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Abstract

The desire to extend human lifespan has spurred much scientific and philosophical interest stemming back to the earliest recorded piece of human literature, the Epic of Gilgamesh, which documents the quest of a mythical king to become immortal. In the intervening years between then and now, and particularly in the last century, human lifespan has increased dramatically. Though it is commonly held that there is an upper biological limit to human lifespan, there are some who believe its recent meteoric rise can continue indefinitely.

The story of human lifespan has two largely separate prongs: that of the important advances in sanitation, agriculture and medicine that ultimately effected the greatest change in life expectancy, and the recurring myth, legend and beliefs surrounding greatly advanced or eternal human life.

In recent years, the myth and science of life expectancy have coalesced, creating a core group of people who believe that immortality is a technically achievable goal. Such claims grossly oversimplify the complexities of human biology and have the potential to mislead the public. Though the science of lifespan is an ever-growing field of scientific research, it is still very much in its infancy and ultimately the paths of science and myth must remain apart.

The desire for immortality has pervaded human culture since the beginning of recorded history; the Epic of Gilgamesh, the earliest surviving piece of human literature, describes the quest of a mythical king living around 3000 BCE who unsuccessfully tries to attain eternal life (Hackler 2006). The history of medicine provides a related story which has played out in parallel; human lifespan has slowly increased since ancient times, owing mainly to increases in sanitation and public health, with our expectation of the upper theoretical limit of lifespan largely based on the oldest known human at the time (Riley 2001).

With the emergence of modern biomedicine, a new assault has begun on the upper limit of lifespan, with some proposing that there is no upper limit to human maximum life span potential (de Grey *et al*. 2002). These claims constitute a unique merger between folklore and science; the topic of immortality is superficially appealing to a wide audience, but many of the claims used to garner attention are highly schematic, theoretical and without firm experimental underpinnings. Such overextensions of very early experimental findings have the potential to deceive the public and to undermine due scientific process.

It is important to clarify the usage of terms such as "lifespan," "life expectancy," "average lifespan," and "maximum lifespan potential," which are frequently used interchangeably. Here, "life expectancy" will be defined as the average number of remaining years a population can expect in their lives. "Average lifespan" will be defined as the mean age at death for a given birth cohort, and "maximum lifespan" will refer to the upper limit of lifespan for a given species. "Immortality" variably refers to a state of continued physical or spiritual existence which can potentially continue indefinitely.

Variations on the theme of immortality have played out in folklore, religion and myth since the Epic of Gilgamesh. In Greek mythology, aging and death were sent by the gods as punishment for Prometheus' disobedience; in Christian beliefs, Adam and Eve were denied eternal life for committing sin. The idea of immortality figures prominently in many religious beliefs but is traditionally confined to the afterlife rather than physical immortality (Edmondson 2005). One exception which was co-opted into popular belief was that the Holy Grail, which was used in the Last Supper and supposed to have caught blood from Christ's side at crucifixion, was endowed with life-restoring and healing properties. The bible also purports that several historical figures lived to extraordinary ages, such as Methuselah, who is said to have died at the age of 969.

Perhaps the most well-known pursuit of eternal life was Ponce de Leon's search for the Fountain of Youth. After hearing tales of a fountain which cured illnesses and could grant eternal youth to those who drank from it, he spent three fruitless years searching Florida and the Bahamas starting in 1512 (Flannary 2002). In a lapse of logic, tales of the Fountain of Youth had been perpetuated because the Arawak chiefs who had set out to find it before de Leon's journey did not return; it was assumed that they were living comfortably in paradise.

In medieval England, alchemists such as Roger Bacon transformed the desire for immortality into a scientific pursuit. Bacon hoped to discover an elixir of life which might also have life-extending properties: "... that medicine which would remove all impurities and corruptions of a baser metal, so that it should become silver and purest gold, is thought by scientists to be able to remove the corruptions of the human body to such an extent that it would prolong life for many ages" (Hackler 2006, 183). Alchemy

was a concerted effort to directly extend human lifespan through experimentation, something which had not been tried before but would prove to be a very popular idea.

The desire to live longer and with a greater quality of life was influenced by many works of civilization in more subtle ways. A survey of the fossil record and dental specimens allows scientists to piece together how average lifespan has changed over the course of history, mainly by examining ratios of old to young in ancient populations (Caspari and Lee 2004). More recently in history, lifespan data is available through mortality data which extends back to the 18th century for some countries (Harman 2006). From this data, we can say with some certainty that average lifespan gradually rose over the past several thousand years, though often perturbed by war, famine and pandemics. Since 1800, average lifespan has risen from a global average of about 30 years to about 67 years, and even higher in industrialized nations; however, such statistics are heavily affected by infant mortality rates, which have declined dramatically due to improvements in childbirth and sanitation.

Theories have emerged which suggest that rather than through the proverbial "magic elixir," average lifespan has largely been determined by sanitation (such as the creation in Rome of the aqueducts), the availability of food (as was afforded by the agricultural revolution), and more recently by public health measures (*e.g*., vaccination; Riley, 2001). The latter have been very effective in lowering rates of infant mortality and have thus influenced average life expectancy figures dramatically over the last hundred years. For this reason, many scientists prefer to discuss life expectancy at a young age past which mortality due to poor infant care is low (*e.g*., the "e_5" value describes average lifespan of a population once its members have reached the age of 5 years).

While improving the survival rates of the young has been an effective means of raising lifespan, authors such as Olshansky *et al*. (2005) hold that such gains cannot continue indefinitely and will likely level off, holding that "past gains in life expectancy have been a product of saving the young … future gains must result from extending life among the old" (Olshansky *et al*. 2005). Indeed, as these authors argue, the unchecked rise of chronic diseases, such as obesity, have the potential to enact an enormous negative impact on average life expectancy in the near future. Critics often point out the remarkably consistent linear increase in average lifespan, at a rate of three months per year for approximately the last 160 years (Oeppen and Vaupel 2002). As a result, there is a wide range of opinion among experts on future trends in life expectancy, which makes predictions of vastly increased lifespan more difficult to refute, and opens the doors for broad statements about the virtues of certain purported "life-extending" discoveries.

This pairing of uncertainty with bold claims is a hallmark of the scientific field of aging science (biogerontology). The field has grown tremendously since the 1950s when Peter Medawar called aging "an unsolved problem in biology" (Holliday 2006). It is illustrative

to examine some of the prominent findings and theories in aging research and to compare the current state of knowledge with the much-publicized claims of how old we can potentially be (or perhaps better put, for how long we can possibly feel young).

Cellular dysfunction plays a central role in modern theories of aging, in which molecular damage leads to cellular pathology, cellular damage leads to tissue pathology, and tissue damage contributes to the overall function of the organism (Rando 2006). Molecular damage to cells is caused and prevented by a variety of factors and has been the focus of much recent aging research.

The concept that the cell is the fundamental unit of aging was first recognized by Leonard Hayflick (1965), who found that cells can only divide a certain number of times *in vivo* (the "Hayflick limit"). As cell division proceeds, repeating sequences of DNA on the ends of chromosomes (telomeres) become progressively shorter, which makes DNA more susceptible to mutation and damage, and changes its shape and structure, thereby affecting gene regulation (Ahmed and Tollefsbol 2001). This progressive shortening of telomeres begins after conception, when cells begin to differentiate, and progresses until cells reach their Hayflick limit. Beyond this finite number of cell divisions, cells enter a period of senescence (aging) in which they cannot proliferate and accumulate damage and mutations (Flanary 2002).

Telomere shortening is opposed by an enzyme called telomerase, which can add additional tandem repeats to the end of chromosomes to allow further division. Telomerase is not expressed in most somatic cells with a limited proliferative potential, but is present in germline cells, stem cells and cancer cells (Ahmed and Tollefsbol 2001). In addition, human fibroblasts, which normally have a Hayflick limit of around 50 divisions, can divide more than 500 times when transfected with telomerase, suggesting that the presence of this enzyme can prevent cell senescence (Bodnar *et al*. 1998).

Molecular damage to cells may occur in a number of complex and likely interrelated ways, including oxidative damage to proteins and DNA, inadequate repair of such damage, chronic inflammation, accumulation of debris that interferes with cell function, and nervous or endocrine dysfunction (Fontana and Klein 2007). In those cells which are no longer able to divide, damage eventually leads to cell death, and this loss of cells can accumulate over time to impair the function of the nervous system or cause tissue atrophy.

Aging related to oxidative damage to cells is known as the free radical theory of aging, which holds that metabolic processes in the body produce free radicals, most prominently in the mitochondria, which in turn cause damage to DNA and proteins (Harman 2006). A direct corollary to the free radical theory is the idea that restricting metabolism by limiting calorie intake will reduce this type of damage, and research into this approach to

extending average life span goes back to the 1930s. In a recent review of the literature on calorie restriction to date, Fontana and Klein (2007) conclude that calorie restriction with adequate nutrient intake may directly affect lifespan in humans, but this is unclear due to a lack of reliable biomarkers for aging. Calorie restriction may also indirectly increase lifespan and quality of life by reducing rates of chronic disease.

It is unlikely that calorie restriction will be widely adopted because of the difficulty of adhering to its strict dietary requirements. As a result, several threads of research into "calorie restriction mimetics" have emerged in the hope of exploiting biochemical pathways in the cell through which calorie restriction may act. One prominent compound which is touted as a potential calorie restriction mimetic is resveratrol, which is found in peanuts and grapes (Ingram *et al*. 2006). Resveratrol is thought to act through the SIRT1 pathway, and may extend life expectancy in humans, but toxicity and efficacy have not been established.

Rather than simply attempting to minimize cellular damage, life extensionists, or "biomedical gerontologists," approach the components of aging as parts of a disease process which can potentially be cured through technical advancements. By slowing and reversing individual processes of aging, life extensionists believe it is possible to perpetually extend life such that mortality remains the same with increasing age. Recently, this approach was formalized in the form of SENS, or "Strategies for Engineered Negligible Senescence" (de Grey *et al*. 2002).

SENS proposes that the cellular and molecular mechanisms of aging can each be targeted by nascent therapies, and that the aging process can be slowed and even reversed. Specific examples of such therapies include deletion of telomerase genes for cancer-causing mutations, phagocytosis of accumulated extracellular debris, addition of genes coding for proteins which destroy other accumulated debris, destruction of senescent cells and their replacement by stem cells and growth factors, and a number of other genetic engineering and chemical augmentation strategies (de Grey *et al*. 2002).

Some of these therapies appear to be at least partially viable at present, while others remain in the realm of science fiction. However, even some of the more familiar ideas such as the use of stem cells may be overblown. Rando (2006) describes the possibility of stem cell "therapeutics" to delay the aging process as "remote" given the current understanding of how stem cells function in different cellular environments, such as that in the aging body. The biology of stem cells, their environment and the interactions between the cell and its environment becomes even more complex in chronic disease states.

The gulf between the reality of where aging research currently stands and the claims of life extensionists may be a function of how scientific funding, research and practice are

structured. In order to validate requests for research funding, researchers must have clear goals, milestones and obstacles to tackle (Mykytyn 2006). Although the aging process is multifaceted and its concepts difficult to organize, researchers must attempt to do so to make it seem like a tractable problem. However, to declare a list of "problems" in the biology of aging to be progress is teleological; this type of thinking relies on the assumptions that these problems can each be solved, and that solving one or several of them will have substantial bearing on the aging process.

With increasing awareness of life extensionists' claims come some dangers, notably the financial gain of individuals or companies eager to exploit public desire for health and longevity. We should not forget the consequences that successful life extension research might bring; would extended life be extended to all, or just a privileged few if it were technically feasible? How, in a medical system already strained by wait times and financial limits, would we find the resources to provide age maintenance therapy when one's proverbial oil was running low? How would extended life affect the family unit, demographics, or the already wide socioeconomic gaps in society?

Referring back to history may provide some caution when considering the future of anti-aging medicine. Charlatans and snake oils abound in history, and should serve as cautions against rapid adoption of new ideas which have not yet stood up to scientific rigor. In the words of Jay Olshansky, "What do the ancient purveyors of immortality all have in common? They are all dead" (Olshansky 2004). Perhaps, like Gilgamesh, we must realize that though we will all die, wisdom lies in accepting our mortality.

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