EMBO reports

science & society

Resistance to debate on how to postpone ageing is delaying progress and costing lives

Open discussions in the biogerontology community would attract public interest and influence funding policy

Aubrey D. N. J. de Grey

A perennial complaint in biogerontology, and one whose legitimacy I would be the last to dispute, is that public funding for ageing research is far lower than it should be. Such funding has roughly kept pace with biomedical research spending as a whole, but much more is warranted because postponement of ageing would have a far greater impact on public health and healthcare spending than postponement of any or all of the major age-related diseases. Here, I discuss whether our obstinately modest funding is due, as most of my biogerontologist colleagues evidently feel, to a failure on our part to communicate the scientific and biomedical realities to our political paymasters, and is therefore best rectified by continuing to repeat the arguments we have used for decades until they sink in. I argue that it is instead because those arguments are genuinely weak. I then discuss whether our neglect of more effective justifications for greater investment in biogerontology research is because we overlook key components of the trade-offs that determine funding policy, or whether the problem is the failure of most biogerontologists to maintain an open mind concerning the scientific options. I conclude that it is for both those reasons. Thus, our field is passing up the opportunity to elevate itself to its rightful level of public appreciation and investment, with the result that much longer healthy lives are being denied those who will die before 'real anti-ageing medicine' arrives unless we start working harder towards it now.

> … our field is passing up the opportunity to elevate itself to its rightful level of public appreciation and investment…

This essay covers controversial and sensitive issues, so I start with the safest one. Most biogerontologists believe, or at least claim, that a legitimate and plausible long-term goal of their research is to extend the healthy human lifespan by intervening in the ageing process. Even that seemingly anodyne description of what biogerontologists seek is replete with land mines, so I prepare the ground by clarifying what biogerontologists, by and large, do and do not mean by it.

First, what is 'the ageing process'? In the context of discussing interventions, ageing can be defined as the lifelong accumulation of various intrinsic side effects of normal metabolic processes, which ultimately reach an abundance that disrupts metabolism and causes severe dysfunction of tissues and the whole organism. Some aspects of this dysfunction are classified as age-related diseases, and some less specifically as 'frailty', but their common cause is the accumulation of damaging metabolic side effects. Accordingly, treatments that either slow the rate of that accumulation or actually reverse it will, if sufficiently comprehensive, postpone the recipient's decline into age-related ill health.

Second, biogerontologists generally focus strongly on healthy lifespan as opposed to total lifespan. There is general agreement that it is not a worthwhile goal to improve our ability to keep severely ill people alive for a long time if, as is the case today, there is no prospect of ever restoring them to better health. But this 'expansion of morbidity'—extension of the average time that people are frail at the end of their lives—is not what most biogerontologists seek. Instead, their goal is 'compression of morbidity'—postponement of the onset of ill health caused by ageing, but with only a shorter postponement, if any, of death.

> Not only is frailty unenviable, it is also extremely expensive…

The merits of this goal seem unassailable. Not only is frailty unenviable, it is also extremely expensive: diverse statistics show that the amount of healthcare resources that people consume during their last year of life, whatever their age at death, is typically more than in the rest of their life in total (Himsworth & Goldacre, 1999). Compression of morbidity would thus not only relieve suffering on a huge scale but also be staggeringly beneficial economically. I do not claim originality for this logic. Indeed, it has been the mantra of gerontology since time immemorial. On the cover of the first issue of the *Journal of Gerontology* in 1946, it appeared in the form of the phrase "to add life to years, not just years to life". The merits of intervening in ageing itself, rather than concentrating on its late-life consequences, are also trumpeted in the equally age-old aphorism that "ageing is not a disease".

One may thus wonder why progress in attracting funds to pursue these goals has been so slow (Perry, 2004). It was not until 1975 that the US National Institutes of Health (NIH; Bethesda, MD, USA) opened the National Institute on Aging (NIA); the NIA still receives only about 3% of the NIH's total budget, no more than it did a decade ago. Moreover, even within the NIA only 10% of funds are directed at the basic biology of ageing *per se*, with the remainder being ring-fenced for research on Alzheimer's disease and behavioural, social or clinical gerontology.

The ultimate power to determine how much public money is spent on ageing research lies, inevitably, with politicians (Mackey, 2004); evidently, therefore, biogerontology's rhetoric is rather ineffective at swaying them. For illustration, I focus here on the USA, whose biomedical research expenditure is the highest in the world, but what I write applies worldwide. The head of each institute of the NIH gives a presentation to the US Congress each year. At these hearings, the NIA's Director consistently delivers the message "adding life to years, not just years to life" to Representatives and Senators. And with the same regularity, the NIA's budget remains in lockstep with those institutes that focus on specific age-related diseases, even though the postponement of the latter would do much less for public health than the achievement of the NIA's goals. Why?

I feel that there are two main reasons for politicians' resistance to the blandishments of gerontologists, one of which many biogerontologists consistently overlook. The one that they wholly appreciate was perhaps best expressed by Rich Miller in his mostly outstanding essay "Extending Life: Scientific Prospects and Political Obstacles" (Miller, 2002): "Senators' and voters' parents died of specific diseases." (That article has been widely acknowledged as the definitive account of the issues it addresses, so I shall return to it repeatedly here, to highlight both the qualities and the shortcomings of its arguments.) Ageing therefore does not ignite politicians' emotions when resources are limited and noble causes are seemingly unlimited. This, biogerontologists mostly believe, is a major mental block that impedes politicians' ability to accept what any objective observer should—in the biogerontologist's view—consider obvious.

> … we see clearly that describing ageing as "not a disease" has severe rhetorical drawbacks…

Before moving on to discuss the second, widely overlooked, source of political resistance to funding ageing research, we can already note how the traditional gerontological rhetoric has become an albatross—and perhaps always was. "Ageing is not a disease", as I noted earlier, has long been a slogan of gerontology. Politicians may be inclined to feel that, well, if ageing is not a disease, it is probably not something we ought to be spending much effort combating, then, is it? When we reflect that this is a gut feeling that most people, and thus most politicians, probably have at the outset—what Miller (2002) termed "gerontologiphobia"—and also that when money is tight its allocators seek excuses to narrow the list of candidate recipients, we see clearly that describing ageing as "not a disease" has severe rhetorical drawbacks, regardless of the value it may once have had in distinguishing biogerontology from other biomedical research.

This problem is in my view dwarfed, however, by the second difficulty that politicians may have in embracing biogerontologists' arguments: the merit of spending money in pursuit of a given goal depends not only on that goal's desirability but also on its feasibility. Those of us who do not suffer from gerontologiphobia are persistently awed by the logical contortions that gerontologiphobes perform when asked to justify their pro-ageing stance. Similar awe—although that might not be the word they would use—may be felt by politicians who encounter the efforts of gerontologists to extract from available data an argument that their work will probably cause substantial compression of morbidity in the foreseeable future.

Although the concept is much older, the term 'compression of morbidity' was introduced by James Fries in a paper published in 1980: "Present data allow calculation of the ideal average life span, approximately 85 years. Chronic illness may presumably be postponed by changes in life style [...] Thus, the average age at first infirmity can be raised, thereby making the morbidity curve more rectangular. Extension of adult vigor far into a fixed life span compresses the period of senescence near the end of life" (Fries, 1980). Even ignoring the questionable assumption of a fixed lifespan, we immediately see that Fries is not predicting that combating ageing will compress morbidity. Instead, he stresses "changes in life style"—not a noted sphere of biogerontological influence. Fries's hope that US morbidity would be compressed has been realized in the meantime, and the details of that change duly support the theory that lifestyle, rather than biomedical progress, is responsible. All the compression observed is in mild to moderate disability, which is substantially achievable by lifestyle changes, whereas absolutely no compression of severe morbidity has occurred (Fries, 2003).

> One must also doubt the biological plausibility that postponing frailty will not similarly postpone death

One must also doubt the biological plausibility that postponing frailty will not similarly postpone death. For this to occur, there must be some aspect of ageing that contributes more to death than to frailty: compression of morbidity might then be achieved by postponing only the other aspects of ageing. But if we have learned anything about ageing over the past decades, it is that ageing consists of multiple interacting processes that are mutually regulated. Altering the rate of some such processes but not others is thus a highly implausible goal. Fries's assumption of a fixed lifespan is certainly wrong, and indeed he may only have been speaking about the time until means of truly postponing ageing are developed. However, whether before that advance or beyond it, compressing morbidity by postponing ageing is a pipe dream.

You would not guess this had you attended, to take just one conspicuous example, an April 2001 presentation to Congress by Richard Hodes, Director of the NIA (Hodes, 2001). As a major plank of his presentation, Hodes cited a report that documents compression of morbidity (Manton *et al*, 1997). He did not state explicitly that biogerontology was substantially responsible for this, but he certainly implied it. I feel he did so in the sincere belief that progress

was being made in combating ageing and that this was compressing morbidity, although, as noted above, that is a gross misinterpretation of Manton *et al*'s data. If this were a successful policy that brought gerontology an ever-increasing share of public research spending, it could perhaps be forgiven—but it has not done that.

I suspect that, in their heart of hearts, many of my colleagues in biogerontology secretly realize or at least fear the futility of compressing morbidity by manipulating ageing. These people face an unenviable problem: they are scientists trapped in a biomedical discipline, so their path of least resistance may be to submit to the gerontologiphobia of society and not rock the boat. I should explain what I mean by this. When many of today's senior biogerontologists entered the field, serious postponement of ageing was not realistic, and they therefore became biogerontologists partly—and in most cases, I believe, mainly—with the curiosity-driven motivations of a basic scientist rather than the goal-directed ones of an engineer or clinician. They find discovery fulfilling, and seek only the resources to carry on discovering more. Any talk of actually doing something about ageing is then a fig leaf—the sort of camouflage that all scientists use to make society value their work without fretting that there is no guarantee that it will ever be useful. Perhaps this is why those who propound the most blatantly invalid reasons why our hitherto minimal rate of progress in postponing ageing cannot be accelerated—reasons transparently based on misuse of logic (Hayflick, 2004) or of extrapolation (Olshansky *et al*, 2001)—are often allowed to carry on espousing their views without challenge. There may be a tacit hope that the blinding unjustifiability of their pessimism will distract the attention of the funding bodies from the subtler contradictions in what mainstream gerontology is saying to justify its existence.

> If I thought that serious postponement of ageing was still an indefinitely distant prospect, I would thus feel that the honest way forward for biogerontology would be to reinvent itself as a basic science…

If I thought that serious postponement of ageing was still an indefinitely distant prospect, I would thus feel that the honest way forward for biogerontology would be to reinvent itself as a basic science, with no pretensions to biomedical relevance other than what may arise from serendipitous discoveries along the way. In reality, however, I contend that we now know enough about ageing and how we might postpone it that it is time to try. Our appropriate course should therefore be in the opposite direction: to declare that our goal is to postpone ageing as much as possible, as soon as possible, to describe how we intend to do this, and to respond to the inchoate gerontologiphobic mutterings of the pro-ageing masses with the systematic dismantling of their logic (de Grey, 2003b) that we biogerontologists all know that we can deliver but are too often tempted to keep to ourselves in the interests of a quiet life.

Let me, therefore, leave the reader in no doubt about what I mean by postponing ageing as much as possible, as soon as possible. I mean developing ways to stop people from getting frailer and more prone to life-threatening diseases as they get older, and moreover to restore the already frail to youthful vitality (de Grey *et al*, 2002; de Grey, 2003a). I mean doing this indefinitely, so that people's vigour and risk of death are not influenced by their age, even at ages many times what we reach today (de Grey, 2004a). Just as the purpose of oncology is to defeat cancer, the purpose of biogerontology is, and should be declared to be, to defeat ageing. Vintage cars do not age, because their owners have the dedication and expertise to give them the necessary maintenance. We will in due course have the expertise to maintain ourselves with similar fidelity, and few can doubt that we will then also have the dedication. Hastening that advance, therefore, is a legitimate and honourable goal of which we have been ashamed for too long.

Until a few years ago, the only reproducible way to make a mammal live longer was to reduce its caloric intake (Masoro, 2003). No one knows quite how this works, so in view of the popularity of eating in most human populations there was little biogerontologists could offer in the way of acceptable life-extension therapies. In recent years, however, some of the main genetic components of the caloric restriction (CR) response have been identified, and lifespans have been extended by genetic manipulation—not only in short-lived species such as flies, but also in rodents (Liang *et al*, 2003). Pharmacological emulation of these results is eminently plausible and several researchers have created start-up companies to accelerate the development of such drugs (Stuart, 2003).

> Just as the purpose of oncology is to defeat cancer, the purpose of biogerontology is, and should be declared to be, to defeat ageing

An alternative approach, which I have spearheaded for the past 4–5 years, is termed SENS: Strategies for Engineered Negligible Senescence (de Grey *et al*, 2002; Arking, 2004). It does not consist of a search for 'magic bullets' that will elicit a latent CR-like response and coordinatedly retard all the processes that contribute to age-related degeneration, but rather a collection of piecemeal interventions to repair specific categories of molecular and cellular damage. As such, it could not be more different from the CR-emulation approach. At first glance it seems unlikely to be feasible, but on closer inspection this is less clear, because SENS consists of interventions that target the initially inert by-products of metabolism, rather than metabolism itself, and thus may be much freer of side effects. Also, because SENS entails repair rather than retardation, its potential to postpone frailty even in those who first receive it in middle age is far greater than with the holistic CR-emulation approach, as is its potential to do this indefinitely. Reversing a process may seem intuitively far more difficult than just slowing it down, but this is not necessarily so: preventing a leaking dinghy from sinking by bailing water over the side requires no greater technological sophistication than doing so by plugging the hole with a rag.

This brings me back to Miller's 2002 commentary. Miller is optimistic about the medium-term prospects for postponing ageing dramatically by emulating CR (Miller, 2002): "CR typically produces in rodents an increase in mean and maximal longevity of about 30–40%. Similarly, the dwarf mutations of mice lead to an increase in both their mean and maximal lifespan of about 25–70%, and the

longest-lived small dog breeds typically outlive average-sized dogs by a similar amount. Restriction of the amino acid methionine, which, like the restriction of calories, also retards growth and extends lifespan, lengthens life by about 30–42%, and a mutation that alters cellular resistance to irradiation seems to produce mice that live 28% longer. Thus one can, with some confidence, expect that an effective antiaging intervention might increase the mean and maximal human lifespan by about 40%, which is a mean age at death of about 112 years for Caucasian American or Japanese women, with an occasional winner topping out at about 140 years."

This is not a passage of which, in my view, Miller should be proud. Elsewhere in the essay he lists several reasons why biogerontology is hard to sell to politicians, students and the public, the first of which is that "Most gerontologists who are widely known to the public are unscrupulous purveyors of useless nostrums." Although he does not name anyone, others have singled out the American Academy of Anti-Aging Medicine (A^4M; www.worldhealth.net) as the archetype of this group. Here, for illustrative purposes, is an excerpt from A^4M's mission statement: "A^4M believes that the disabilities associated with normal aging are caused by physiological dysfunction which in many cases are amenable to medical treatment, such that the human life span can be increased, and the quality of one's life improved as one grows chronologically older." One needs little experience of promotional literature to spot the selective omissions here—there is no mention of whether this medical treatment is already available, or whether its effect will be on the lifespan of all, most or only a few people. But that degree of rose-tinting is typical of those who want to make money—which A^4M's leaders do not conceal, although A^4M itself is a non-profit entity; society considers this acceptable and lays the blame for any disappointment with non-performance of products at the door of the over-gullible consumer.

Let us now similarly analyse Miller's prediction quoted above. "Thus" is a strong word among scientists—one that should be avoided unless it can be robustly defended with data. However, Miller finds it possible to extrapolate "with some confidence" from mammalian interventions begun at either conception or weaning to implicitly foreseeable anti-ageing interventions for humans. The long-lived mammals that Miller describes are much smaller than normal members of the same species—not something most people would impose on their children even if long life resulted—and Miller ignores the complete failure of CR to extend lifespan when initiated in rats in late life (Lipman *et al*, 1995, 1998). The more encouraging results of Stephen Spindler's group (Dhahbi *et al*, 2004; Rae, 2004) greatly post-date Miller's essay so do not excuse this. There is a modest effect if CR is begun earlier in adulthood (Weindruch & Walford, 1982), but again, when mentioning this, Miller fails to acknowledge that taking any CR-mimetic pill throughout one's adult life is unwise when one weighs the necessarily unknowable risk of long-term side effects against the rather large chance of something coming along in the subsequent decades whose greater efficacy outweighs its later initiation. Miller also mentions one mouse mutant that has shown life extension without growth retardation (Migliaccio *et al*, 1999), but omits that this was in a strain so short-lived that most gerontologists considered the result highly preliminary (Lithgow & Andersen, 2000). Finally, in common with most gerontologists, he neglects the clear inverse correlation across the animal kingdom between the normal lifespan of a species and the proportion by which that lifespan can be increased by nutrient deprivation, even though this was noted in independent publications a decade earlier (Harrison & Archer, 1989; Holliday, 1989).

This departure from the critical incisiveness that earned Miller the influence he now wields in biogerontology is made worse by the fact that he is not in this business for the money. Several gerontologists who share Miller's view have started biotech companies, so observers are suitably careful in analysing what they say on these matters. Miller has not, and is thus in a position of greater authority than ever—authority that is abused by selectivity such as the above.

I have recently published (de Grey, 2005) a detailed critique of the biological underpinnings of the CR-emulation approach, extending the arguments just cited (Harrison & Archer, 1989; Holliday, 1989), in which I conclude, on the basis of a wide variety of data and evolutionary theory, that even *bona fide* CR initiated in early adulthood, let alone pharmacological CR emulation initiated later in life, will probably confer a maximum addition of 2–3 years of healthy and total life in humans. My pessimism concerning this approach to human life extension is therefore available for open discussion—whether in the academic literature, at the conference bar or in the wider media.

Many biogerontologists are similarly pessimistic about the prospects for SENS. Some of their criticisms are easily dismissed (de Grey, 2003b). The fact that SENS originates from someone without experimental training is irrelevant—I indeed know less than most biogerontologists about how to run a gel, but I certainly know more than they about the hitherto non-biogerontological fields that I have brought to bear on the ageing problem, as I have thoroughly researched the experimental literature in these areas and discussed my proposals with the researchers who published that literature, which most biogerontologists have not done. The absence of modest life-extension results from existing precursor technologies to SENS means nothing for the efficacy of the complete SENS panel, any more than the failure of windscreens, steering wheels and carburettors to move slowly along the ground when petrol is poured on them implies anything about their combination. The intuition that repairing age-related damage must be far harder than preventing it was rebutted above in general terms and fares no better when the specifics are examined, because the hardest parts of both approaches—if one wishes to go further than what pharmacological CR emulation can promise—are in the delivery of genes and cells to somatic tissues, technologies that will work as well for SENS as for any other medical purpose.

This does not, of course, suffice to show that SENS is promising: what is needed is public scrutiny of its feasibility by researchers who may be better placed than its author to identify its flaws. In contrast to my critique of the CR-emulation model, this scrutiny has not been forthcoming. Is this because my colleagues are otherwise engaged? Doubtless it largely is. But not entirely, as shown by the following sentence from an anonymous review of the first manuscript describing SENS (de Grey *et al*, 2002): "I think it would be irresponsible to publish the work as it stands, because it could engender quite unwarranted optimism in readers." Even

more blatantly, an anonymous review of a recent manuscript (Rae, 2005) in which Michael Rae, a newcomer to biogerontology, bemoans the lack of such discussion, stated: "Rae laments that he 'has yet to hear a cogent rejoinder…' from the anti-aging skeptics; in my view it's because we skeptics have yet to see [anything] even remotely convincing from de Grey and his ilk, and don't wish to draw further public attention to this fringe movement." While in a certain respect it is cheering to note that those scientists who would rather suppress debate than engage in it at least acknowledge that I have an ilk, most biogerontologists would have some difficulty in regarding the co-authors of my SENS papers (see de Grey *et al*, 2002) as a 'fringe movement'. One might thus question whether the author of these comments entirely lives up to the scientific ideal of open debate.

It virtually goes without saying that the above state of affairs may be costing lives. Perhaps the CR-emulation approach is more promising than I believe at present, in which case the flaws in my arguments will be identified; my publication of those arguments will hasten that event and stimulate the development of CR mimetics. Conversely, perhaps the SENS approach is the more promising, and if so it will eventually attract the funding necessary to realize it. That funding will not be readily forthcoming, however, until SENS has withstood detailed scrutiny by the biogerontology and other relevant communities. Delaying such a test by the above stratagems thus risks a corresponding delay in the development of the first 'real anti-ageing medicines'. As the risk of death from accidents and infections as well as 'intrinsic' causes rises steeply with age (Carnes & Olshansky, 1997), it is safe to say that fewer people die of truly age-independent causes above the age of 65 than of age-related causes below 65: in other words, the death rate from ageing exceeds the death rate of those over 65. Thus, ageing claims on the order of 100,000 lives per day (de Grey, 2004b). Those lives should be in biogerontologists' minds when we exercise our influence on research directions.

REFERENCES

Arking R (2004) A new age for aging? Ethical questions, scientific insights, and societal outcomes. *Rejuvenation Res* **7:** 53–60

Carnes BA, Olshansky SJ (1997) A biologically motivated partitioning of mortality. *Exp Gerontol* **32:** 615–631

de Grey AD (2003a) An engineer's approach to the development of real anti-aging medicine. *Sci Aging Knowl Environ* **2003:** VP1

de Grey AD (2003b) The foreseeability of real anti-aging medicine: focusing the debate. *Exp Gerontol* **38:** 927–934

de Grey AD (2004a) Escape velocity: why the prospect of extreme human life extension matters now. *PLoS Biol* **2:** 723–726

de Grey AD (2004b) Three self-evident life-extension truths. *Rejuvenation Res* **7:** 165–167

de Grey AD (2005) The unfortunate influence of the weather on the rate of ageing: why human caloric restriction or its emulation may only extend life expectancy by 2–3 years. *Gerontology* **51:** 73–82

de Grey AD, Ames BN, Andersen JK, Bartke A, Campisi J, Heward CB, McCarter RJ, Stock G (2002) Time to talk SENS: critiquing the immutability of human aging. *Ann NY Acad Sci* **959:** 452–462

Dhahbi JM, Kim HJ, Mote PL, Beaver RJ, Spindler SR (2004) Temporal linkage between the phenotypic and genomic responses to caloric restriction. *Proc Natl Acad Sci USA* **101:** 5524–5529

Fries JF (1980) Aging, natural death, and the compression of morbidity. *N Engl J Med* **303:** 130–135

Fries JF (2003) Measuring and monitoring success in compressing morbidity. *Ann Intern Med* **139:** 455–459

Harrison DE, Archer JR (1989) Natural selection for extended longevity from food restriction. *Growth Dev Aging* **53:** 3

Hayflick L (2004) "Anti-aging" is an oxymoron. *J Gerontol A Biol Sci Med Sci* **59:** B573–B578

Himsworth RL, Goldacre MJ (1999) Does time spent in hospital in the final 15 years of life increase with age at death? A population based study. *BMJ* **319:** 1338–1339

Hodes RJ (2001) FY 2002 Hearing on Life Span. House Subcommittee on Labor-HHS-Education Appropriations. Apr 4. www.nia.nih.gov/AboutNIA/BudgetRequests/LifeSpan2001April4.htm

Holliday R (1989) Food, reproduction and longevity: is the extended lifespan of calorie-restricted animals an evolutionary adaptation? *Bioessays* **10:** 125–127

Liang H, Masoro EJ, Nelson JF, Strong R, McMahan CA, Richardson A (2003) Genetic mouse models of extended lifespan. *Exp Gerontol* **38:** 1353–1364

Lipman RD, Smith DE, Bronson RT, Blumberg J (1995) Is late-life caloric restriction beneficial? *Aging (Milano)* **7:** 136–139

Lipman RD, Smith DE, Blumberg JB, Bronson RT (1998) Effects of caloric restriction or augmentation in adult rats: longevity and lesion biomarkers of aging. *Aging (Milano)* **10:** 463–470

Lithgow GJ, Andersen JK (2000) The real Dorian Gray mouse. *Bioessays* **22:** 410–413

Mackey T (2004) A policy analysis of funding for ambitious interventional gerontology: the possibility of rejuvenation research at the National Institute on Aging. *Rejuvenation Res* **7:** 211–222

Manton KG, Corder L, Stallard E (1997) Chronic disability trends in elderly United States populations: 1982–1994. *Proc Natl Acad Sci USA* **94:** 2593–2598

Masoro EJ (2003) Subfield history: caloric restriction, slowing aging, and extending life. *Sci Aging Knowl Environ* **2003:** RE2

Migliaccio E, Giorgio M, Mele S, Pelicci G, Reboldi P, Pandolfi PP, Lanfrancone L, Pelicci PG (1999) The p66shc adaptor protein controls oxidative stress response and life span in mammals. *Nature* **402:** 309–313

Miller RA (2002) Extending life: scientific prospects and political obstacles. *Milbank Quart* **80:** 155–174

Olshansky SJ, Carnes BA, Desesquelles A (2001) Prospects for human longevity. *Science* **291:** 1491–1492

Perry D (2004) Someone's knocking on the laboratory door. *Rejuvenation Res* **7:** 49–52

Rae M (2004) It's never too late: calorie restriction is effective in older mammals. *Rejuvenation Res* **7:** 3–8

Rae MJ (2005) All hype, no hope? Excessive pessimism in the "anti-aging medicine" special sections. *J Gerontol A Biol Sci Med Sci* **60:** 139–140

Stuart M (2003) The genomics of longevity. In *Start Up: Windhover's Review of Emerging Medical Ventures* p22. Norwalk, CT, USA: Windhover Information, Inc

Weindruch R, Walford RL (1982) Dietary restriction in mice beginning at 1 year of age: effect on life-span and spontaneous cancer incidence. *Science* **215:** 1415–1418

Aubrey D. N. J. de Grey is in the Department of Genetics, University of Cambridge, Cambridge, UK. E-mail: ag24@gen.cam.ac.uk

doi:10.1038/sj.embor.7400399