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Will Human Life Expectancy Quadruple in the Next Hundred Years? Sixty Gerontologists Say Public Debate on Life Extension Is Necessary

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ABSTRACT

Sixty gerontologists were asked for estimates regarding the development of future life expectancy. For a person born in the year 2100, life expectancy estimates had a median of 100 years and a mean of 292 years. Changes in biogerontology suggest that the search for the "fountain of youth" is gaining respectability, becoming competitive with compression of morbidity as the predominant scientific goal. Appropriate debate should address questions raised by such a goal and prepare for sudden advances that may have a large impact on society.

INTRODUCTION

GIVEN LIKELY SCIENTIFIC PROGRESS over the next century, could the average life expectancy at birth (now approximately 75 years in developed nations) increase to 292 years? Within a historical perspective, such a prediction is certainly dramatic. In the twentieth century, life expectancy roughly doubled. What justification exists for extraordinarily optimistic projections, such as a quadrupling of life expectancy? Over 60 demographers, gerontologists, and aging researchers (Table 1) were asked to estimate life expectancy for a baby born in the year 2100. The mean estimate was 292 years. None of those interviewed thought that life expectancy would decrease (as it apparently has in Russia and other former states of the USSR): half thought that a year 2100 newborn would live at least 100 years old (the median), while nine interviewees provided estimates ranging from 200 to 5000 years.

Press reports asserting breakthroughs in genetics and in drugs targeting specific age-related diseases provided the impetus for this survey. Most such reports include unsubstantiated claims that are difficult to put into scientific perspective. In the current survey, rather than analyzing nuances, scientists provided a single number: the average life expectancy for a baby born in 2100. In some respects, this approach parallels the stock market, in which the share price reflects investor confidence. Similar methods have been employed in more scientific venues, such as www.foresight.org. One researcher[1] has used this method to predict the outcome of political elections with 30 percent more accuracy (and at considerably less cost) than conventional polling services.

While no one can know or reliably predict the life expectancy for a newborn in 2100, what these figures accurately convey is the belief of many scientists that there will be a large increase in life expectancy. Such a potential increase should therefore be taken seriously. In the case of the greenhouse effect, it was the perceived threat and a majority of scientific belief, not proof, that convinced many governments to act. We are bombarded by scientific and government conferences, newspaper discussions, and public campaigns on the greenhouse effect, but there is little corresponding concern for a potentially marked increase in life expectancy. This is disappointing to many gerontologists. According to Knook, "The discussions in gov-

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ernment bodies are usually about increases in life expectancy on the order of months, but I frequently ask 'Suppose there is a real breakthrough?' No one is prepared for that."[2]

A HISTORY WRITTEN BY CHARLATANS

Blame lies at least partly with gerontologists, many of whom consider speculation about fu-

TABLE 1. 60 QUESTIONNAIRE RESPONDENTS

Name	*Affiliation*	*Average life expectancy (for a newborn in the year 2100)*
Heinz Osiewacz	Goethe University, Frankfurt/Main Germany	75
Alan Hipkiss	Kings College University of London, UK	80
Rajindar Sohal, Ph.D.	University of Southern California, Los Angeles, CA	80
Bengt Winblad	Karolinska Institutet, Stockholm, Sweden	83
Morris Rockstein (Emeritus)	University of Miami, Miami, FL	85
Georg Wick	Universiteit van Innsbruck	85
Vincent Monnier	Case Western Reserve University, Cleveland, OH	90
A. Sancar	University of North Carolina	90
J. Mueller-Hoecker	Ludw-Maximilians U Munchen	90
Lester Packer	University of California at Berkeley	90
Giuseppe Attardi, Ph.D.	California Institute of Technology, Pasadena, California	90
Gino Cortopassi	University of California at Davis	90
Nikki Holbrook	Gerontology Research Center; NIA, Baltimore, Maryland	90
Tom Kirkwood, Ph.D.	University of Newcastle, UK	90
Steven Aust	Utah State University	90
David Gershon	Technion Israel	90
James W. Curtsinger	University of Minnesota	90
Sten Orrenius	Karolinska Institutet, Stockholm, Sweden	90
I. Mathias Jucker	University of Basle	92
John Wilmoth, Ph.D.	University of California at Berkeley	95
Judd M Aiken	University of Wisconsin	95
Thomas von Zglinicki	University of Newcastle	95
Richard JC Adelman	University of Michigan	100
Arlan Richardson	University of Texas	100
Jaime Miquel	NASA (Emeritus)	100
Eino Heikkinen	University Jyvaskyla, Finland	100
Andrus Viidik	University of Aarhus, Denmark	100
Denham Harman, M.D., Ph.D.	University of Nebraska	100
Barry Halliwell	University of Singapore	100
Steven N.Austad, Ph.D.	University of Idaho	100
Robert Arking	Wayne State University	100
Paula Bickford	University of Colorado	100
Kenichi Kitani	National Institute of Longevity Sciences, Japan	100
George Roth, Ph.D.	NIA, F. Scott Key Center Baltimore	100
Hans Joenje	Vrije Universiteit Amsterdam, The Netherlands	100
James Vaupel. Ph.D.	Max Planck Institut, Germany	102
J. H. Hoeijmakers	Erasmus University, Rotterdam	105
Ben van Houten	NIEHS North Carolina	105
Balz Frei	Oregon State University	110
Dick Knook	Centrum voor Verouderingsonderz, TNO Leiden	110
H. Niedermuller	Veterinaire Universitaet Wenen	110
Vincent Cristofalo	Thomas Jefferson University	120
Vladimir N. Anisimov	Petrov Research Institute, St. Petersburg, FL	120
Brian Clark	University Aarhus DK	120
Michael R Rose, Ph.D.	University of California at Irvine	130
Richard Weindruch, Ph.D.	University of Wisconsin in Madison	130
Vladimir Khavinson	Institute of Bioregulation and Gerontology, St. Petersburg, FL	130
Shripad Tuljapurkar	Mountain View Research, CA	130
Claudio Franceschi	Universita di Bologna, Italy	150
Olivier Toussaint	Universiteit van Namen	170
Elizabeth Blackburn	University of California at San Francisco	175
Alexander Sidorenko	UN Program on Aging	200
Jan Vijg	San Antonio Cancer Institute, TX	200
Gordon Lithgow	University of Manchester, UK	200
Simon Melov. Ph.D.	The Buck Institute, Novato, CA	200
Michael Fossel, M.D. Ph.D.	Michigan State University, Ada, MI	500
Roy Walford, M.D. (Emeritus)	UCLA, Los Angeles, CA	600
Joao Pedro Magalhaes	Universiteit van Namen	1,200
Robert Bradbury	Independent; Seattle, Washington	2,100
Aubrey de Grey, Ph.D.	University of Cambridge, UK	5,000
Average Age		292.70

ture life expectancy to be taboo. This is understandable, as the history of the field has largely been written by quacks and charlatans claiming to have discovered the Fountain of Youth—be it monkey glands, yogurt, herbals, transcendental meditation, or alleged centenarian lifestyles in the Caucasus mountains (generally fraudulent centenarians). Most gerontologists, wanting to be perceived as serious scientists, avoid discussions about life extension when possible.

Although the high estimates of some scientists may be surprising, many of those interviewed stated that they chose a relatively conservative figure, believing it "unethical to raise false hopes." Some felt that there is so much suffering among geriatric patients in nursing homes today that we had better add more vitality to their final years and relieve their suffering, instead of extending that suffering by adding more years to an already decrepit life, confusing lifespan with prolonged pathology. Their underlying concepts, such as successful aging and compression of morbidity, which have been gerontological gospel for several decades, have recently come under attack.[3,4]

Such criticism suggests that, while scientists should avoid raising false hopes, they also have an obligation to alert society to potentially dramatic change. A quadrupling of average life expectancy to 292 years may be desirable for the individual, but may have negative consequences for society in general.[5] De Grey calls aging a "barbaric phenomenon that shouldn't really be tolerated in polite society" and is optimistic, estimating life expectancy as 5000 years.[6] Regardless of whether such a high number will ever be reached, the current trend of increasing life expectancy is very likely to go on, and public debate is needed to mitigate the profound social implications[5] as well as more trivial concerns, such as potentially disruptive arguments over the ownership or legal rights to life-extension technologies.

Tuljapurkar's previous study on increasing life expectancy used a 2050 time horizon.[7] At my request (personal communication, 2001), he extended this to 2100, resulting in a life expectancy estimate of 130 years, perhaps the most scientific of the estimates in the survey. Lacking data, the implications of ongoing genetic research was not allowed for in Tuljapurkar's forecast. In his original report, he criticized the governments of the Group of Seven highly industrialized countries (G7) for poor planning for future pension funds: "Compared with official forecasts, we predict that in 2050, Japan will need to spend 39 percent more on the retired than they currently expect to. Our forecasts imply that even currently pessimistic projections of the costs of pensions and other costs of an aging society are underestimates."[7]

In the literature,[5,8] overpopulation is mentioned as a possible negative consequence of increasing life expectancy, but those surveyed here did not see this as an insurmountable problem (personal communications). Birth rates are more important to population growth than are death rates, and birth rates are projected to decline.[9] This decline may be all the more precipitous as a result of increasing life expectancy. Kirkwood and Westendorp[10] have shown a strong negative correlation between fertility and life expectancy. Where women have many children each (multiparity), their life expectation declines; conversely, living longer increases the likelihood of fertility problems.

"SUCCESSFUL AGING" IS IMPLAUSIBLE

Another point of debate is whether "successful aging" is biologically plausible.[3] This concept implies that one remains uniformly healthy until old age and expires suddenly, presumably in one's sleep. Participants at a meeting organized at UCLA found this scenario unrealistic.[6] Apart from accidents, homicide, and suicide, an increasing incidence of disease before death is difficult to avoid. This in borne out by the increased incidence of undiagnosed disease in the elderly. Many older men, for example, have prostate cancer discovered only at autopsy.[11]

Undiagnosed disease may be "successful aging," but most people prefer to find occult disease when it can still be cured. Apart from the biological and medical barriers to successful aging, "it is also very far from what elderly people actually do see as desirable—the fitter they are, the more they wish to live, regardless of how old they are. Thus, public and professional policy regarding biogerontology research is in dire need of re-examination, since this policy does not presently reflect the expectations of laymen."[12]

Since chronic diseases increase with age, De Grey proposes that, instead of working to develop individual therapies against a myriad of age-related diseases, we should attack the process of aging itself. After all, if one didn't age, one's chances of getting cancer or heart disease would be enor-

mously reduced.[13] Whether this strategy will succeed or not, it is seen as the road to be taken. Many gerontologists, however, are concerned that such an approach will blur the distinction between quacks and scientists.[27] Ironically, some gerontologists are already back where gerontology began: explicitly searching for the fountain of youth, albeit under more euphemistic rubrics, such as "engineered negligible senescence" or "non-detectable aging." The difference between scientists (with equipment, journals, and critical peer review) and charlatans is unlikely to be lost in the fray. Quacks, mountebanks, and charlatans will always be present, and their presence is no reason to avoid the ubiquitous questions of the public: "Could I live longer?" or "Could I live a lot longer than the average person my age is currently expecting to live, and if so, what would I have to do to make it happen?"

This issue is distinct from that of immortality. Regardless of seemingly magical achievements of science and technology, the grim reaper will always be waiting in the wings in the form of accidents, homicides, and suicides.[5] But as Alexander Sidorenko, chief of the United Nations Program on Aging, put it, referring to "do not resuscitate" orders, "it will also be more and more acceptable for people to make their own choice about how long they wish to live" (personal communication, 2001). This is exemplified in a new Dutch law on euthanasia and the continued debate about this in most countries. Sidorenko estimates a life expectancy of 150 years, although he stresses that this is not the official UN-position on this point.

AGING IS NOT ITSELF A PROGRAM

How realistic is such speculation? The Gompertz curve, dating from the nineteenth century, predicts how many people in a cohort will reach a certain age. Given current data on life expectancy, the Gompertz curve suggests that an average life expectancy of 292 years for a person born in 2100 is impossible. But as De Grey argues: "In 1900, similar logic would have firmly predicted that the minimum time taken in 1950 to travel between London and New York would have to be several days."[13] The advent of powered flight made this estimate wrong by more than an order of magnitude. But on what pending developments is the enthusiasm of those in our survey based?

One of the first is disposable soma theory, which explains aging as a by-product of evolution (the "blind watchmaker," uninterested in consequences), and suggests that aging is not supposed to make sense.[15] Evolution optimized our biochemical machinery for species reproduction. From the evolutionary perspective, what happens post-reproductively is irrelevant. It is like a house with no occupants: it is not maintained and finally collapses as a result of indifference.

More precisely, aging is not a specific program intended to slowly destroy a living being so as to create space on an otherwise overcrowded planet. There is no such thing as a single "death" gene that is responsible for aging. Reasoning by contradiction, if there were such a gene, then, as a result of inevitable point mutations in copying, a small number of individuals would be born without this gene and would live forever. This subspecies being would have a reproductive advantage, and, as a result, many more immortals would be born. Since this is not the case, there is apparently no single or small group of aging genes. Aging, then, is an epiphenomenon, the side effect of our genetic endowment for developing into an adult that essentially runs out of new instructions. There is no new genomic programming waiting in the wings, as in the case of a caterpillar that has yet to become a butterfly.

There are, however, several longevity determining or gerontic genes that appear to make humans more resistant to wear-and-tear over time.[16] This is apparent from an analysis of the relatives of Madame Jeanne Calment from Arles, France, who lived to the age of 122 (and smoked most of her life). Many of her relatives lived considerably longer than others in their cohort.[17,18] Other studies[16] confirm this, and show that while the chance of dying seems to increase exponentially with age, it apparently lowers slightly after 80–85 years of age.[15,19] At the age of 105, for example, your chance of dying, while not negligible, is actually less than is that of a 79 year old. These and other studies suggest that lifespan is, in principle, mutable.

At the beginning of the last century the major killers were infectious diseases such as diphtheria, tuberculosis, influenza, and pneumonia and average life expectancy at birth in the United States was only 47 years.[20] At the beginning of the present century the current major killers of our post-antibiotic age are chronic diseases such as cardiovascular disease, cancer, and stroke and

average life expectancy at birth has risen to 76.9 years (73 years for males and 80 years for females).[21] Age-related diseases were present all along, waiting to be uncovered by the widespread elimination of infectious disease. What if chronic diseases were also largely eliminated by medical progress over the next fifty years? Would there be a corresponding advance in average life expectancy? Some, including Hayflick, suggest otherwise: "The complete elimination of these three diseases, by whatever means, could only be expected to add just 15 years to average life expectancy."[22]

What new diseases may be waiting in the wings to be uncovered by the potential elimination of heart disease, cancer, and stroke? Future major killers may be the diseases of the natural aging process, diseases afflicting today's supercentenarians, who are typically blind and deaf. Such diseases are characterized by molecular infidelity, in which organelles within cells are no longer able to perform their functions, leading to the loss of tissue and organ function, and ultimately to the failure of the entire system.

WHAT IS GOING ON IN THIS FIELD IN PRACTICE?

Over the past decade, vitamins and antioxidants have drawn considerable attention, but initial enthusiasm has received little scientific support. There is no doubt that antioxidants play a major role in survival, but intrinsic and baseline dietary antioxidants work sufficiently well that supplementation offers relatively little benefit. According to the editor of this journal, "there are no currently available substances that affect fundamental aging" (M. Fossel, personal communication, 2001). The potential remains, and antioxidants and other substances with life-extending capabilities are constantly being sought after and investigated. One example is ALT-711 (Alteon Pharmaceuticals), now undergoing phase III clinical testing for hypertension. This compound can increase vascular flexibility and make endothelial surfaces smooth, thereby lowering blood pressure.[23] The rejuvenating effect of ALT-711 is due to reversal of crosslinking, with its attendant loss of tissue flexibility and integrity. Whether this is clinically effective remains to be seen, but there is little doubt of the mechanism. Using genetic manipulation, other studies have demonstrated rejuvenated immune systems in several species, including fruit flies and worms, as well as considerable extension of their lifespan.[8,24]

The benefits of caloric restriction (CR) have been known since the 1930s.[24,25] At the University of Wisconsin, as well as at the National Institute of Aging (NIA), primates are being tested, in the final step before human clinical trials, and initial results are consistently encouraging. In the case of humans, although Walford[14] and others have followed a CR regimen, the consensus is that the rigorous diet is too onerous for the general public. The result is a search for CR mimetics.

Any one of these approaches might lead to success. Practical advances will, nevertheless, have to come from genetic modification. De Grey[13] describes how deeply within the mitochondria, the energy producing or metabolic organelles of our cells, changes would have to be made in order to arrest aging altogether. De Grey also suggests various methods to excrete the undigestible pigments that remain as a byproduct of metabolism. Many others suggest comparably dramatic changes by the use of telomerase to reset the pattern of gene expression.[5] The latter approach has the benefit of interventional work to support it. Initial results using telomerase, for example, have been dramatic, permitting the rejuvenation of transplanted human dermal analogs from aged human skin cells.[26] Both of these approaches will require more data as well as animal and human trials.

Despite the current developments, the practical clinical question remains. What can currently increase the likelihood of a longer life? The currently generally agreed on answers have essentially remained unchanged over the past few decades:[28–37]

- eat a nutritious and low calorie diet (perhaps with supplements)
- exercise regularly
- drink red wine in moderation
- do not smoke
- have an optimistic attitude
- have a life partner and a wide social support network
- continue lifelong education
- avoid stress, and, most importantly,
- choose long lived parents.

Unfortunately, while the last choice is the most important, it is not up to us.

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