Is human aging still mysterious enough to be left only to scientists?

**Aubrey D.N.J. de Grey,[1]* John W. Baynes,[2] David Berd,[3]
Christopher B. Heward,[4] Graham Pawelec,[5] and Gregory Stock[6]**

Summary

The feasibility of reversing human aging within a matter of decades has traditionally been dismissed by all professional biogerontologists, on the grounds that not only is aging still poorly understood, but also many of those aspects that we do understand are not reversible by any current or foreseeable therapeutic regimen. This broad consensus has recently been challenged by the publication, by five respected experimentalists in diverse subfields of biogerontology together with three of the present authors, of an article (Ann NY Acad Sci 959, 452–462) whose conclusion was that all the key components of mammalian aging are indeed amenable to substantial reversal (not merely retardation) in mice, with technology that has a reasonable prospect of being developed within about a decade. Translation of that panel of interventions to humans who are already alive, within a few decades thereafter, was deemed potentially feasible (though it was not claimed to be likely). If the prospect of controlling human aging within the foreseeable future cannot be categorically rejected, then it becomes a matter of personal significance to most people presently alive. Consequently, we suggest that serious public debate on this subject is now warranted, and we survey here several of the biological, social and political issues relating to it.

***BioEssays* 24:667–676, 2002.**

Introduction

In a recent article,(1) five eminent researchers with wide-ranging biogerontology expertise joined with three of the present authors (A. de G., C. H. and G. S.) to make an unprecedentedly bold forecast concerning mammalian life extension in the medium term. They stated that, within about a decade, it might be possible to reverse (not merely retard) mouse aging. Specifically, we might be able to take a mouse with a remaining life expectancy of six months and give it one of eighteen months, something that would require restoration of broadly youthful physiology. The authors did not claim that this would occur in about a decade, nor even that it was probable. They did state, however, that its possibility could no longer be considered remote, since no intervention considered necessary requires dramatic biotechnological advances. It was further noted that the undoubtedly formidable obstacles to translating such technology (if developed) to humans are already being tackled, e.g., by gene therapy research, so might fall only a few decades thereafter.

Hayflick has energetically argued(2–4) that many tumultuous challenges would confront civilisation were we greatly to extend human longevity. However, few others have joined that debate, perhaps because of the apparently unanimous expert consensus that this scenario (which has been termed "engineered negligible senescence" or ENS Ref. 5.) is vanishingly unlikely to occur in the foreseeable future. Such consensus no longer exists, as noted above(1).

Here we examine several issues arising from this more optimistic outlook. First, we propose some concrete definitions of key concepts. Then we consider:

- whether the range of cellular and molecular aspects of aging whose reversal was discussed in Ref. 1 is comprehensive;
- whether their translation from mice to humans is plausible on a comparable time scale;
- whether such considerations call for a redistribution of our investment in anti-aging research and development versus other medical research; and
- whether they motivate a readjustment of how biogerontologists present their work and its purpose to policy-makers and the public.

Can reversal and retardation of aging be rigorously distinguished?

A statement given great prominence in Ref. 1 was that "reversing mammalian aging is not necessarily any harder

[1] Department of Genetics, University of Cambridge, Cambridge UK.
[2] Department of Chemistry and Biochemistry, University of South Carolina, Columbia.
[3] Department of Medicine, Thomas Jefferson University, Philadelphia.
[4] The Kronos Group, Phoenix.
[5] University of Tübingen Medical School, 2nd Department of Internal Medicine, Tübingen,Germany.
[6] UCLA School of Medicine, Los Angeles.
*Correspondence to: Dr. Aubrey D. N. J. de Grey, Department of Genetics, University of Cambridge, Downing Street, Cambridge CB2 3EH, UK. E-mail: ag24@gen.cam.ac.uk
DOI 10.1002/bies.10113

than dramatically postponing it". Initially this assertion seems preposterous: for example, surely the postponement of mouse aging by caloric restriction (CR) qualifies as dramatic, and we can do that already. Moreover, CR "mimetics" are under development.(6)

However, CR exerts progressively less effect on rodent lifespan the later in life it is imposed,(7) and evolutionary theory suggests that any other inducible but endogenous life-extending metabolic adjustment would share this property. Children will not be given such treatments, lest they have long-term side-effects (which, by definition, cannot quickly be ruled out). Only those already concerned with their own aging (i.e., older people) are likely to consider such drugs, and for them the potential benefit is slight, even if CR works as well in humans as in rodents (which is unproven). Only much more dramatic retardation of aging will be biomedically significant.

Several life-extending genetic and pharmacological manipulations of model organisms,(8,9) including mice,(10,12) have now also been reported. Unfortunately, they have much in common with natural life-extending strategies of the organism in question (dauer, diapause, CR, etc.). Hence, they may merely constitute crude approximations of these natural phenomena, rather than new mechanisms for postponing aging, and thus are unlikely to lead to interventions that postpone aging to a biomedically relevant extent.

Why is retarding mammalian aging so hard? Mammals have had to tolerate the toxic side-effects of metabolism throughout their evolution, and have turned them to advantage: as signalling molecules, for example.(13) Interfering in the pathways from metabolism to damage will thus tend also to interfere with these other, positive roles of the damaging agent. Hence, the organism will tend to respond to such well-meaning interventions by compensatory adjustments to maintain the normal concentration of such agents—and if the intervention were powerful enough to overcome these homeostatic responses, the net result would generally be harm to the organism, not benefit (e.g., Ref. 14). Evolutionary pressure can select for retarded aging over thousands of generations,(15) but the panoply of adjustments of gene expression and function that are probably involved is far beyond our present biotechnological (let alone biomedical) expertise to emulate.

Why might reversing aging be easier? Reversing aging can be defined as removing the end-products of these side-effects of metabolism, as opposed to the reactive intermediates. Thus, the above logic does not apply here: overcoming normal homeostatic responses should not be necessary. The endpoints of oxidative and other damage are either the simple depletion of something (cells of a particular type, telomeric repeats . . .) or else stable, inert molecules, with no positive role to be balanced against their deleterious properties (Table 1). Hence, removing such damage may have few deleterious side-effects, so reversing aging may indeed be easier than retarding it. (Clearly this is logically impossible if retarding aging is defined to include reversing it more slowly than it is occurring, but that is not the definition used above.)

Table 1. Interventions found or predicted to extend lifespan in model organisms and (in most cases) potentially humans, classified according to whether they reverse aging, retard aging or elicit a naturally slow-aging phenotype

Category	Example of intervention	Example of treatment
Environmental manipulation	Caloric restriction	Low-calorie diet, adequate nutrition(7)
	Slowed rate of living	Starvation, cold, respiration block(16–18)
	Hormonal manipulation	Royal jelly(19)
Retardation of aging	Enzymatic free radical scavenging	Superoxide dismutase(8)
	Nonenzymatic free radical scavenging	EUK-134(9)
	Enzymatic inhibition of glycation	Amadoriases(20)
	Nonenzymatic inhibition of glycation	Pyridoxamine, aminoguanidine(21)
Reversal of aging	Digestion of lysosomal aggregates	Bacterial/fungal hydrolases(22)
	Apoptosis of senescent cells	Senescence marker-targeted toxins(1)
	Killing of age-related tumours	Angiostasis,(23) vaccination,(24) etc
	Nuclear rescue of mtDNA mutations	Allotopic mt-coded proteins(25)
	Immune system restoration	IL-7-mediated thymopoiesis(26)
	Cleavage of AGE cross-links	Phenacyldimethylthiazolium chloride(27)
	Clearance of extracellular aggregates	Immune-mediated phagocytosis(28)
	Cell replacement	Stem cell therapy(29)
	Hormone restoration	Genetically engineered muscle(30)

For details, see text and Ref. 1.

Can aging and age-related disease be operationally distinguished?

Great confusion surrounds the distinction (if any) between aging and age-related disease. Many aspects of aging distinguish it from typical diseases, including its universality, intrinsic origin, post-pubertal onset and promotion of vulnerability to diseases. However, none seems clear-cut. All males over 70 have prostate cancer detectable at autopsy.(31) Many age-related diseases result purely from side-effects of metabolism, not infection. Arterial foam cells, the first stage of atherosclerosis, are present before puberty.(32) Some age-related diseases predispose to others, such as diabetes doubling the risk of heart disease.(33)

Finding an operational definition of human aging that encapsulates its relationship to disease entails deciding what we mean by "disease" in the first place. Though death certificates do not often use the term "natural causes" these days, the cause of death in the elderly often spans many organ systems and transcends our usual definitions of disease. This leads us to suggest that, for purposes of clarifying how it relates to age-related diseases, human aging can be described as:

> a set of early-onset, slowly progressive, mutually synergistic degenerative processes, whose later stages are fatal but tend to be given "disease" status only if they often kill or severely debilitate people before they reach their society's life expectancy.

This description suggests that if we continue to raise the mean age of death from major age-related diseases, without postponing the aspects of aging that cause death by "natural causes", we will take progressively more interest in the latter category. This is because life expectancy will increase, so the age that we consider "a good innings" will increase, so increasingly many people will die of "natural causes" before that age, so we will want to study their specific cause of death, so we will name it. Thereby, we would elevate progressively more causes of death to the status of "disease". The distinction between aging and age-related diseases is, in this view, highly fluid; similar conclusions have been reached concerning the post-genomic definition of "disease".(34)

Some aspects of aging that may be very hard to reverse

Here we address some important components of mammalian aging that merit more detailed analysis than they received in Ref. 1.

The accumulation of random chemical modifications and cross-links termed advanced glycation and lipoxidation end-products, or AGE/ALEs, in long-lasting extracellular protein may be a major cause of age-related loss in extracellular matrix function and elasticity.(21) Some such changes may be of limited consequence, but others may be significant contributors to age-related pathologies such as hypertension(35) and cataract(36) and age-related losses in renal and pulmonary function. AGEs also accumulate in amyloid plaques in neurodegenerative diseases and dialysis-related amyloidosis.(37) Phenacyldimethylthiazolium chloride (PMTC) has been reported(38) to reverse this loss of elasticity, but its mode of action remains controversial; firstly because it would not cleave any AGE/ALE crosslink yet identified in vivo, and secondly because the proposed(27) cross-link cleaved by PMTC should be relatively reactive, i.e., transient.(39) However, impressive restoration by PMTC of elasticity in various tissues of several organisms, including humans, has been reported.(27,28,40,41) One possibility is that PMTC cleaves cross-links that have not been identified chemically, due perhaps to their lability to standard isolation procedures. Another is that the apparent reversal of cross-linking is actually only a retardation of both enzymatic and non-enzymatic cross-linking, which appears as reversal because of turnover of proteins in the vascular wall.

Immunosenescence may be largely responsible for the diminished ability of older individuals to overcome infection and maintain anti-cancer surveillance.(42) It is principally a result of the declining efficacy of T cells and possibly NK cells: B-cell decline is broadly a consequence of diminished T-cell stimulation, and antigen presentation capacity appears well retained in the elderly.(43) The T-cell population progressively shifts to a lower ratio of naive to memory cells, thereby shrinking the repertoire of cells available to respond to antigenic challenge from previously unencountered pathogens. Those T cells remaining, especially the CD8$^+$ (cytotoxic) subset, also show increased oligoclonality with age.(44) Memory cells can survive for at least two years in mice and possibly longer (though probably not as long as the memory itself) in humans; they, as well as naive cells, may thus face many of the intracellular maintenance challenges that affect postmitotic cells, such as accumulation of undegradable material. This could underlie their progressively more sluggish activation in response to antigen, since cross-age transplantation experiments(45) indicate that many T-cell functional deficits are intrinsic to the T cell rather than determined by the age of the host. Naive (and hence, subsequently, memory) T-cell functional decline is accompanied by involution of the thymus, which loses up to 90% of its cells by middle age (though with much inter-individual variation);(46) a causal link remains hypothetical but may now be testable using assays of T-cell rearrangement excision circles.(47) Interleukin 7 (IL-7) injections have reversed thymic involution in mice,(26) but associated restoration of naive cell number was, at best, restricted to CD4$^+$ (helper) cells. Immune system function is an emergent property of a complex network of cell types in dynamic equilibrium; if the gross changes in this system (such as loss of naive cells) were reversed, endogenous homeostatic mechanisms might or might not restore its subtler aspects.

Cancer is unique among age-related pathologies in its ability to evade both endogenous and medical challenges (including denial of blood supply, immune attack and cell division-associated telomere shortening) by selection for additional mutations. (Not all cancers are age-related, of course, but here we restrict consideration to those that are.) Angiogenesis inhibitors have shown promise in mice(23) but their efficacy in humans remains unclear.(48) Telomere maintenance is usually (but not always, Ref. 49) achieved by reactivating telomerase, whose inhibition is therapeutic only if selective enough to spare the many telomerase-dependent cell types, including T and B lymphocytes and diverse stem cells. Immune stimulation also faces numerous difficulties, most fundamentally the relatively subtle antigenic difference between tumour cells and the non-tumour cells from which they arose. Hence, it is perhaps unsurprising that attempts to induce tumour regression using specific peptides are often ineffective.(50) Immunising patients against whole cells from their own tumour elicits a response against many antigens without even having to identify them in advance, and has long shown encouraging results.(24) However, the tumour load against which it is effective remains limited. The availability of such varied therapeutic approaches, many of them novel, which can potentially be used in combination, makes it plausible that the age at which cancer typically becomes life-threatening could be increased rapidly enough (in mice, then in humans) to achieve the goals set out in Ref. 1. However, the slow rate of progress hitherto warns us that this may not occur and that cancer may remain a formidable obstacle to dramatic life-extension for some time.

In summary, we caution that any one of the above aspects of aging, or of those discussed in Ref. 1, could easily turn out to be so intractable that the one-year mouse rejuvenation goal is thereby thwarted. One might infer that the chance of turning a 2-year-old mouse into functionally a 1-year-old one in 10 years' time is thus extremely small, since all key components of aging must be reversed simultaneously, an eventuality whose probability is the product of those of the component reversals. But this does not follow, because of the synergistic inter-dependencies of these processes (which are only partly understood mechanistically(51–53) but are decisively demonstrated by the fact that several single-gene mutations independently extend mouse lifespan(10–12)). If the most influential few processes can be robustly reversed, the others may be so retarded that the mouse will obtain the requisite extra year of healthy life.

Of mice but not men?

Let us now suppose that the proximate goal, rejuvenating a 2-year-old mouse by a year, were indeed achieved within a decade. How plausibly could translation of that technology to humans who are already alive be achieved relatively soon thereafter, and would this proportionally increase human healthy lifespan (roughly, giving a 60-year-old an extra 30 years)?

Many major age-related human pathologies do not afflict mice, so are tangential to the one-year mouse rejuvenation goal. However, researchers in many such areas are working to "humanise" the mouse, causing it to develop these pathologies (such as atherosclerosis(54) and neural amyloid deposition(55)). If these mice were also rejuvenated by a year, the result would be correspondingly more relevant to humans.

Some interventions discussed in Ref. 1 are transgenic, and the technique proposed there for applying them to 2-year-old mice is not truly late-onset: drug-mediated induction of *loxP* recombination to activate transgenes introduced in an inactive configuration by germ-line transformation. Truly late-onset transgenesis requires comprehensive somatic gene therapy. Presently, transfection efficiency of gene therapy is limited, as is often the persistence of transgene expression.(56) However, progress is rapid in these areas. In particular, vectors exist that can transfect non-dividing cells.(57)

Nonetheless, a daunting amount of additional progress is required if somatic gene therapy is to become as sophisticated as seems necessary for anti-aging purposes. Hence, if and when substantial aging-reversal were developed in mice and analogous transgenes were designed for humans, many individuals might seek to have children harbouring such transgenes.(58) This initially appears worrying in safety terms (irrespective of ethical or moral considerations). However, it may not be so problematic. Since (in this scenario) the interventions in question will reverse, rather than retard, aging, it will be preferable to construct these transgenes in the same inactive, drug-inducible form that has been advocated(1) for mice. Then, an individual could choose to turn on his or her anti-aging genetic arsenal at age 50, say, if and only if his or her desire for extended life outweighed any side-effects that those transgenes had, in those 50 years, been found to possess. In those same 50 years, however, huge advances would surely have been made both in somatic gene therapy and in what transgenes were available. Accordingly, our 50-year-old might perceive greater aging-reversal benefit from contemporary somatic gene therapy than from the outdated (albeit ubiquitously expressible) technology with which he or she was born. If so, germ-line therapy to reverse human aging might be implemented in inactive form, but never—at least, not purposely—activated.

Finally, it has been suggested(4) that indefinite postponement of aging is incompatible with the retention of self, because it necessarily entails the periodical replacement of all body parts, including the brain. However, a key distinction between animate and inanimate objects is that the former do indeed, autonomously, replace their components throughout life. Most proteins, for example, have a half-life of only a few days, even in postmitotic cells. This is a key reason why we live so long: for example, titanium is vastly stronger than cartilage, but titanium knees last only ten years.(59) Wholesale, en bloc replacement of the brain would be a different matter altogether, however. There must, therefore, be a threshold granularity of replacement that is compatible with continued identity. It seems plausible that the individual neuron is below this threshold, and thus that cell therapy (such as has already been used, albeit with serious side-effects in these early studies, Ref. 60) is a legitimate component of brain rejuvenation that would not endanger the recipient's continued identity.

What do recent centuries predict?

One way to estimate the future pace of progress in combating aging is by extrapolation from the past. A reasonable approach is to compare our present knowledge about how to combat aging with our past knowledge about goals that were subsequently achieved. The most direct comparison is with infectious diseases, which accounted for 40% of US deaths in 1900 but only 3% in 1950.(61) We do not obviously understand less today about aging and how to combat it than we understood in 1870 about infectious diseases and how to combat them: indeed, some would say we understand more. Hence, one cannot dismiss as absurd the prospect of achieving the same degree of progress against aging in the next 80 years as was achieved against infection in the period 1870–1950. Of course, one also cannot confidently infer that we will achieve such progress. Doing so would, clearly, be much more dramatic than extending a 2-year-old mouse's lifespan by a year. Indeed, it would constitute true "engineered negligible senescence" (ENS).

Recent data indicate that we are already accelerating the rate at which we postpone death of the most robust subset of the population.(62) The age of the oldest Swede rose by over one year per decade in the period 1969–1999, twice the rate during 1861–1969(62) and necessarily much more than that relative to the preceding millennium. Although we may fail to continue this trend, or even to maintain the present rate of increase, there is no obvious reason why it should not continue. To achieve ENS, "all" that is required is to continue this acceleration until the rate of increase reaches one year per year, which a logarithmic regression to the above data(62) predicts could happen this century (Fig. 1). This might be termed the "anti-aging escape velocity", where aging still exists but is being postponed (by successive medical advances) faster than time is passing.

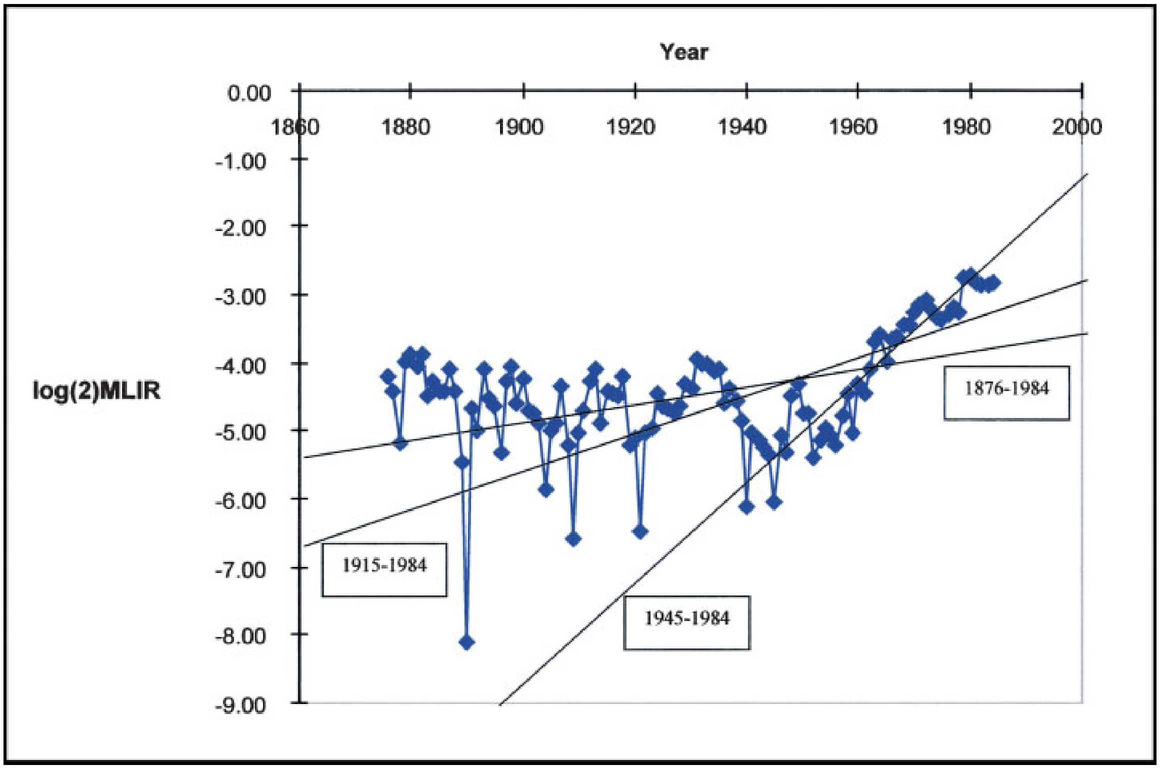

Figure 1. Logarithmic analysis of the rate of increase of the maximum lifespan in Sweden, 1861–1999. Each year's data point is the logarithm to base 2 of the rate of increase during the 30-year period centred on that year (MLIR = maximum lifespan increase rate). The regression lines are for the date ranges shown; they reach $\log_2$MLIR = 0 in year 2297 (1876–1984), 2099 (1915–1984) and 2019 (1945–1984). Data are available from the Berkeley Mortality Database, http://demog.berkeley.edu/wilmoth/mortality.

Anti-aging medicine for age-related diseases: who is missing the point?

Only 1% of the US National Institutes of Health (NIH) budget goes to research on the basic biology of aging, and the situation in western Europe is similar. A frequent argument for increasing this proportion is that even a modest extension of healthspan would hugely impact the incidence of age-related diseases. Thus, money should be spent on the effort to increase healthspan, despite the uncertainty of rapid progress. This logic has consistently fallen upon deaf ears outside the biogerontology research community. Why?

Various popular explanations seem inadequate. The dictum that prevention is better than cure is easily accepted in other contexts, so it should be easy to communicate here, to government if not to the private sector. Comprehension of the argument cannot be wholly lacking: those with influence in national government surely possess sufficient acumen. Religious opposition may be an issue in the US, but is much less so in Europe. The reallocation of funds from elsewhere in the system is not necessarily the issue, since total funding is not fixed.

Perhaps it is biogerontologists, not their interlocutors, who are guilty of a critical oversight. Their focus on making aging less debilitating has given rise to phrases such as "successful aging" and "compression of morbidity" as goals towards which biogerontology strives. However, diverse statistics show consistently that the period of late-life frailty is not being shortened by medical advances.(63–66) Its onset is being steadily postponed, but so is its conclusion (i.e., death). For example, between 1982 and 1994 the proportion of Americans over 65 who were disabled (defined as chronically unable to perform at least one basic activity of daily living, such as cooking or bathing) declined impressively, from 24.9% to 21.3%,(67) but this was due to a later age of onset, not a shorter period, of disability (Table 2).

Thus, the non-biogerontologist may conclude that increased research into aging will not deliver the stated benefit of less age-related debilitation. After all, why should medical advances that benefit robust people (delaying their frailty) not also, generally, benefit frail people (delaying their death)? The biogerontologist may counter that future interventions into aging would differ in this respect from past ones addressing specific age-related diseases, but given the difficulties in distinguishing the two this is not convincing. Two noted biogerontologists have recently voiced similar views.(70,71)

Which is the greater risk—false hopes, or a false sense of security?

The 2000/2001 chair of the world's largest biogerontology society stated recently(72) that the first 150-year-old human is probably already alive. This prediction, with all that it implies for increases in average lifespan in the same timeframe, has been widely publicised on account of a wager to which it led.(73) However, what little comment has been forthcoming within the biogerontology community has usually been one of mild distaste. This is noteworthy, because a prediction of what will happen over 100 years hence is scientifically just as meaningless as one with no timescale at all attached, and the latter is much more common in this field.

A major explanation for biogerontologists' wariness regarding even such distant timescales may be the intrinsic inertia of scientific research funding. A recent survey(74) found that only 8% of Americans expect to live to 100, and only 20% even expect the average lifespan of Americans born in 2010 to exceed 100. Ultimately, the reason that this is the prevailing view is that it is the consensus of public statements by those perceived—rightly or wrongly—as being most likely to know: namely, biogerontologists. While governments and the public perceive human ENS as unachievable in their or their children's lifetimes, they will not agitate for research directed at bringing it about. Those who allocate research funds (be they funding agencies or peer reviewers) are thus reluctant to risk their reputations for prudence by favouring ambitious but expensive anti-aging research. This, in turn, forces bioger-

Table 2. Comparison of the average time spent with age-related disability in 1982 and 1994 in the USA

Year	1982	1994
Disabled (see text) over 65 (millions)(67)	6.38	7.10
Population over 65 (millions)(67)	26.9	33.7
Percentage over 65 disabled	6.38/26.9 = 24.9%	7.10/33.7 = 21.3%
Total population (millions)(68)	231.66	260.29
% of total pop. with age-related disability	6.38/231.66 = 2.75%	7.10/260.29 = 2.73%
Life expectancy(69)	74.45	75.65
Average years with age-related disability	74.45 × 2.75% = 2.050	75.65 × 2.73% = 2.064

These calculations assume nobody suffered age-related disability below age 65, whereas the actual numbers probably fell between 1982 and 1994; however, they also neglect the effects of immigration between 1982 and 1994, which is disproportionately of young, healthy people so introduces the opposite bias.

ontologists to focus on more conservative projects. The circle is closed because such scientists cannot bite the hands that feed them by drawing attention to this chain of events, so they continue to avoid raising the public's sights. Additionally, many influential biogerontologists sincerely believe that human ENS really is unforeseeable,(2,75) making this logjam even more immovable.

Another reason is that any positive remark about the feasibility of ENS risks two undesirable reactions: in the public the engendering of unwarranted optimism, and in the research community the pigeon-holing of oneself with snake oil-peddling charlatans. Both are unjustified overreactions, but they still happen.

However, these arguments may be unsatisfactory. Firstly, the alleged danger of unwarranted optimism is that it will rebound as a reduction in the field's funding if today's incautious predictions are not fulfilled. If so, why has this not happened to cancer research, which was trumpeted in the 1960s as likely to yield results within a few years far exceeding what it has actually yielded even by today? Surely funding of aging research would be similarly maintained if reasonable progress were made, even if that progress fell short of present-day predictions. Secondly, however meaningless it may be in scientific terms to say that human ENS may be developed within a few decades, it is very significant in social terms. Profound personal decisions, such as investment in life insurance and pension plans, are based on the perceived likelihood of events a few decades hence. Governments are even more reliant on the best possible long-term prediction. Izn such circumstances, if a biogerontologist feels that the probability of a big anti-aging breakthrough within a few decades is non-negligible, can he or she justify keeping that view private?

This is not to say that the reasons given previously for remaining silent on these matters are wrong, only that they must be weighed against counterarguments. In doing so, the biogerontologist must consider the wider social consequences of ENS and the extent to which debate on it now can influence those consequences. A key consideration(2) is whether society would eventually need to impose stringent population-limiting regulations upon itself. This entirely depends on whether global population continues to grow, which is rendered uncertain by the present rapid decline in birth rates among affluent societies worldwide. Nobody knows whether children will continue to become less popular, nor whether that trend is or will be influenced by perceptions of one's remaining healthy life expectancy. Our inability to predict future birth trends accurately, even presuming no medium-term anti-aging breakthroughs, is eloquently illustrated by the United Nations' policy of publishing projections based on three different sets of assumptions, leading to world populations in 2050 differing by three billion.(76) (2050 is well before any anti-aging regimen could have this much effect on population.) Other questions, such as whether life with ENS would be boring or shallow,(77) are if anything even more unanswerable, since answers rely on highly fragile assumptions about the retention of present cultural norms. Apprehensions concerning political and distributive justice (tyrants reigning indefinitely, treatments being too costly to be universally available) cannot realistically restrain technological advance and must be solved as they arise. The morality of ENS is perhaps the least knowable of all: until ENS is here, and new norms develop concerning what constitutes an appropriate length of life given the options available, society cannot morally evaluate it.(78)

If social and ethical arguments concerning life with ENS are inconclusive, what of society's transition to that state? If ENS becomes widely perceived as achievable many years before it can actually be implemented, society has all those years to plan for the transition and make it as smooth as possible, without (for example) a long period when such medicine is only available to the wealthy. A seductive conclusion is that we can safely delay public debate until mouse aging is well under control, because the time from then until the arrival of human ENS will be ample for society to prepare. But we must also consider the immediate effects of ENS becoming widely perceived as foreseeable. Many people would consider themselves likely to benefit personally from this anticipated breakthrough—but only if they survive until it is developed. This might sharply increase the demand for health care, which already takes a large share of Western nations' wealth. The effects on the global economy could be severe. Recruitment into dangerous but socially vital professions, such as fire and police services, might fall; improved financial rewards might adequately mitigate this, or they might not.

Present-day societal considerations

Whatever the strength of arguments that aging is actually a good thing, people do not like it. In the same survey of public expectations mentioned earlier,(74) fully 63% of Americans said that they would like to live to 100.

Perhaps the only safe prediction about a post-aging world is the one that most deeply motivates the quest for it: the huge consequent reduction in chronic disability. Consideration of society's present attitudes towards ill health can and should influence what biogerontologists tell the public. No society in history (to our knowledge) has experienced a sustained compression of morbidity; nor, as we have argued above, is there any realistic prospect of this. Hence it may be misleading to promote it as our goal. Conversely, essentially everyone agrees that postponing age-related diseases is desirable. If society came to regard aging as it regards age-related diseases—that is, as potentially preventable—it would probably also regard it, again like age-related diseases, as an affront to human dignity whose prevention, however difficult, should be ardently sought. Then the funding logjam described earlier would evaporate and research to develop human ENS would surely be much accelerated. The effort that society invests in postponing specific diseases and/or postponing aging depends heavily on this issue, so it is one on which individuals and governments deserve to be better informed than at present.

One way to increase society's understanding of biogerontology is to increase their interest in it. The aforementioned wager(73) is an example. Prizes are another approach—one that has historically attracted talent to hard problems at relatively little cost and reliably captures the public imagination. One option(79) is to identify specific goals that experts believe are feasible within a decade or so and attach rewards to their accomplishment. This might distort the field's research priorities; also, many scientifically valid goals may be too esoteric to capture the public's imagination. Both problems are avoided by another proposal,(80) to award a prize for the oldest ever *Mus musculus*. This has its own difficulties, however, including validation that a mouse is really as old as claimed and decisions on what types of intervention are permitted. The two concepts are largely complementary: many key anti-aging questions are not best studied by making long-lived mice, and would be candidates for specific prizes.

The public include wealthy individuals, who may avoid investing in biogerontology because they feel that their dollars cannot yet make much difference to the rate of progress. The repeated awarding of a prize whose goal such individuals understand may alter that perception, sidestepping the sometimes ponderous rate at which public funding policy responds to changed circumstances.

Conclusion?

This article has, purposely, drawn few conclusions. Rather, we hope to stimulate debate on the issues raised by the prospect of ENS being developed soon enough to benefit many who are already alive—a prospect on whose likelihood experts (and we) are divided.(1,2,75) However, we do not identify any unambiguous, show-stopping obstacle to the development of a panel of interventions sufficient to rejuvenate a two-year-old mouse by a year (with all that that may entail for public expectations and demands concerning human aging) within about a decade. We therefore submit that the possibility of that occurrence, although unquantifiable, is not remote enough to justify society's prevailing complacency about it.

Some years ago, Rose predicted(81) that eventually we will double human lifespan—and that, when we do, we will be ashamed that we did not do it much sooner. Now is the time for society to prove him wrong, one way or the other: either to establish that human lifespan cannot be greatly increased, or to develop such technology without unnecessary delay.

Acknowledgments

We are much indebted to Jay Olshansky and Adelaide Carpenter for critical reading of the manuscript, and to David Gems, Len Hayflick, Rich Miller, Huber Warner and John Wilmoth for their invaluable contributions to the debate from which it arose. The meeting at which that debate began took place at the UCLA Center for the Study of the Evolution and the Origin of Life, hosted by the Program on Medicine, Technology and Society of the UCLA School of Medicine and funded by the Maximum Life Foundation.

References

1. de Grey ADNJ, Ames BN, Andersen JK, Bartke A, Campisi J, Heward CB, McCarter RJM, Stock G. Time to talk SENS: critiquing the immutability of human aging. Annals NY Acad Sci 2002;959:452–462.
2. Hayflick L. How and why we age. New York, NY: Ballantine Books; 1994.
3. Hayflick L. How and why we age. Exp Gerontol 1998;33:639–653.
4. Hayflick L. The future of ageing. Nature 2000;408:267–269.
5. de Grey ADNJ. The Mitochondrial Free Radical Theory of Aging. Austin, TX: Landes Bioscience; 1999. p. 189.
6. Mattson MP, Duan W, Lee J, Guo Z, Roth GS, Ingram DK, Lane MA. Progress in the development of caloric restriction mimetic dietary supplements. J Anti-Aging Med 2001;4:225–232.
7. Weindruch R, Walford RL. Dietary restriction in mice beginning at 1 year of age: effect on life-span and spontaneous cancer incidence. Science 1982;215:1415–1418.
8. Vanfleteren JR. Oxidative stress and ageing in *Caenorhabditis elegans*. Biochem J 1993;292:605–608.
9. Melov S, Ravenscroft J, Malik S, Gill MS, Walker DW, Clayton PE, Wallace DC, Malfroy B, Doctrow SR, Lithgow GJ. Extension of life-span with superoxide dismutase/catalase mimetics. Science 2000;289:1567–1569.
10. Migliaccio E, Giorgio M, Mele S, Pelicci G, Reboldi P, Pandolfi PP, Lanfrancone L, Pelicci PG. The $p66^{shc}$ adaptor protein controls oxidative stress response and life span in mammals. Nature 1999;402:309–313.
11. Brown-Borg HM, Borg KE, Meliska CJ, Bartke A. Dwarf mice and the ageing process. Nature 1996;384:33.
12. Bartke A, Coschigano K, Kopchick J, Chandrashekar V, Mattison J, Kinney B, Hauck S. Genes that prolong life: relationships of growth hormone and growth to aging and life span. J Gerontol A Biol Sci Med Sci 2001;56:B340–B349.
13. Rhee SG. Redox signaling: hydrogen peroxide as intracellular messenger. Exp Mol Med 1999;31:53–59.
14. Raineri I, Carlson EJ, Gacayan R, Carra S, Oberley TD, Huang TT, Epstein CJ. Strain-dependent high-level expression of a transgene for manganese superoxide dismutase is associated with growth retardation and decreased fertility. Free Radic Biol Med 2001;31:1018–1030.
15. Austad SN. Retarded senescence in an insular population of Virginia opossums (*Didelphis virginiana*). J Zool 1993;229:695–708.
16. Loeb J, Northrop JH. Is there a temperature coefficient for the duration of life? Proc Natl Acad Sci USA 1916;2:456–457.
17. Klass M, Hirsh D. Non-ageing developmental variant of *Caenorhabditis elegans*. Nature 1976;260:523–525.
18. Larsen PL, Clarke CF. Extension of life-span in *Caenorhabditis elegans* by a diet lacking coenzyme Q. Science 2002;295:120–123.
19. Page RE Jr, Peng CY. Aging and development in social insects with emphasis on the honey bee, *Apis mellifera* L. Exp Gerontol 2001;36:695–711.
20. Takahashi M, Pischetsrieder M, Monnier VM. Molecular cloning and expression of amadoriase isoenzyme (fructosyl amine:oxygen oxidoreductase, EC 1.5.3) from *Aspergillus fumigatus*. J Biol Chem 1997;272:12505–12507.
21. Baynes JW. The role of AGEs in aging: causation or correlation. Exp Gerontol 2001;36:1527–1537.
22. de Grey ADNJ, Archer JAC. Why don't graveyards fluoresce? Anti-aging applications of the bacterial degradation of lysosomal aggregates. J Am Aging Assoc 2001;24:118.

23. Bergers G, Javaherian K, Lo KM, Folkman J, Hanahan D. Effects of angiogenesis inhibitors on multistage carcinogenesis in mice. Science 1999;284:808–812.
24. Berd D. Autologous, hapten-modified vaccine as a treatment for human cancers. Vaccine 2001;19:2565–2570.
25. de Grey ADNJ. Mitochondrial gene therapy: an arena for the biomedical use of inteins. Trends Biotechnol 2000;18:394–399.
26. Aspinall R, Andrew D. Thymic atrophy in the mouse is a soluble problem of the thymic environment. Vaccine 2000;18:1629–1637.
27. Vasan S, Zhang X, Zhang X, Kapurniotu A, Bernhagen J, Teichberg S, Basgen J, Wagle D, Shih D, Terlecky I, Bucala R, Cerami A, Egan J, Ulrich P. An agent cleaving glucose-derived protein crosslinks in vitro and in vivo. Nature 1996;382:275–278.
28. Brazil MI, Chung H, Maxfield FR. Effects of incorporation of immunoglobulin G and complement component C1q on uptake and degradation of Alzheimer's disease amyloid fibrils by microglia. J Biol Chem 2000;275: 16941–16947.
29. Armstrong RJ, Svendsen CN. Neural stem cells: from cell biology to cell replacement. Cell Transplant 2000;9:139–152.
30. Ketonen LM. Neuroimaging of the aging brain. Neurol Clin 1998;16:581–598.
31. Arenas MI, Romo E, Royuela M, Ruiz A, Fraile B, Sanchez-Chapado M, Paniagua R. Morphometric evaluation of the human prostate. Int J Androl 2001;24:37–47.
32. Stary HC. Lipid and macrophage accumulations in arteries of children and the development of atherosclerosis. Am J Clin Nutr 2000;72:1297S–1306S.
33. Kendall DM, Bergenstal RM. Comprehensive management of patients with type 2 diabetes: establishing priorities of care. Am J Manag Care 2001;7:S327–S343.
34. Temple LK, McLeod RS, Gallinger S, Wright JG. Essays on science and society. Defining disease in the genomics era. Science 2001;293:807–808.
35. Li YM, Steffes M, Donnelly T, Liu C, Fuh H, Basgen J, Bucala R, Vlassara H. Prevention of cardiovascular and renal pathology of aging by the advanced glycation inhibitor aminoguanidine. Proc Natl Acad Sci USA 1996;93:3902–3907.
36. Swamy MS, Abraham EC. Lens protein composition, glycation and high molecular weight aggregation in aging rats. Invest Ophthalmol Vis Sci 1987;8:1693–1701.
37. Munch G, Schinzel R, Loske C, Wong A, Durany N, Li JJ, Vlassara H, Smith MA, Perry G, Riederer P. Alzheimer's disease–synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. J Neural Transm 1998;105:439–461.
38. Asif M, Egan J, Vasan S, Jyothirmayi GN, Masurekar MR, Lopez S, Williams C, Torres RL, Wagle D, Ulrich P, Cerami A, Brines M, Regan TJ. An advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness. Proc Natl Acad Sci USA 2000; 97:2809–2813.
39. Thornalley PJ, Minhas HS. Rapid hydrolysis and slow alpha, beta-dicarbonyl cleavage of an agent proposed to cleave glucose-derived protein cross-links. Biochem Pharmacol 1999;57:303–307.
40. Vaitkevicius PV, Lane M, Spurgeon H, Ingram DK, Roth GS, Egan JJ, Vasan S, Wagle DR, Ulrich P, Brines M, Wuerth JP, Cerami A, Lakatta EG. A cross-link breaker has sustained effects on arterial and ventricular properties in older rhesus monkeys. Proc Natl Acad Sci USA 2001;98: 1171–1175.
41. Kass DA, Shapiro EP, Kawaguchi M, Capriotti AR, Scuteri A, deGroof RC, Lakatta EG. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. Circulation 2001;104:1464–1470.
42. Pawelec G, Barnett Y, Forsey R, Frasca D, Globerson A, Mc Leod J, Caruso C, Franchesci C, Fülöp T, Gupta S, Mariani E, Mocchegiani E, Solana R. T cells and aging, January 2002 update. Front Biosci 2002;7:d1056–d1183.
43. LeMaoult J, Szabo P, Weksler ME. Effect of age on humoral immunity, selection of the B-cell repertoire and B-cell development. Immunol Rev 1997;160:115–126.
44. Miller RA. The aging immune system: primer and prospectus. Science 1996;273:70–74.
45. Miller RA. In: Handbook of the Biology of Aging. San Diego, CA: Academic Press; 1996. pp. 355–392.
46. Bertho JM, Demarquay C, Moulian N, Van Der Meeren A, Berrih-Aknin S, Gourmelon P. Phenotypic and immunohistological analyses of the human adult thymus: evidence for an active thymus during adult life. Cell Immunol 1997;179:30–40.
47. Douek DC, McFarland RD, Keiser PH, Gage EA, Masey JM, Haynes BF, Polis MA, Haase AT, Feinberg MB, Sullivan JL, Jamieson BD, Zack JA, Picker LJ, Koup RA. Changes in thymic function with age and during the treatment of HIV infection. Nature 1998;396:690–695.
48. Kerbel RS. Tumor angiogenesis: past, present and the near future. Carcinogenesis 2000;21:505–515.
49. Bryan TM, Englezou A, Gupta J, Bacchetti S, Reddel RR. Telomere elongation in immortal human cells without detectable telomerase activity. EMBO J 1995;14:4240–4248.
50. Pawelec G, Heinzel S, Kiessling R, Muller L, Ouyang Q, Zeuthen J. Escape mechanisms in tumor immunity: a year 2000 update. Crit Rev Oncog 2000;11:97–133.
51. Kristal BS, Yu BP. An emerging hypothesis: synergistic induction of aging by free radicals and Maillard reactions. J Gerontol 1992;47:B107–B114.
52. von Zglinicki T, Saretzki G, Docke W, Lotze C. Mild hyperoxia shortens telomeres and inhibits proliferation of fibroblasts: a model for senescence? Exp Cell Res 1995;220:186–193.
53. Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. Cancer Res 1999;59:4161–4164.
54. Breslow JL. Mouse models of atherosclerosis. Science 1996;272:685–688.
55. Guenette SY, Tanzi RE. Progress toward valid transgenic mouse models for Alzheimer's disease. Neurobiol Aging 1999;20:201–211.
56. Verma IM, Somia N. Gene therapy—promises, problems and prospects. Nature 1997;389:239–242.
57. Klimatcheva E, Rosenblatt JD, Planelles V. Lentiviral vectors and gene therapy. Front Biosci 1999;4:D481–D496.
58. Stock G. Redesigning humans: our inevitable genetic future. Boston, MA: Houghton Mifflin; 2002 p. 78–96.
59. Fanning JW, Joseph J, Kaufman EE. Follow-up on uncemented total knee arthroplasty. Orthopedics 1996;19:933–999.
60. Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, Fahn S. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001;344:710–719.
61. Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999;281: 61–66.
62. Wilmoth JR, Deegan LJ, Lundstrom H, Horiuchi S. Increase of maximum life-span in Sweden, 1861–1999. Science 2000;289:2366–2368.
63. Olshansky SJ, Rudberg MA, Carnes BA, Cassel C, Brody J. Trading off longer life for worsening health: the expansion of morbidity hypothesis. J Aging Health 1991;3:194–216.
64. Crimmins EM. Mortality and health in human life spans. Exp Gerontol 2001;36:885–897.
65. Kelly S, Baker A. Healthy life expectancy in Great Britain, 1980–96, and its use as an indicator in United Kingdom Government strategies. Health Statistics Quarterly 2000;7:32–37.
66. Himsworth RL, Goldacre MJ. Does time spent in hospital in the final 15 years of life increase with age at death? A population based study. BMJ 1999;319:1338–1339.
67. Manton KG, Corder L, Stallard E. Chronic disability trends in elderly United States populations: 1982–1994. Proc Natl Acad Sci USA 1997;94: 2593–2598.
68. US Census Bureau. Historical national population estimates: July 1, 1900 to July 1, 1999. 2000; http://www.census.gov/population/estimates/nation/popclockest.txt.
69. Noymer A, Schoen R, Garenne M. The 1918 influenza epidemic's effects on sex differentials in mortality in the United States. Pop Dev Review 2000;26:565–581.
70. Masoro E. "Successful aging"—useful or misleading concept? Gerontologist 2001;41:415–418.
71. Kirkwood TBL. Reith Lectures: The end of age. Lecture 5: new directions. 2001; http://www.bbc.co.uk/radio4/reith2001/lecture5.shtml.

72. Brown K. How long have you got? Sci Am Presents 2000;11:9–15.
73. McCann J. Wanna bet? Two scientists wager on whether humans can live to 130 or 150 years. The Scientist 2001;15:8.
74. Alliance for Aging Research. Great expectations: Americans' views on aging. 2001; http://www.agingresearch.org/survey/webversion/summary.html.
75. Holliday R. Understanding ageing. Cambridge, UK: Cambridge University Press; 1995.
76. United Nations. World population prospects, 2000 Revision. 2001; http://www.un.org/esa/population/publications/wpp2000/.
77. Kass LR. L'Chaim and its limits: why not immortality? First Things 2001;113:17–24.
78. Gems D. Treatment, enhancement and the retardation of ageing: is more life always better? Manuscript in preparation.
79. Stock G. The Prometheus Prize. 1999; http://research.mednet.ucla.edu/pmts/agingprz.htm.
80. Cutler RG, Heward CB, Stock G, Ingram D, de Grey ADNJ. The Methuselah Mouse prize idea. 2001; http://www.gen.cam.ac.uk/MM.htm.
81. British Broadcasting Corporation. Future fantastic. 1996; http://www.bbc.co.uk/tw/future.html.