, no further increases were found since about the 1990s [16; see also 17]. This is in spite of the accelerating pace of the increase in the numbers of centenarians over the same period [18]. Therefore, one could wonder if MRAD has reached its natural limit and will never increase again.

As mentioned above, maximum life span does not depend on environmental or lifestyle factors to the same extent as life expectancy. Hence, rather than further improving the human conditions, promoting prevention, and developing new treatments for chronic disease, increasing maximum life span to, say, 150 years or beyond, would surely require intervention in the aging process itself. It could be argued that results with model organisms suggest that this is feasible, based on the discovery of conserved pathways of growth and metabolic processes that when suppressed increase life span as well as health span [19]. However, most model organisms used in aging research (e.g., nematodes, mice, rats) are reproducing in a single season, and increasing their life span when starved is their only means to save reproduction, because they cannot emigrate to discover new food sources (for rodents, see [20]). By contrast, humans reproduce in successive years and can emigrate when facing starvation, like other species do (e.g., elephants). This difference can account for the lack of selective pressure for the emergence of mechanisms to extend life span when humans are starved [21]. Indeed, while dietary restriction (DR) has been very successful in some model organisms, its effect on non-human primates, other than improving health, is minor if present at all (compare [22] and [23]). The positive effect on life span observed in one of these studies [22] could be linked to the use of a bad control diet (discussion in [21]). Thus, it is not sure if modulating metabolic processes by DR or DR mimetics will increase maximum life span in humans.

Is a plateau of 20–25 years, even if during that same period the source of potential new record oldest individuals, i.e., healthy centenarians, is exponentially increasing, sufficiently long to rule out the possibility that in the future the increase in maximum life span will resume, above and beyond 115 years [16]? Time will tell! However, we would argue that human life history strategies make this improbable. Isolated cases of extremely long-lived individuals, maybe even higher than the current record holder, Jeanne Calment, who died in 1997 at the age of 122, will likely continue to occur, but this will probably not affect the plateau, i.e., the MRAD observed during a long period, which has been shaped during the evolution of *Homo sapiens*.

We still know little about the causes of human aging as the ultimate mechanisms that limit life span, but the most likely explanation resides in the logic of life itself, which is based on turnover, with genetic variation and natural selection as the mechanisms that gave rise to the bewildering diversity of life on our planet. Because the life span of a species is linked to life history strategies, a species does not need to live for eternity to thrive, which essentially rules out selection of perfect living systems. Hence, aging is likely due to imperfection, imperfection at the molecular, cellular, and physiological level [see e.g., 24]. Some life history strategies, for instance long gestation and care for few offspring (such as in humans) impose long lives, while other strategies make a long life span useless (many offspring with nearly no care, as in rodents). Therefore, in certain environmental conditions, upgraded mechanisms of somatic maintenance and longer life spans had a selective advantage, which explains the emergence of long-lived organisms such as humans. However, the process of aging continues to operate also in long-lived species, albeit at slower pace as compared to short-lived species. Hence, a limit to life span is something we humans have to live with.

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