

Has the time come to take on time itself?

Staying healthier for longer has benefits for society as well as individuals.

Colin Farrelly examines the efforts of science to delay ageing

Has the time come to get more serious about the effort to slow human ageing? The advocates of the longevity dividend believe it has.¹ On 12 September 2006 the not-for-profit citizen advocacy organisation Alliance for Aging Research held a Capitol Hill symposium entitled "Going for the longevity dividend: scientific goals for the world's aging populations." This campaign calls on Congress to invest \$3bn (£1.5bn; €2bn) annually into understanding the biology of ageing. That would amount to about 1% of the current Medicare budget.

In an era where media headlines are dominated by the war on terror and global warming, and much of the world's population live in conditions of poverty and disease, it might seem insensitive and unfair to suggest that we should divert more scarce public funding into tackling ageing. But such a knee jerk reaction can be overcome once you consider the science and ethics behind the proposal.

Science of ageing

So is there any reason to believe that real, tangible benefits could be reaped through slowing down ageing? The scientists working in these areas certainly believe there is. Just two or three decades ago, research on ageing was a backwater.² But cellular, molecular, and genetic studies using in vitro models and short lived invertebrates have resulted in an impressive pace of discovery.³ Success in increasing longevity in laboratory organisms has shown that ageing is not an immutable process.

For example, many studies have found that the lifespan of organisms such as worms, flies, and mice can be extended by restricting food intake. Dietary restriction delays and slows the progression of various diseases associated with age, including neoplasia, and maintains many physiological processes in a youthful state on to very advanced ages.⁴

Energy restriction would be a burdensome means to promote health. Nevertheless, its effect on our susceptibility to age related disease is important because it gives us hope that we may better understand the causal biological mechanisms underlying ageing and thus, ultimately, develop safe and effective ways of



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modulating the ageing process to extend the healthy human life span.

The transmembrane protein Klotho, for example, may affect ageing in mammals. Kurosu and colleagues showed that overexpression of the Klotho gene in mice extends life span.⁵ Other research has supported the role of free radicals in ageing.⁶ The formation of reactive oxygen species that can damage cellular constituents is prevented

“There is a credible scientific basis for believing that we could slow ageing in the foreseeable future”

by catalase.⁷ Schriener and colleagues found that overexpression of human catalase in the mitochondria of mice extends the median and maximal life span by about 20%.⁶ And Baur and colleagues showed that resveratrol, an antioxidant found in wine, can shift the physiology of middle aged mice on a high energy diet towards that of mice on a standard diet and greatly increase their survival.⁸

This research suggests that new approaches to treating obesity related disorders and the diseases of ageing could be viable. Understanding of the ageing process is a crucial component of such innovations and must have a prominent role in new strategies for extending the health of a population that is highly susceptible to the diseases of ageing. Cancer, for example, largely affects elderly people. Most tumours arise in the last quarter of life, with the incidence increasing exponentially with

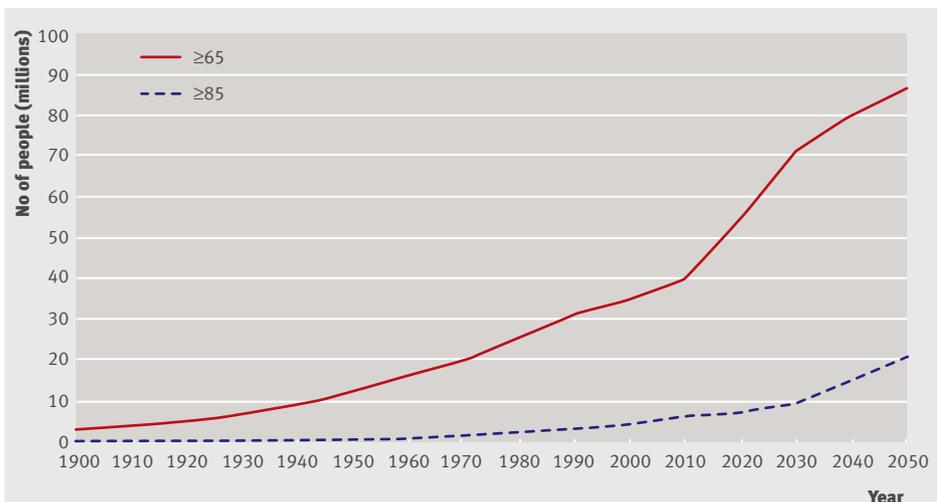
time.⁹ The efficiency of the pathway controlling the tumour suppressor protein p53 also declines with age, predicting the increased rates of mutation (caused by a fall in DNA repair) and fixation of mutations (caused by a decline in p53 mediated apoptosis) in older people, especially in response to stress.⁹

And finally, researchers have been able to increase the life expectancy of mice by 20% by lowering their body temperature by 0.3–0.5°C.¹⁰ The lower body temperature was achieved by inserting an uncoupling protein 2 gene into the brain cells of a mouse's hypothalamus, near to the region that senses and controls body temperature. The gene then tricked the mouse's internal thermostat into thinking it was heating up and thus the body was cooled.

Improving on nature

Studies like these should dislodge any presuppositions that our current biological design is optimal. The evolution of humans is an amazing story but one that may require (further) human intervention to help alleviate or postpone some of the intrinsic fallibilities we have inherited from our evolutionary legacies.

Of course, potential interventions to counter ageing have a long way to go before they can be tested in humans. Current strategies to administer antioxidant chemicals such as vitamins A, E, and C as a supplement to counter free radical damage or prolong survival have



Number of people aged over 65 and 85 in US, 1900-2050 (data for 2010-50 are projected)¹³

questionable effectiveness.^{11 12} But there is a credible scientific basis for believing that we could slow ageing in the foreseeable future. Research in basic biogerontology may lead to a pill that slows ageing and, as a pleasant side effect, delays all age related diseases.⁷ And the amount of public funding we invest into such research will determine the likelihood and timescale of success for ageing interventions.

Why stop ageing?

Perhaps the greatest obstacle facing the advocates of the longevity dividend is convincing the general public that the aspiration to slow ageing is a laudable goal that deserves a larger share of the public funds available for scientific research. Proponents of research into slowing ageing have gone to great lengths to emphasise how, given the current demographics, even modest success would reap large and diverse socioeconomic benefits across generations.

If we succeed in slowing ageing by seven years, the age specific risk of death, frailty, and disability will be reduced by about half at every age. People who reach the age of 50 in the future would have the health profile and disease risk of today's 43 year old; those aged 60 would resemble current 53 year olds, and so on. Equally important, once achieved, this seven year delay would yield equal health and longevity benefits for all subsequent generations, in much the same way that children born in most nations today benefit from the discovery and development of immunisation.¹

The predicted growth in the number of people aged over 65 shows the importance of slowing ageing (figure). The rapid rise in older people over the next few decades will be accompanied by an increase in the number of people with disease and chronic illness.

Almost half (45.1%) of the current popula-

tion over 75 years of age have their activity limited by chronic conditions.¹⁴ Older people are less resistant to injury, whether from physiological events (for example, surviving a heart attack) or environmental trauma (for example, bone fracture), and they are less resistant to infection.¹⁵

Furthermore, ageing is a major risk factor for developing complex diseases like cancer. According to the National Cancer Institute, the lifetime risk of being diagnosed with cancer is currently 45.7% for males and 38.1% for females in the US. But these risks drastically change as we get older. The risk of being diagnosed with cancer in the next 20 years for men who are cancer-free is 1.1% at age 20, 21.4% at age 50, and 34.5% at age 60.¹⁶ These statistics are important given that in 2007, cancers cost the US an estimated \$219bn, including \$130bn for lost productivity and \$89bn in direct medical costs.¹⁷ With a rapidly expanding aged population these costs are set to also rapidly increase.

Given the current predicament we face, we cannot ignore the call to tackle ageing more aggressively. To those who ask: "Can we really afford to invest more in such research?" we can reply: "Can we really afford not to tackle ageing?" That is the really important question. And the answer is clearly no. By extending the life span when higher levels of physical and mental capacity are expressed, people would remain in the workforce longer, personal income and savings would increase, age entitlement programmes would face less pressure from shifting demographics, and national economies would flourish.¹

The ultimate goal of retarding ageing is the same goal that cancer therapies strive for—namely, to extend healthy living. This can be achieved by curing disease but it can also be achieved by increasing the duration of disease-

free life. There is no reason why we cannot pursue both strategies—aggressively tackling individual diseases and ageing. Given the high stakes involved, policy makers must be both imaginative and ambitious. So considering where the science actually is, the magnitude of the benefits of even modest success, and the certainty and severity of the costs of inaction, the longevity dividend campaign deserves a prominent place on the policy agenda.

Competing interests: None declared.

Contributors and sources: CF is a political philosopher who has published widely on the ethical and social implications of the genetic revolution. This article was written during the tenure of a research fellowship he held in 2006-7 at the Centre for the Study of Social Justice at Oxford University.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Colin Farrelly associate professor, Department of Political Science, University of Waterloo, Waterloo, Canada N2L 3G1 farrelly@uwaterloo.ca

Accepted: 27 March 2008
Cite this as: *BMJ* 2008;337:a1414

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New model of health promotion and disease prevention for the 21st century

Our susceptibility to disease increases as we grow older. **Robert Butler and colleagues** argue that interventions to slow down ageing could therefore have much greater benefit than those targeted at individual disease

Many countries now have ageing populations and are facing an increased prevalence of age related diseases and escalating healthcare costs. However, if ageing is combined with extended years of healthy life, it could also produce unprecedented social, economic, and health dividends. In recent decades, scientists have shown that the underlying biological processes of ageing, which give rise to most diseases and other age related health problems, can be delayed. We argue that a concerted effort to slow ageing would provide a broad strategy for primary prevention that would greatly enhance and accelerate improvements in health at all ages.

Rise of human longevity

Life expectancy at birth rose by a remarkable 30 years in developed countries during the 20th century, initially because of reductions in infant, child, and maternal mortality and then because of declining mortality in middle and old age.^{1,2} In 1900, about 40% of babies born in countries for which reliable data existed were expected to live beyond age 65.³ Today

in these same countries more than 88% of all newborns will live past age 65 and at least 44% will live beyond age 85. This dramatic extension of life has provided social and economic benefits.

The traditional medical approach to ameliorating modern chronic diseases has been to tackle them individually, as if they were independent of one another. This approach flows naturally from our experience with acute diseases, where patients seek medical care for one condition at a time. In fact, applying this same strategy to infectious diseases in the 20th century helped to deliver the first longevity revolution.⁴ Although some infectious diseases have chronic effects on health (such as malaria and HIV infection), and others remain difficult to treat (including tuberculosis and most viral diseases), public health efforts to combat these diseases have made it possible for people in today's developed nations to live long enough to experience one or more of the degenerative and neoplastic diseases that are now the dominant causes of morbidity and death.

Diminishing returns from disease specific model

Medical research worldwide has already accomplished much, and is certain to achieve more in decades to come, but its effectiveness will become limited unless there is an increased shift to understanding how ageing affects health and vitality. Most medical research teams are oriented towards the analysis, prevention, or cure of single diseases, despite the fact that nearly all of the diseases and disorders experienced by middle aged and older people still show a near exponential increase in the final third of the life span. Now that comorbidity has become the rule rather than the exception, even if a "cure" was found for any of the major fatal diseases, it would have only a marginal effect on life expectancy and the overall length of healthy life.⁵

The change in strategy we are calling for requires a systematic attack on ageing itself. Although such a strategy was clearly articulated more than a quarter of a century ago,^{6,7} there has been little progress towards making the necessary changes.⁸ However, recent



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A playground designed specifically for pensioners has opened in a park in north Manchester. The "Older People's Play Area" in Dam Head Park, Blackley is the country's first for the over-60s. It features six pieces of equipment to keep senior citizens fit by strengthening hips, toning legs, and training the upper body. The local residents' association got the idea to set up the facility after being inspired by a similar playground in Germany

advances in understanding the complex biological mechanisms responsible for ageing suggest that it is feasible to translate this strategy into practice.⁹ Evidence in models ranging from invertebrates to mammals suggests that all living things, including humans, possess biochemical mechanisms that influence how quickly we age and that they are adjustable. It is possible—for example, by dietary intervention or genetic alteration, to extend life span and postpone ageing related diseases such as cancer, cataracts, cognitive decline, and autoimmune diseases.¹⁰⁻¹⁴

We are not calling for the modification of human genes to extend healthy life—that would not be practical, useful, or ethical. However, investigating how genetic mutations influence the basic rate of ageing is likely to provide important clues about how to develop drugs that do much the same thing.^{15 16}

Attempts to develop preventive measures against individual conditions related to ageing have been, for the most part, frustrating and unsuccessful. But in striking contrast, all of these conditions, and more, can be ameliorated or postponed simultaneously by well validated interventions that slow ageing.¹⁷⁻¹⁹ The interventions that have worked in laboratory animals are not now appropriate for disease prevention in humans. However, we believe that exploration of the mechanisms by which ageing can be postponed in laboratory models will yield new models of preventive medicine and health maintenance for people throughout life, and the same research will also inform a deeper understanding of how established interventions, such as exercise and healthy nutrition, contribute to lifelong wellbeing.

Recommendations

The potential of fundamental research into ageing to contribute practical benefits to improve health at all ages, but particularly at older ages, has been under-recognised by most of the scientific establishment, and, importantly, by many of those who decide on allocation of resources for health research.²⁰ Now that most people in developed nations reach old age in reasonable health, and scientific progress has been made on interventions capable of postponing nearly all the diseases and disabilities that affect older people, the time has arrived for national policies to support and develop practical interventions that slow ageing.

The research strategy that we propose is

intended to supplement, rather than substitute for, research into specific diseases, which will continue to discover new and improved therapies and approaches to preventive medicine. We propose, however, a large increase in resources available for investigations into how diseases such as type 2 diabetes, congestive heart failure, Alzheimer's disease, Parkinson's disease, osteoporosis, sarcopenia, and most cancers, either interact with ageing or share mechanisms in common with it. We further propose greatly increased funding for basic research into the fundamental cellular and physiological changes that drive ageing itself.

The pursuit of extended healthy life through slowing ageing has the potential to yield dramatic simultaneous gains against many if not all of the diseases and disorders expressed in later life. The most efficient approach to combating disease and disability is to pursue the means to modify the key risk factor that underlies them all—ageing itself. Pursuing an aggressive research strategy to devise interventions against ageing suitable for humans requires that it is a goal worth pursuing (it is), and that we have good leads to follow (we do), but it does not require that we know, in advance, which of the current ideas about mechanisms affecting the rate of ageing are most likely to produce effective interventions. A fresh emphasis on ageing should vastly accelerate the health, economic, and social benefits of the extension of healthy life, which we refer to collectively as the longevity dividend.²²

Competing interests: None declared.

Contributors and sources: This article arose from the authors' efforts to get physicians, scientists, and politicians to understand and appreciate the public health benefits that would accrue from efforts to slow ageing, and distinguish those benefits from the current medical approach to attacking one disease at a time. All authors participated in the drafting and editing of the article and approved the final version. RNB is guarantor.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Robert N Butler president, International Longevity Center, New York, USA

Richard A Miller professor, University of Michigan, Ann Arbor, MI, USA

Daniel Perry executive director, Alliance for Aging Research, Washington, DC, USA

Bruce A Carnes professor, University of Oklahoma, Oklahoma City, OK, USA

T Franklin Williams professor emeritus, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Christine Cassel president, American Board of Internal Medicine, Philadelphia, PA, USA

Jacob Brody professor, University of Illinois at Chicago, 1603 West Taylor Street, Chicago, IL 60612, USA

Marie A Bernard professor, University of Oklahoma, Oklahoma City, OK, USA

Linda Partridge director, Institute of Healthy Ageing, University College London, London

Thomas Kirkwood director, Institute for Ageing and Health, Newcastle University, Newcastle

George M Martin scientific director, American Federation for Aging Research, Seattle, WA, USA

S Jay Olshansky professor, University of Illinois at Chicago, 1603 West Taylor Street, Chicago, IL 60612, USA
sjayo@uic.edu

Accepted: 19 May 2008

Cite this as: *BMJ* 2008;337:a399

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