THE NEW FUTURE OF OLD AGE

Science promises a longer and healthier old age, writes **Peter W. Gallagher**

> 'If you live to be one hundred, you've got it made. Very few people die past that age.'
>
> — George Burns,
> US actor and comedian
> (1896–1996)

Just a few years ago, in 2008 or thereabouts, for the first time in two thousand centuries, a statistically average baby was born expecting to live the full characteristic span of our species: about seven decades.

At first glance, this seems an unremarkable milestone; perhaps troubling that it took so long. On a second glance, it seems more disturbing—for it implies that growth in life expectancy, which made a huge contribution to standards of living in the past century, is nearly exhausted. It would be surprising if newborns could on average expect to live longer than the characteristic span of 70 years—unless the age of death were to be somehow uncharacteristically postponed.

Surprisingly, that may be on the cards.

The 70 years of human life

Through all of human history until 2008, the rate at which babies and infants died was high enough to pull life expectancy at birth—a statistic that averages survival rates in a population— below 70 years. Yet modern anthropologists have shown that among people living in primitive conditions, and with no exposure to modern medicine, foods or standards of living, the largest number of deaths occur in the seventh decade.[1]

Among early contact groups as diverse as the Hazda of Tanzania, the Ache of Paraguay, and the Aborigines of the Northern Territory in Australia, the number of deaths was high in infancy but fell sharply through childhood, after which the risk of dying in the next year remained essentially constant to about the age of 40 years. After that, mortality rose steadily in a statistically predictable way, doubling roughly every seven to eight years, a trend that is identical to mortality in modern societies.[2] In about the seventh decade, senescence set in rapidly, followed by death. There is no reason to doubt that these survival histories, and the late clustering of the modal age at death, the age at which the largest number of people die, reveal the intrinsic capacity of our species for a life span of about 70 years.

It turns out that settlement, especially urban living, was toxic. From Roman times, through the Middle Ages, up to the end of the

Peter W. Gallagher is a former Australian trade negotiator and now an independent consultant on trade and public policy based in Melbourne. He teaches post-graduate classes on trade at Adelaide and Melbourne Universities and is the author of a number of monographs, journal articles, and research publications. His blog can be found at petergallagher.com.au

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eighteenth century, populations living in towns and cities scored barely half of this seven-decade life expectancy at birth.

The rapid recovery in life expectancy after the mid-nineteenth century may be the greatest humanitarian achievement of the industrial era. The pace of change was breathtaking. But most of the progress in life expectancy was a harvest of low-hanging fruit: big improvements in the survival of infants mainly due to better nutrition, improved sanitation, and better maternal education.[3] The global rate of infant mortality plummeted from 148 per 1,000 live births in 1955 to 59 in 1995 and will likely be below 30 in 2025.[4]

Survival is curiously like compound interest: to them that hath, more will be given.

Since almost all infants now survive, the 'modal' age of death, will tend to determine average longevity.[5] The modal horizon continues to recede, partly due to improved public health measures and more effective treatments for the degenerative diseases of old-age such as cancers, diabetes, and circulatory and heart disease. But progress has slowed. The fall in infant mortality cut early deaths by almost three-fifths in the second half of the twentieth century. Even in countries with the highest survival rates, however, the modal age at death rose by little more than a decade from the mid-seventies to the upper-eighties over the whole of the 20th century.[6]

But survival is curiously like compound interest: to them that hath, more will be given. For most of our lives, our expected remaining years increase as we get older. Australian men, today, add almost a year to their expected survival after age 30 and another 3.3 years after they reach 65. Those who celebrate their 85th birthday this year have earned another six-year extension of life expectancy to almost 91 years, 32 years more than seemed likely in the year of their birth.[7] Australian women also enjoy an extended life expectancy in their later years; 85-year-olds this year are likely to see their 92nd birthday.

This means that although the upper bounds of life-expectancy are moving more slowly, as middle-age survival improves, more people are reaching old age.[8] The proportion of deaths that take place around the rising 'modal' age of death is increasing.

The added value of human life

Survival gains during the twentieth century at both ends of the age spectrum added a staggering amount to the world's wealth. Although in principle a life is priceless, in practice economists can place a value on an additional year of life by observing what people are willing to pay or be paid for, say, taking on jobs with a known higher risk of death. The estimated value of such a statistical life year was around $270,000 in Australia in 2008; in the same range as estimates of the value of a U.S. life-year.[9]

That may look like a small price at first, but the sum of yearly benefits for a population over the course of a generation adds up to an astonishing sum. One estimate puts the value of the 30-year (1970–2000) US longevity gains in 2000 at about $95 trillion split between persons then alive (two-thirds of the benefit) and future generations. Put another way, the addition to the stock of national wealth due to longevity gains was roughly 10 times the measured output of the US economy in 2000.

Admittedly, these are the gross gains; expenditures on health consumed about 36% of these gains over the same 30-year period, leaving a net gain of about $61 trillion. But even the net gain is more than six times the annual value of the entire US economy in 2000 as measured by the standard GDP.[10]

Although new increments to survival may be slowing, the flow of benefits from past gains continues. Access Economics puts the value of Australian health gains up to 2045 at more than $370 billion (2008 dollars).[11] Their work seems to put the present gross value of the stream of health span benefits to Australians between 1993 and 2045 at more than A$10 trillion or about 13 times our 2000 GDP.

Even these astronomical sums are probably underestimates because they use today's value of a statistical life year. The extension of the health span will be still more valuable in the future

than it is today for two reasons. First, the value of a life year rises as incomes rise because people are willing to pay more when they're richer. Second, people are willing to pay more for a higher quality, not only a greater quantity, of life years. For example, delaying the onset of Alzheimer's disease does not necessarily extend the number of years, but people are 'willing to pay' more for an extra year of life gained, say, through improvements in the treatment of cancer if, in that extra year, Alzheimer's disease becomes a reduced threat.[12]

The income-linked value of survival means that the most impressive gains are occurring, not in high-income countries such as the United States or Australia but in emerging economies such as China and India. Here, the added value is world-changing. The enormous size of their populations and their much greater 'head-room' for healthy life span improvements (they start from a lower base) lead to galactic gains. For example, the value of a statistical life-year in India has been assessed (2003) as US$10,000 to US$20,000. Given India's gains in life expectancy of about 25 years since 1950, and a population in 2000 of about 1 billion, the gains in life expectancy in India alone over the period are worth about US$400 trillion (about four times the gains in the United States in the last three decades of 20th century).[13]

Even as population growth in the emerging economies falls, the aggregate value of longevity soars because people are ready to pay more for an additional year of life as they grow richer. In poor countries, the value of that extra year has been shown to rise about half as fast as income rises (or a little bit faster). So a doubling of national income leads to a rise of 50%–60% in the value of a year of life.[14] In China, for example, growth in real per capita income from 1980 to 2000 was about 8% per year while the observed growth in Chinese life expectancy at birth from 40 to 70 years between 1950 and 1990 represented an increase of about 2% per year. The aggregate value of survival in China over that period, therefore, potentially grew by as much as 6% annually (4% increase in value + 2% increase in life expectancy) for two or three decades, to more than 300 times its starting value.

The beneficiaries of this giant private stimulus will swell the most influential demographic of the first half of this century: the new global middle class. By 2030, there are likely to be at least 1.3 billion people, or just over 16% of the projected global population, whose estimated purchasing power will be somewhere between that of the Brazilians and Italians in the year 2000. The biggest group (38%) of this global middle class will be found in China, where by 2030, the modal income-earner will be a member of the global middle class.[15] By sheer numbers, the new entrants to the middle class will define tastes, aspirations, global demand, and trade patterns.[16]

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Crucially, a high proportion of these new bourgeois will be middle-aged, and constitute 35% of the Chinese population and 25% of the Indian population by 2030.[17] A discounted lifetime-income hypothesis suggests that the years of middle age are when the private valuation of longevity is the highest, both because personal wealth is at a life-time peak, implying greatest willingness to pay, and a personal interest in survival to see their grandchildren.

The science of extending life

Why does their willingness to pay matter? You can't buy even one more day, can you? There are well-known recipes for an incrementally longer life: research shows that slim, non-smoking, vegetarian, exercise-prone Seventh Day Adventists outlive their neighbours.[18] But that takes more effort and maybe a faith that few of us aspire to. There is no longevity potion, and before the 1990s at least, there was no warrant from research to believe that there would ever be. The US Food and Drug Administration (FDA) does not even approve trials of compounds whose sole purpose is life-extension.[19]

In the last decade or so, however, the outlook for pro-longevity treatments that

extend life rather than reverse ageing has changed fundamentally and in ways that give surprising support to ideas that formerly seemed implausible.[20] Leading biologists, who once held that ageing is little more than a process of inevitable but haphazard deterioration in the tissues, now have a profoundly different view: the process no longer appears haphazard.[21]

Many puzzles remain: the map of ageing is a jumbled, incomplete graph of cell chemistry and epi-genetics. But as the map has grown more ordered and more detailed, it has revealed that many aspects of ageing in animal models for human biology are due to paradoxical operations of certain genes that control cell growth and metabolism. Today, many researchers and several drug companies are investigating substances that in different ways modify these controls by mimicking the metabolic effects of nutrient restriction: a technique discovered, almost a century ago, to prolong life in mice and other small animals.[22]

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Current research is not primarily focused at extending life span—given the FDA rule this would be futile—but on cellular mechanisms implicated, for good or ill, in metabolic or degenerative diseases: for example, the control of early tumour development, or degenerative processes such as Alzheimer's disease, or sensitivity to insulin and the production of cholesterols.

In mouse and worm-models for human biology, genetically controlled cell mechanisms that have vital functions in young, healthy cells are also implicated in the ageing of cells and the degeneration of organisms in later life. They comprise processes that switch on or off cell growth, resist cell stress, maintain normal cell metabolism, or control enzymes that dispose of foreign substances in cells. These age-dependent, paradoxical gene switches have been conserved by evolution in a wide range of species, probably to ensure that young organisms are able to grow rapidly, resist infection, and deal with the wear and tear of life long enough to reach reproductive age.[23] But their actions in older individuals may weaken the cell's response to tumours or allow inflammatory responses associated with many age-related diseases to get out of hand.

For example, some vital organs such as the liver and the lining of the gut continue to regenerate throughout life, thanks to the activity of adult stem cells. These stem cells can replicate many more times than other cells because, under genetic control, they are sufficiently supplied with an enzyme (telomerase) that enables DNA to replicate through many more than the usual 40–60 generations.[24] But, in most cells, telomerase-extended DNA regeneration also allows uncontrolled tumorous growths to develop, dramatically curtailing survival.

Many research projects are evaluating the impact of substances that vary the expression of these paradoxical genes, up-regulating or down-regulating their activity.[25] Among these, the immunosuppressant drug Sirolimus (rapamycin) is one of the most frequently cited. Rapamycin is a natural toxin excreted by a bacterium, *Streptomyces hygroscopicus*, found in the depleted soils of the remote Pacific island of Rapa Nui (Easter Island), famous for the beetle-browed moai statues that puncture its long-deforested slopes. Hygroscopicus uses its toxin to induce fungi competing with it for scarce nutrients in the soil to starve themselves. When the Wyeth pharmaceutical company synthesised the molecule in the early 1970s, it sought approval to market rapamycin as an anti-fungal. But physicians soon found that the drug also down-regulated the action of the human immune system. This was a much more valuable function in the then-emerging era of transplant surgery because it helped control tissue-rejection, and it remains rapamycin's primary use.[26]

More intriguing discoveries followed. The cell protein whose activity rapamycin inhibits, known by its patronymic as the Target of Rapamycin (TOR), has been implicated in the suppression of tumour growth and the extension of life span in worms and mice. TOR

is a key switch in a powerful chemical sensing and signalling chain within a cell; it integrates a cell's responses to nutrients, changes in energy status, growth factor stimulation, and response to various types of stress. Its function is to slow down cell protein synthesis and cell growth when the cell is stressed, for example, by a lack of nutrients permitting growth to resume only after the source of stress has passed.

Inhibiting TOR with rapamycin significantly prolongs the life span of ageing mice, just as the stress of starvation does. In a 2005 experiment funded by the US National Institute on Ageing (reported in 2009), 20-month old laboratory mice, the equivalent to 60 years in humans, were fed modest doses of the drug and survived between 20% (males) and 30% (females) longer than their life expectancy at the time the treatment started. Their maximum life span, defined as the age at which 90% of the group had died also increased by 9% and 14% respectively. Similar life-prolongation due to TOR inhibition has been found in flies, yeast and worms.[27]

Like longevity-enhancing nutrient restriction, inhibiting TOR appears to have other serendipitous late-life benefits such as reducing the incidence or severity of cancers, auto-immune disease such as rheumatoid arthritis, and metabolic disease. But rapamycin inhibits TOR without starvation and works in mice late in life, whereas the miseries of nutrient restriction must be lifelong to prolong life. The fact that life span was extended by a treatment that started relatively late in life suggests that it is not necessary to start treatment in the young. In the case of rapamycin, starting too early in life could even be detrimental because the TOR switch is critical for growth and development of the organism at an early stage. Pharmaco-dynamic tests on cancer patients who were prescribed synthetic analogs of rapamycin suggest that at therapeutic doses, it does not act as an immunosuppressor or suppress appetite, if the mice are a guide.[28]

There are important caveats. What works in small animal models such as mice frequently fails to translate into humans. Both organisms are complex; not even a partly shared genome guarantees similar responses. For example, some cancer treatments that work in mice do not work in humans. There can be genomic variation even in the same species: starvation therapies that work to prolong the life of laboratory mice do not work as well in wild mice. It may turn out that mice are simply more amenable to life span extension than humans. In addition, many diseases such as arteriosclerosis, diabetes, dementia, osteoporosis, osteoarthritis and cancer that are the cause of most deaths among old people, have environmental as well as genetic origins. They pose a challenge to longevity that is distinct from age-related degeneration at the cellular level. Finally, testing the impact of interventions on human longevity takes a long time because humans, unlike our animal models, are long-lived. It remains possible that serious, unanticipated, side-effects will turn up.

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Although it seems a speculative project today, evidence of the willingness-to-pay for additional years of healthy life suggests that life span extension research would quickly become a global priority if one or other of the several compounds (in addition to rapamycin) proves as effective in humans as rapamycin has been in the model animals. It seems safe to predict that funding and regulatory support would swing sharply behind the research because a mid-life improvement in life-expectancy will attract the keen attention of precisely those middle-aged, middle-class voters, including the billions of new entrants from the emerging economies, who are likely to place the highest subjective value on more years of life. The complementary nature of health benefits (e.g. fewer cancers) and longer life will add significantly to the value of such research for the middle-aged, who are likely to have both the wealth to pay for treatment and expectations

of enjoying a high proportion of the additional time it could win for them.

The older future

Summarising his 2005 research report on the implications of an ageing population, Productivity Commission Chair Gary Banks said that because ageing brings us longer and healthier lives, we shouldn't see it as a problem. The opportunity to afford an ageing population is in our hands; realising it depends chiefly on lifting economic productivity, increasing workforce participation rates including for older Australians, and pursuing health care service improvements at lower cost.[29] The prospect of a population that ages more slowly but for longer, with a higher proportion of individuals remaining healthy and capable of work, does not seem to call for any important change to those recommendations. It implies a postponed, potentially smaller drain on health care facilities, although the aged will likely still make the largest calls on facilities. It may also imply a need for greater emphasis on workforce participation incentives, and almost certainly, some reconsideration of retirement and superannuation savings rates and benefits thresholds to ensure that individuals are capable of self-funding a longer old age.

A baby girl born today in Australia can expect to live until 2093 and a baby boy to 2089, which is longer than infants in all but two other countries, Japan and Iceland. The recent history of rapidly growing life spans suggests that in fact both will outlive their birth-year expectations and probably see the dawn of the twenty-second century.

But if the promise of current research holds, Australians in a not-too-distant future, if not today's children then theirs, will live well past their centenary. On average, they will enjoy a much higher standard of life than we do, partly because they will be healthier, even robust, and independent for most of their long lives. But medical advances will likely not be sufficient to secure a bright future for the new old age. We will also need new approaches to, and expectations of, employment and career; new regulatory frameworks for savings and retirement; and possibly new objectives in education to support individuals whose employment, household composition, location, and interests are sure to evolve as they enjoy eight, nine or 10 decades of maturity.

Endnotes

1 The data on characteristic life spans of pre-modern populations are from a review article by Michael Gurven and Hillard Kaplan, 'Longevity Among Hunter-Gatherers: A Cross-Cultural Examination,' Population and Development Review 33:2 (June 2007), 321–365.

2 This discovery was first made by Benjamin Gompertz, the eponymous inventor of the standard survival curve.

3 The trend in OECD countries, whose data are captured in the Human Mortality Database (www.mortality.org), shows the predominance of infant mortality reductions up to the 1920s. But infant mortality was still more important in countries where the majority of people lived until much later in the twentieth century. See also Kaare Christensen, et al. 'Ageing Populations: The Challenges Ahead,' *The Lancet* 374:9696 (October 2009), 1196–1208.

4 WHO (World Health Organization), *50 Facts: Global Health Situation and Trends 1955-2025* (1998).

5 Discussed in Vladimir Canudas-Romo, 'The Modal Age at Death and the Shifting Mortality Hypothesis,' *Demographic Research* 19 (July 2008), 1179–1204.

6 As above.

7 Based on the estimated life expectancy of Australian males born in 1920–22. ABS (Australian Bureau of Statistics), *Australian Historical Population Statistics 2008* Cat. No. 3105.0.65.001 (Canberra, 2008).

8 The survival curves for 1900 to 2100 (projections) are taken from the US Social Security Administration Life Tables. For other data, see Jim Oeppen and James W. Vaupel, 'Broken Limits to Life Expectancy,' *Science News* 296 (March 2002), 1029; Canudas-Romo, 'The Modal Age at Death and the Shifting Mortality Hypothesis,' as above.

9 Admittedly, courageous assumptions and straightforward calculations using data on risk-of-death premiums give a discounted present-dollar value to a 'statistical life' of about $US6 million. David Meltzer, 'Economic Approaches to Valuing Global Health Research,' in Dean T. Jamison, et al. (ed.), *Disease Control Priorities in Developing Countries*, second edition (Washington, DC: World Bank, 2006), chapter 7, 157–163.

10 Kevin M. Murphy and Robert H. Topel, 'The Value of Health and Longevity,' *Journal of Political Economy* 114:5 (October 2006), 871–904.

11 Access Economics, *Exceptional Returns: The Value of Investing in Health R & D in Australia II* (Sydney: The Australian Society for Medical Research, 2008).

12 Kevin M. Murphy and Robert H. Topel, 'The Value of Health and Longevity,' as above.

13 David Meltzer, 'Economic Approaches to Valuing Global Health Research,' as above.

14 As above.

15 Half of the 740 million new entrants to this global middle class between 2000 and 2030 will be Chinese. India will add another 6%. In total, developing country nationals will account for 90% of the coming global middle class by 2030. Data and projections are from World Bank income distribution projections as reported by Maurizio Bussolo, et al. 'Global Growth and Distribution: Are China and India Reshaping the World?' in Amelia U. Santos-Paulino and Guanghua Wan (eds.), *Southern Engines of Global Growth* (OUP, April 2010).

16 A recent OECD report on the rapid growth of the global middle class observes that their willingness to pay for specific qualities in products seems to be an important factor driving product differentiation in goods and services markets, feeding production and marketing investments and helping to explain why most trade expansion has been occurring at the extensive margin—that is, by broadening product choice rather than deepening trade in existing products. See Homi Kharas, 'The Emerging Middle Class in Developing Countries,' OECD Development Centre Working Paper No. 285 (2010).

17 Middle-age is deemed here as 45–70 years. Both countries are projected to have populations of about 1.4 billion in 2030. In each, the largest number of people are in the 16–44 age group, but the middle-aged group is next in size. US Census Bureau International Database (2011).

18 A US study that followed 34,000 Adventist men and women over a 12-year period showed that their lifestyle choices of vegetarianism, exercise, eating nuts, maintaining a mean Body Mass Index of 25 (24 for women), and not smoking resulted in expected ages at death that were 10–11

years greater than other Californians in 1985. Gary E. Fraser and David J. Shavlik, 'Ten Years of Life,' *Archives of Internal Medicine* 161 (2001), 1645–1652.

19 See Jan Vijg and Judith Campisi, 'Puzzles, Promises and A Cure for Ageing,' *Nature* 454 (August 2008), 1065–1071.

20 As recently as 2002, some of the most distinguished biologists and demographers of ageing co-authored a sceptical rebuttal to proponents of life-extension research in S. Jay Olshansky, Leonard Hayflick, and Bruce A. Carnes, 'No Truth to the Fountain of Youth,' *Scientific American* (June 2002), 92–95.

21 Robin Holliday, a distinguished geneticist in the 1970s and 1980s, subscribed to the view that 'normal' ageing was the consequence of a long, inevitable deterioration at the cellular level: 'One of the main causes of ageing is the inability of the organism to replace cells in vital organs, such as the heart or brain. Individual cells die either through the accumulation of genetic damage in their genes and chromosomes, or through the inability to get rid of defective proteins, or by breaking down such proteins to harmful smaller fragments.' Robin Holliday, *Aging: The Paradox of Life* (Dordrecht, The Netherlands: Springer, 2007), 16. The change of biological opinion on ageing is described by Cynthia J. Kenyon, 'The Genetics of Ageing,' *Nature* 464 (March 2010), 504–512.

22 Jan Vijg and Judith Campisi, 'Puzzles, Promises and A Cure for Ageing,' as above.

23 The correct term is pleiotropy rather than paradox. An explanation of this genetic mechanism, first proposed by Gregory Mendel, can be found in Ingrid Lobo, 'Pleiotropy: One Gene Can Affect Multiple Traits,' *Nature* (2008).

24 This is the so-called Hayflick limit for somatic cell reproductive life. It is a boundary that most cells never reach, thanks to the wear and tear of ordinary metabolism. See Geraldine Aubert and Peter M. Lansdorp, 'Telomeres and Aging,' *Physiological Reviews* (2008), 557–579. Leonard Hayflick's views on the link between cell senescence and ageing are detailed in Leonard Hayflick, 'How and Why We Age,' *Experimental Gerontology* 33:7–8 (November. 1998), 639–653.

25 Two review articles that summarise some of the current research on IGF-1, TOR, Sirtuins, AMP kinase, etc. are Cynthia J. Kenyon, 'The Genetics of Ageing,' as above; Jan Vijg and Judith Campisi, 'Puzzles, Promises and A Cure for Ageing,' as above.

26 An account of the early work on rapamycin is contained in Joseph Camardo, 'The Rapamune Era of Immunosuppression 2003: The Journey from the Laboratory to Clinical Transplantation,' *Transplantation Proceedings* 35:3 (May 2003).

27 Reported in Zelton D. Sharp and Randy Strong, 'The role of mTOR signaling in controlling mammalian life span: What a fungicide teaches us about longevity,' *The Journals of Gerontology* Series A, Biological Sciences and Medical Sciences 65:6 (June 2010), 580–589.

28 As above and Cynthia J. Kenyon, 'The Genetics of Ageing,' as above.

29 See Productivity Commission, *Economic Implications of an Ageing Australia* (Commonwealth of Australia, 2005).