A Revolution in Ageing: The New Biology of Ageing and its Implications

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Summary

Until recently the biology of ageing, like that of consciousness, seemed an unassailable topic. Ageing was to biologists an intractable labyrinth of diverse deteriorative processes within which primary causes were impossible to locate. But around 15 years ago, discoveries in the genetics of ageing initiated a startling forward march in biogerontology (the study of the biology of ageing). In particular, studies of long-lived mutants in simple organisms, including a tiny nematode worm with a long name (*Caenorhabditis elegans*), have lead to the discovery of genes and biochemical pathways that control the pace of the ageing process. Recent discoveries imply that some of these ageing-control mechanisms are operative in higher animals, perhaps including human beings. Given the present rapid rate of progress in studies of ageing, the prospects are that we may quite soon attain, at long last, a real understanding of the biology of this determinant of the human condition. How easily such a knowledge will translate into treatments for human ageing is unclear. However, in animal models, scientists have not only achieved striking increases in lifespan but also a postponement of the infirmity and illness associated with ageing. This last finding is of critical importance, since it demonstrates that biological ageing is an effective point of intervention for prophylaxis against ageing-related diseases. In humans, these include the major mortal illnesses of the developed world: cardiovascular disease, type II diabetes, neurodegenerative diseases such as Alzheimer's and Parkinson's disease, and cancer. While these advances are exciting, it is sometimes said that one should be cautious of achieving one's innermost desires. Since the dawn of culture, we have sought cures for ageing; but would their discovery be a good thing? Given the benefits of treating ageing in terms of protection against disease and of alleviating human suffering, this, surely, is something that we must pursue. However, current studies suggest that treating ageing may reduce incidence of age-related diseases at any given age, but not overall, lifetime incidence. Such findings direct us to a question of growing importance: What should the goals of biogerontology be?

The new biology of ageing

Biogerontology, the study of the biology of ageing, is a relatively immature field, but one that is now bursting with life; for comprehensive overviews of the field, see for example (Austad, 1999; Finch, 1990). It is not a unified field, but rather a loose federation of fragments of a field that, in fits and starts, are coalescing. Some aspects of biogerontology are older, including some fairly moribund elements, such as the rate of living theory, while others, such as the genetics of ageing, are nascent and full of life. One reason why the study of ageing is so fragmented is that it is each

existing field within biology has its own sub-field of ageing research. Evolutionary biologists ask: Why did ageing evolve? Geneticists ask: How do genes control ageing? Biochemists ask: What biochemical processes determine the ageing process? As an introduction to biogerontology, here are some examples of key questions asked in different facets of the field.

Comparative Biology: How does ageing differ between species?

Although the anatomy and life cycle of countless species of animal, plant, fungus and microbe have been described in great detail, there is relatively little information about ageing in most cases. This is a pity because one of the most remarkable features of comparative biology is the way that different species age so very differently. This is true of mammalian species, which age at very different rates. This means that individual animals grow old and decrepit, and develop diseases of ageing, at different rates, and have different lifespans. These differences are seen even under conditions that are ideal for survival, i.e. excluding mortality from causes other than ageing, such as predation, starvation and injury. For example, the maximum lifespan of the standard laboratory mouse is only 4 years, while humans can live up to 122 years. In a way this is surprising, since both are composed of similar basic constituents in terms of cell and organ types, and anatomy and physiology: each is formed of skin, blood, bone, and has a heart, a liver, kidneys and so forth that function in similar ways. Why, then, do they age at such different rates? Even our closest relative, the common chimpanzee, has a very different lifespan, living only up to 74 years. This demonstrates that lifespan can differ in even closely related species. Other mammals are longer-lived even than humans. For example, bowhead whales can live for at least two centuries (George et al., 1999). This tells us that human longevity does not reflect the presence of a ceiling for mammalian longevity, and this is good to know. More broadly, the striking variation in lifespan between different species tells us that ageing, like other traits, is subject to evolution, and can even evolve rapidly. It also implies that, just like other traits, ageing is controlled by genes.

Among lower animals, unusual patterns of ageing provide further insights into the nature of ageing. For example, one sometimes sees striking variation in ageing between members of the same species. Take the nematode worm *Strongyloides ratti*, which I have worked on a little. This unusual creature has two distinct adult forms, one of which lives in the soil, and the other which is a parasite that calls home the interior of rats. The soil-dwelling form ages and dies after only 5 days, while the parasite can live for over a year: an 80-fold difference in lifespan (Gardner et al., 2006). Strikingly, these two forms are genetically identical, illustrating how animals can show very high levels of phenotypic plasticity in ageing. Such plasticity seems also to occur in human beings where women live on average 4-6 years longer than men (probably due to the effects of testicular hormones on men). More strikingly, some simple animals show no signs of ageing at all: they are potentially immortal. This appears to be true of many coelenterates, including this the tiny, betentacled, fresh water animal Hydra. Painstaking, long-term observational studies have failed to detect any sign of ageing in this species (Martínez, 1998). Thus, ageing is not an inevitable characteristic of organisms. Why, then, does it occur in some species but not others?

Evolutionary Biology: What is ageing for?

Most animal species, particularly higher animals, do age, and the variation in ageing rate between animal species shows that ageing rate is subject to evolution. This raises the question: Does ageing contribute in any way to organismal fitness? After all, most features of living organisms contribute to fitness: we know what, say, eyes, fur, teeth are for; but what about ageing? What is *it* for? Surely its presence implies that must have a purpose, in terms of

contributing to biological fitness? An early theory took just this view. Alfred Russel Wallace, a contemporary of Charles Darwin, proposed that ageing occurs for the good of the species, and serves to get rid of old, worn out individuals to prevent them from competing with their offspring for scarce resources. However, this idea does not survive close scrutiny. Under most conditions natural selection would favour individuals who refused to bow out gracefully, but instead continued to live and reproduce. So what is ageing for? The true answer is, sadly: Nothing.

The central idea of the modern evolutionary theory of ageing was conceived by the geneticist J.B.S. Haldane in 1941 when thinking about Huntington's disease, a hereditary neurodegenerative condition. Huntington's is unusual in that it is relatively common despite being caused by a dominant mutation, i.e. one mutant copy of the gene is sufficient to cause the disease. (Most genes are present in two copies, and most mutations are recessive such that the one good copy of the gene assures normal function). It also has a late onset, typically manifesting itself when people are in their 30s. Haldane deduced that the reason why Huntington's mutations persist in populations is because by the time that disease symptoms appear, carriers have already had children to who they pass on the Huntington's mutation half of the time. But Haldane also made a further, highly imaginative observation. He reasoned that the persistence of the Huntington's mutation reveals a novel evolutionary principle: That the force of natural selection to remove from populations mutations with harmful effects must decline with increasing age. Consequently, the later that the effect of any mutation is expressed in adulthood, the weaker the force of natural selection acting against it will be. This predicts that all species will accumulate late-acting deleterious mutations. Potentially, this could explain the ageing process: it is the sum of the harmful effects of all of these accumulated deleterious mutations with late-acting effects.

After Haldane, the evolutionary theory of ageing itself evolved. Many genes have not one but many phenotypic effects which may occur at different points in the life history. Mutations (changes) in such genes can have multiple effects, a phenomenon known to geneticists as pleiotropy. One possibility is that some pleiotropic mutations may have a combination of beneficial and harmful effects. Peter Medawar observed that mutations that enhanced fitness early in life, but had harmful effects later in life, might enhance fitness overall, i.e. there might be a trade off between good early and bad late life effects. This theory, sometimes referred to as antagonistic pleiotropy (Williams, 1957), has been well supported by laboratory testing (Partridge and Gems, 2002).

The evolutionary theory of ageing has profound implications in terms of the meaning of human ageing, some of them bleak. Ageing, with its attendant illnesses (and death) is the most terrible thing that many of us will experience; that and witnessing what it does to our loved ones. The evolutionary theory adds insult to injury by telling us that it is a process without any kind of benign function in the cycle of life; moreover, it is, essentially, a form of genetic disease, that everybody has and that is invariably fatal. We, all of us, have inherited a horrible and invariably fatal genetic disease. If you find this a difficult idea to accept, it may be because of the word "ageing" has multiple meanings. Human ageing can be viewed as the sum of benign or neutral maturational changes (for example, growing wiser), and the deleterious, deteriorative changes that engender disability, illness and death (senescence). By convention, ageing in the latter sense is not viewed as a disease by doctors; but from the biogerontological perspective (including the evolutionary theory), there is really no other way to see it (Caplan, 2005).

On the other hand, the evolutionary theory makes clear that the existence of ageing does not reflect the impossibility of indefinitely maintaining biological systems; instead ageing is the result of a relatively trivial detail of the evolutionary process. The striking differences in lifespan between even closely related species implies that there is relatively little constraint on the evolution of ageing and longevity: it evolves easily and quickly when the selective conditions change. This evolutionary plasticity suggests that if we could understand how genes control ageing we would find that it was relatively easy to manipulate.

Genetics: Do genes control ageing, and if so which genes?
What would it mean to understand how genes control ageing? To understanding life one has to understand the cell, which is the main building block of living organisms. The human body, for example, contains some 50 trillion (i.e. 50 million million) of them. A typical animal cell, which is about 0.01 mm across, is an immensely complex, self-replicating molecular machine. Much of the cellular machinery is formed from thousands of different protein components, each of which has a distinct function in the life process, for example in energy generation, chemical synthesis and cellular maintenance. Information for synthesis of each protein is contained in a corresponding gene, made of DNA (deoxyribonucleic acid).

One of the aims of genetics is to understand how traits are controlled by genes and the proteins that they encode. For example, eye colour is a genetically controlled trait. Eye colour variation is due to differences in levels of pigment (e.g. melanin) in the iris of the eye. Genes that control eye colour encode proteins (specifically, enzymes) involved in synthesis of iris pigments. In principle, one could understand the biology of eye colour by identifying the genes that control this trait. By reading the genetic code of such eye colour genes we can discover the identity of the enzymes that they encode, and discover their function (how they control iris pigment levels). Thus, understanding how genes control a trait tells us how the molecular machinery of life works. This knowledge can engender the power to manipulate the machinery; we might, for example, develop drugs that alter the properties of eye pigment enzymes, which could, in principle, be used to change eye colour (which might be useful e.g. for treating albinism). Most drugs work in a similar way: by altering protein function.

Geneticists often use organisms that are convenient to work with in the laboratory (so called model organisms) to study the determination of traits by genes. Such model organisms include the bacterium *Escherichia coli*, the nematode worm *Caenorhabditis elegans*, the fruitfly *Drosophila melanogaster*, and the mouse *Mus musculus*. A starting point for many genetic studies is to isolate mutants, strains with mutations (changes) in genes affecting the trait of interest. This sort of genetic approach has been used for over a century to study how genes control many aspects of living things, including development, morphology and behaviour.

This standard genetic approach was only belatedly applied to the study of ageing, initially in *C. elegans*. This is a rather dull, soil-dwelling worm that is barely visible to the naked eye (adults grow to about 1.2 mm in length). However, it is a very cheap and versatile animal model to work with in the laboratory. For studying ageing *C. elegans* are excellent since they age and die within 2-3 weeks, which is very convenient for biogerontologists.

The first long-lived *C. elegans* mutants were isolated by Michael Klass in 1983 (Klass, 1983), but the magnitude of this achievement was not fully appreciated until around a decade later. Since then, scores of genes have been identified which influence the rate of ageing. Moreover, it

has been found that genes similar to those which control ageing in *C. elegans* also control ageing in fruit flies and mice (Kenyon, 2005). The effects of some of these mutations are striking; for example, mutation of the gene *age-1* can increase *C. elegans* lifespan almost 10-fold (Ayyadevara et al., 2008), and mutation of the gene *Prop-1* can increase mouse lifespan by up to 80% (Brown-Borg et al., 1996).

The last 15 years has seen a gold rush in the genetics of ageing, which has been rapidly unravelling the biology of ageing. A number of control systems that regulate the rate of ageing have been identified, for example the insulin/IGF-1 signaling pathway (Partridge and Gems, 2002). Yet these are still early days for the field. Critical objectives at the moment are to work out which genes and pathways control ageing not just in nematode and fruit flies, but also in mammals, starting with mice (which is a costly and time-consuming endeavour); and developing drugs that can influence the critical gene products to alter ageing rate. Perhaps the most important question is: What sorts of proteins directly control the ageing process? Here lies the key to really understanding the central mechanisms of the biology of ageing.

Biochemistry: What sort of biochemical processes contribute to ageing and longevity?
There are many different theories about what actually happens during ageing, and the nature of its root cause - over 300 by one estimate (Medvedev, 1990). However, one premise common to many of them is that ageing is linked to the accumulation of damage to the proteins, lipids and DNA constituents of living systems. It is as if, with time, the molecular machinery of life eventually wears out. Such an increase in damage with increasing age is well documented, and has been observed in organisms ranging from budding yeast to humans.

What remains unclear is why this accumulation of damage occurs, and why it happens at such different rates in different species (or not at all, in some cases). A plausible theory is that the rate of ageing is determined by the balance between generation of molecular damage, and the cellular maintenance processes that protect against it. There are three major mechanisms of cellular maintenance providing protection against molecular damage accumulation. Firstly, the causes of molecular damage can be reduced; for example, antioxidant enzymes can lower levels of damaging pro-oxidants. Secondly, damage can be repaired, for example DNA repair processes can counteract damage accumulation to DNA. Thirdly, damaged molecules, organelles or cells can simply be turned over, i.e. destroyed and replaced by pristine new ones. One possible reason why Hydra are non-ageing is that they can replace all the cells in their body, thereby preventing damage accumulation and ageing.

This view of ageing and longevity as reflecting damage and maintenance, respectively, represents a sort of standard theory of biogerontology. Although it is plausible and, I suspect, true, it has not yet been firmly demonstrated. The theory predicts that boosting of somatic maintenance mechanisms should increase lifespan. Many studies have tried to demonstrate this, but the results have often been equivocal. For example, damage from reactive oxygen species (ROS) clearly contributes to age increases in oxidative damage to proteins, lipids and DNA, as predicted by in Denham Harman's free radical theory of ageing (Harman, 1956). If oxygen damage is a major contributor to ageing, one might expect that boosting antioxidant defense should slow ageing, but tests of this have yielded inconsistent results (Muller et al., 2007). It also remains unclear whether long-lived mutants owe their increased longevity to improved cellular maintenance, or to some other anti-ageing mechanisms. Here it is worth noting that increased molecular damage is characteristic of most forms of pathology. For example, stroke involves the

rupture of blood vessels in the brain, and its pathological consequences involve devastating molecular damage to brain tissue. Clearly, molecular damage is not the primary cause of stroke, but rather a downstream consequence of it. Thus, whatever the primary cause of ageing, one would expect an associated increase in molecular damage; this leaves open the possibility that the age increase in molecular damage is not its primary cause, but the consequence of other, as yet unidentified causes.

Medicine: How does ageing cause diseases of ageing?

Reader, you and I cannot know how we will die, but we can make educated guesses: probably as the result of cardiovascular disease (e.g. heart disease, stroke), cancer, Alzheimer's disease, type II diabetes, or a contagion such as influenza that is not life-threatening to a younger person, but will kill us because our ageing immune system is shot. All of these are illnesses associated with ageing: our probability of getting them increases dramatically as we get older. In fact, the evidence is that the ageing process *causes* such diseases of ageing. This means that all of these horrible and often fatal diseases are really just different symptoms of the same underlying condition, just as a sore throat, a runny nose and tendency to sneeze are all symptoms of the common cold. This includes cancer: most people who get cancer are old, and ageing has been described as "the most potent of all carcinogens" (DePinho, 2000).

That ageing causes diseases of ageing is best demonstrated by studies of long-lived animal models. A widely used approach to increase longevity in rodents (rats and mice) is to reduce their dietary intake to around 70% of what they would eat given unlimited access to food. This simple procedure, called dietary restriction (or caloric restriction), can increase average and maximum lifespan by up to about 50% (Masoro, 2000). More recently, a number of long-lived mouse mutants have been identified (Bartke, 2005). As well as increasing lifespan, both types of intervention cause animals to stay younger for longer: they remain active in later life, their fur stays glossy and relatively free of grey, and their eyes unclouded by cataracts. They also remain free of disease for longer.

Elderly rodents suffer from some, but not all, of the ailments that afflict older people; for example, aged rats suffer from hypertension (high blood pressure), type II diabetes, nephropathy (ailing kidneys), autoimmune problems, cataracts and, particularly, cancer: they get breast, prostate, stomach and intestinal cancer, and leukaemia. Amazingly, dietary restriction protects them against all of these diseases. Similar observations have been made in long-lived mutant mice. For example, here at University College London we recently discovered that a mouse with a mutation a gene in the insulin/IGF-1 pathway (*Irs1*) shows not only a 30% increase in lifespan, but also resistance to all ageing-related changes examined, including osteoporosis, type II diabetes, loss of motor coordination and age changes in the immune system (Selman et al., 2008). Aged normal-lived control mice also developed a skin condition which caused their fur to fall out, leaving unsightly bald patches. Mutation of *Irs1* prevented this from happening too.

By what mechanisms do these interventions achieve such miracles? This question leads to another, perhaps the most critical in biogerontology: How does ageing give rise to diseases of ageing? The answer here may lie in the biochemistry of damage and maintenance. For example, the primary cause of cancer is damage to DNA. This can cause mutations affecting control of the cell cycle, resulting in cells that proliferate out of control, forming tumours. Processes that help maintain DNA free from damage may protect not only against cancer, but also ageing, since molecular damage is the primary cause of both. Genes encoding proteins that act in this way are

known as caretaker tumour suppressor genes; such genes are predicted to protect against ageing too. It therefore seems likely that both dietary restriction and life-extending mutations protect against the accumulation of molecular damage that causes ageing and its attendant diseases.

Such long-lived animal studies show us that ageing can be used as a point of intervention to provide protection against a broad spectrum of diseases of ageing. This establishes an important principle, and one that is revolutionary with respect to the way that medical research currently tackles diseases of ageing. The present approach is to investigate such diseases piecemeal: the research communities studying, for example, cardiovascular disease, type II diabetes and Alzheimer's disease are largely separate. This means that treatments developed are largely disease specific; for example, a treatment for hypertension is likely to be of little use in treating cancer. Speaking polemically, one might comment that this is like having one research discipline studying sore throats, and another one studying runny noses, while a third specializes in sneezes, when instead they should all be studying the common cold, and it's predominant cause, the rhinovirus.

The possibility of developing prophylactic treatments for a broad spectrum of ageing-related illnesses is one of the areas of greatest promise within the new biogerontology. However, to achieve it will require a radical change in the way that research on diseases of ageing is carried out. It will require close collaboration between biogerontologists and medical researchers studying a range of ageing-related diseases, effectively defining a new field: translational biogerontology. My own research setting, the Institute of Healthy Ageing, part of University College London, was recently created for research of this type, but many more such research centres are needed.

What is biogerontology likely to achieve?

I occasionally get asked how soon biogerontology will generate treatments for ageing, and how powerful will they be. Given our current relative ignorance of the biology of ageing, this is impossible to say. Although much progress has been made, at a fundamental level we still do not really understand the biological mechanisms of ageing and longevity assurance. However, it does currently appear likely that the basic biology of ageing will be understood quite soon, perhaps within the next decade or two. When we reach that point, the prospects for treatments for ageing should be much clearer.

Understanding a malady can lead directly to a method for eradicating it, but this is not always the case. The understanding of the nature of bacterial pathogens, discovered in the late 19th Century, enabled the development of broad spectrum antibiotics in the 1930s. On the other hand, the biology of cancer, first properly understood with the identification of tumour suppressor genes and proto-oncogene in the early 1970s, has not yet lead to treatments for cancer as simple and potent as antibiotics: no magic bullet has been developed. Arguably, this reflects the extreme complexity of cancer which has some 200 basic forms.

We cannot yet say that we understand ageing in the same way that we understand bacterial infection or cancer. However, the complex nature of ageing, the numerous mechanisms of molecular damage accumulation and of its amelioration, might suggest that in terms of treatability ageing is likely to be more intractable even than cancer. However, ruling out the possibility of treatments for ageing is as unjustifiable as ruling out the possibility of a magic bullet cure for cancer. Moreover, the plasticity of ageing is well demonstrated, both by model

organism studies, and the rapidity with which it evolves. If this plasticity can be harnessed it could lead to powerful therapies to protect against ageing-related illness.

What should the goals of biogerontology be?

However uncertain the prospects for treatments for human ageing may be, recent developments in biogerontology make this a pressing question. Views on what biogerontology should be trying to achieve vary widely, and three sorts of goal have been identified: compressed morbidity, arrested ageing and decelerated ageing (Juengst et al., 2003). The compressed morbidity view is that research on ageing should seek treatments for ageing-related illness that do not alter the underlying ageing process. This would produce improvements in health among the elderly without any major extension of lifespan, and a reduction of the period of disability experienced by many elderly people in their final years (compression of morbidity).

This would have good outcomes both in terms of quality of life, and reduced healthcare costs. While these are attractive goals, a weakness of the aims of compressed morbidity is that they are somewhat unrealistic. For one, they only make sense if ageing and age-related disease are clearly distinguishable, but from the biogerontological perspective they are not. It is therefore not surprising that model organism studies have achieved slowed ageing and delayed age related illness, but not compressed morbidity without life extension.

Arrested ageing involves the search for the fountain of youth. Its goals are complete cessation and even reversal of ageing, and eternal youth. Arguably, since arrested ageing appears, at best, a very remote possibility, its many practical and philosophical implications are not now a pressing concern for biogerontology.

Decelerated ageing is not so much an aspiration for what research on ageing should seek to achieve as a view on what it is likely to achieve. I believe it is the predominant view among working biogerontologists. Work on animal models has shown us that that it is possible to slow ageing and delay the onset of diseases of ageing. Based on rodent studies one can extrapolate (though with little real confidence) to humans; one biogerontologist suggested that approaches currently used in rodents and applied to humans might "produce 90 year olds who are as healthy and active as today's 50 year olds" as well as "increase the mean and maximum lifespan by about 40%, which is a mean age of death of about 112 years, with an occasional winner topping out at about 140 years" (Miller, 2002). A virtue of decelerated ageing is that it is realistic: It is based on actual achievements of science, and it does not require a distinction between ageing and diseases of ageing. On the other hand, it may well not result in compression of morbidity, and it involves extension of lifespan, something that is not universally held to be a benefit.

Although the goals of decelerated ageing seem worth pursuing, during the 15 years that I have worked as a biogerontologist I have often wondered about them. In ethical terms, decelerated ageing is complex. In an earlier essay (Gems, 2003) I argued that achieving it would result in two main outcomes. Firstly, it would greatly reduce the frequency of ageing related illness at any given age. The result of would be an amelioration of human suffering on an immense scale, potentially comparable in magnitude to that resulting from the development of antibiotics. Secondly, it would lead to extended lifespan, possibly of a large magnitude. Of course, life expectancy has increased greatly over the course of the last century due to better sanitation and nutrition, and advances in medicine and health care provision. Yet the possibility of very large increases in lifespan, say to 150 years, or 200 years, is one that many find unsettling. Arguably,

an intervention resulting in radical life extension would constitute an enhancement technology, belonging in the same category of interventions as cosmetic surgery, cognitive enhancement and perceptual enhancement (Parens, 1998). Unlike medical treatments, the perceived value of enhancement technologies are often highly sensitive to local differences in cultural perspective, and can involve difficult questions about human identity, and life extension has these properties (Gems, 2003).

Of these two outcomes, protection against disease and life extension, the first has ethical primacy; the possibility of alleviating suffering on such a scale simply must be pursued, however ambivalent we may feel about the second outcome. Some commentators, including so-called life cycle traditionalists, have argued that ageing is a good thing, such that preventing it to any degree would be wrong (Callahan, 1994; Fukuyama, 2002; Kass, 1983). But given the health benefits of decelerated ageing, although we may not want life extension, we may just have to lump it.

Further problems with decelerated ageing

I still find decelerated ageing a difficult objective to get comfortable with. When I was teaching about biogerontology and its goals, students sometimes objected that decelerated ageing would be of limited therapeutic value since it is not predicted to change the life time risk of disease. This interesting concern is illustrated in Figure 1.

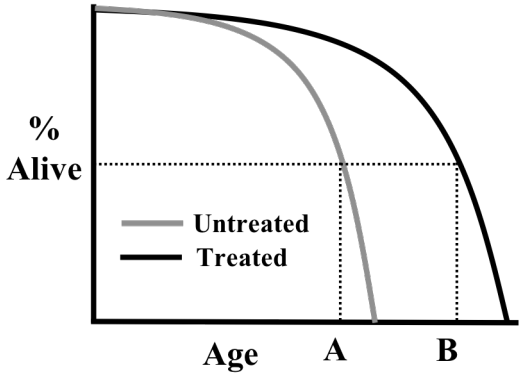

Figure 1: Decelerated ageing may not change lifetime risk of disease. Risk of, say, cancer is greatly reduced at age A in the treated population. However, risk of cancer may well be the same at age A (untreated) and age B (treated).

This depicts the effects of a treatment that causes decelerated ageing, which extends lifespan and greatly reduces the frequency of ageing-related diseases (e.g. cancer) at any given age, for example age A. However, at age B one might expect a similar incidence of cancer; overall, the life time probability of developing ageing related diseases might change little.

Is this an argument against the benefits of decelerated ageing? I believe that it is not, by reason of the following argument. Consider a disease that it not ageing related: smallpox, caused by the *Variola* virus. This pestilence was finally eradicated in 1977, one of the great achievements of medical science; yet one of its consequences was to increase the frequency of Alzheimer's disease. This it must have done, since it increased the number of individuals surviving to a ripe old age, at which this condition is more frequent. This illustrates the principle that a consequence of the successful control of any given disease is to substitute it for a range of later life pathologies. There is no such thing as life time protection against pathology, only deferral of pathology. This deferral is precisely what decelerated ageing would achieve. The only difference is that instead of substituting smallpox now with Alzheimer's later, it will substitute Alzheimer's now for Alzheimer's later. Like curing smallpox now, this is, in terms of its outcome, as good as curing Alzheimer's now.

Yet a lingering doubt remains. Surely smallpox taking the life of a child is more serious than an old woman at the end of her life developing and eventually dying from Alzheimer's? Perhaps, but one of the errors of youth is to think that with age comes a readiness to accept the consequences of ageing, and to tolerate its attendant illnesses. Tolerance of diseases of ageing likely has its roots in the ancient attitude of considering ageing a necessary part of the cycle of life. This tradition, called apologism by the historian Gerald Gruman, is especially strong in Europe, and has its roots in the stoic philosophy of ancient Rome (Gruman, 1966).

The example of small pox can be used illustrate another odd characteristic of decelerated ageing. One may ask: What should the goals of small pox research be? Here the answer is clear: The eradication of small pox. But consider the consequences of success with respect to decelerated ageing, say using R.A. Miller's projection: greatly reduced rates of ageing related illness, an average lifespan of 112 years, and a maximum lifespan of 140. Given that lifetime risk of ageing related illness would not be expected to change, people would still die from diseases of ageing in similar numbers, just later. Thus, the major imperative driving the research - to relieve suffering from diseases of ageing - would not have been fulfilled; the urgency of further research to decelerate ageing still further would be unchanged. It seems that we would be morally obligated to continue on indefinitely, seeking ever greater decelerations of ageing, ever later postponements of illness, and greater extensions of lifespan. In contrast to small pox research, there is no end point. This is rather unsettling, and reminiscent of bioethicist Leon Kass's anxious characterization of biomedical research as a "runaway train headed to a post-human future" (Kass, 2001). Yet, in the end, the shape of the future is so uncertain and subject to future discoveries within the field, and the potential benefits so great, that none of these arguments seem to come even close to being reasons for stopping research that may lead to deceleration of human ageing.

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References

Austad, S.N. (1999) Why We Age: What Science is Discovering About the Body's Journey Through Life. John Wiley and Sons, New York.

Ayyadevara, S., Alla, R., Thaden, J.J. and Shmookler Reis, R.J. (2008) Remarkable longevity and stress resistance of nematode PI3K-null mutants. Aging Cell 7, 13-22.

Bartke, A. (2005) Minireview: role of the growth hormone/insulin-like growth factor system in mammalian aging. Endocrinology 146, 3718-23.

Brown-Borg, H.M., Borg, K.E., Meliska, C.J. and Bartke, A. (1996) Dwarf mice and the ageing process. Nature 384, 33.

Callahan, D. (1994) Aging and the goals of medicine. Hastings Cent Rep 24, 39-41.

Caplan, A.L. (2005) Death as an unnatural process. Why is it wrong to seek a cure for aging? EMBO Rep 6 Spec No, S72-5.

DePinho, R.A. (2000) The age of cancer. Nature 408, 248-254.

Finch, C.E. (1990) Longevity, Senescence and the Genome. University of Chicago Press, Chicago and London, pp. 0.

Fukuyama, F. (2002) Our Posthuman Future: The Consequences of the Biotechnology Revolution. Profile Books, London.

Gardner, M.P., Gems, D. and Viney, M.E. (2006) Extraordinary plasticity in aging in Strongyloides ratti implies a gene-regulatory mechanism of lifespan evolution. Aging Cell 5, 315-23.

Gems, D. (2003) Is more life always better? Problems arising from the new biology of aging. Hastings Center Report 33, 31-39.

George, J., Bada, J., Zeh, J., Scott, L., Brown, S., O'Hara, T. and Suydam, R. (1999) Age and growth estimates of bowhead whales (Balaena mysticetus) via aspartic acid racemization. Can. J. Zool. 77, 571-580.

Gruman, G.J. (1966) A history of ideas about the prolongation of life. Transactions of the American Philosophical Society 56, 1-97.

Harman, D. (1956) Aging: A theory based on free radical and radiation chemistry. J. Gerontol. 11, 298-300.

Juengst, E.T., Binstock, R.H., Mehlman, M., Post, S.G. and Whitehouse, P. (2003) Biogerontology, "anti-aging medicine," and the challenges of human enhancement. Hastings Cent Rep 33, 21-30.

Kass, L. (1983) The case for mortality. The American Scholar 52, 193-191.

Kass, L. (2001) Preventing a brave new world: Why we must ban human cloning now. In, The New Republic.

Kenyon, C. (2005) The plasticity of aging: insights from long-lived mutants. Cell 120, 449-60.

Klass, M.R. (1983) A method for the isolation of longevity mutants in the nematode *Caenorhabditis elegans* and initial results. Mechanisms of Ageing and Development 22, 279-286.

Martínez, D.E. (1998) Mortality patterns suggest lack of senescence in hydra. Experimental Gerontology 33, 217-225.

Masoro, E.J. (2000) Caloric restriction and aging: an update. Exp Gerontol 35, 299-305.

Medvedev, Z.A. (1990) An attempt at a rational classification of theories of ageing. Biological Reviews 65, 375-398.

Miller, R.A. (2002) Extending life: scientific prospects and political obstacles. Milbank Q 80, 155-74.

Muller, F.L., Lustgarten, M.S., Jang, Y., Richardson, A. and Van Remmen, H. (2007) Trends in oxidative aging theories. Free Radic Biol Med 43, 477-503.

Parens, E. (1998) Enhancing human traits: Ethical and social implications. Georgetown University Press, Washington, D.C.

Partridge, L. and Gems, D. (2002) Mechanisms of ageing: Public or private? Nature Reviews Genetics 3, 165-175.

Selman, C., Lingard, S., Choudhury, A.I., Batterham, R.L., Claret, M., Clements, M., Ramadani, F., Okkenhaug, K., Schuster, E., Blanc, E., Piper, M.D., Al-Qassab, H., Speakman, J.R., Carmignac, D., Robinson, I.C., Thornton, J.M., Gems, D., Partridge, L. and Withers, D.J. (2008) Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice. Faseb J 22, 807-18.

Williams, G.C. (1957) Pleiotropy, natural selection and the evolution of senescence. Evolution 11, 398-411.