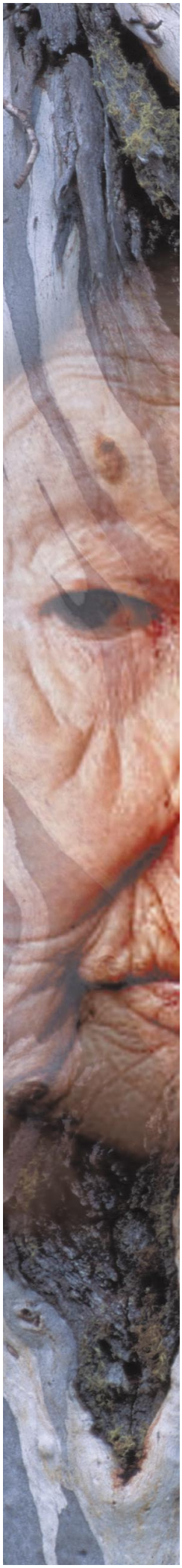

The future of ageing

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Advances in our knowledge of age-associated diseases have far outpaced advances in our understanding of the fundamental ageing processes that underlie the vulnerability to these pathologies. If we are to increase human life expectancy beyond the fifteen-year limit that would result if today's leading causes of death were resolved, more attention must be paid to basic research on ageing. Determination of longevity must be distinguished from ageing to take us from the common question of why we age to a more revealing question that is rarely posed: why do we live as long as we do? But if the ability to intervene in ageing ever becomes a reality, it will be rife with unintended and undesirable consequences.

Research on ageing entered the main stream of biological inquiry about 30 years ago, but since then no notable advances have occurred in our understanding of the human ageing process. Success has been achieved only in our knowledge of age-related diseases.

The failure to distinguish between ageing research (biogerontology) and research on age-associated diseases (geriatric medicine) has been, and still is, a source of misunderstanding. And there is little evidence that this failure, with its important scientific, political and societal consequences, will soon be rectified. Thus, the present imbalance will continue, in which resources available for research on the diseases of old age far exceed those available to address the core question: why are old cells more vulnerable to disease than are young cells?

Policy-makers, properly impressed with the future demographics of the greying of all economically developed countries, are basing important policies and decisions on a flawed understanding of what constitutes ageing research and what they believe might be accomplished.

Disease and ageing

Ageing is not a disease and the distinction is central to an understanding of why the resolution of the leading causes of death in old age — cardiovascular disease, stroke and cancer — will tell us little about the fundamental biology of age changes. The resolution of all three conditions would result only in an increase of about 15 years in human life expectancy in the developed world[1], after which ageing will be revealed as the leading cause of death.

Disease processes can be distinguished from age changes for at least four criteria. Unlike any disease, age changes (1) occur in every animal that reaches a fixed size in adulthood; (2) take place in virtually all species; (3) occur in all members of a species only after the age of reproductive success; and (4) occur in animals removed from the wild and protected by humans even when that species has not experienced ageing for thousands or even millions of years.

The study of age-associated diseases and manipulation of development in lower life forms dominates what is mistakenly described as the field of ageing research. One example is that more than half the budget of the US National Institute on Ageing is spent on Alzheimer's disease research, yet motor vehicle accidents cause twice as many deaths[1] and from age 65 on, it is not even one of the five leading causes of death[2]. The likelihood of dying from Alzheimer's disease is 0.7% (ref. 3) and the complete resolution of this disease would add about 19 days onto average life expectancy[1].

In the minds of the public, policy-makers and many biomedical scientists, no one suffers or dies from ageing. We suffer and die from the diseases associated with the ageing process. But no one over the age of, say 75, has or will die from what is written on their death certificate. Death results from the inevitable increase in systemic molecular disorder that living long enough incurs. That disorder simply increases vulnerability to whatever was, or will be, diagnosed as the cause of death. There are multiple pathologies in older people and, because there are few autopsies and little research, the true cause of death is rarely known.

Box 1
Ageing in feral animals

Ageing rarely if ever occurs in feral animals because it is unusual for them to live long enough to experience the phenomenon. The same observation can be made for prehistoric humans. Natural selection could not select for a process like ageing when few, if any, animals ever lived long enough to participate in the selection process.

If, through human intervention, feral animals are kept as pets or deposited in zoos and thus protected from predation, disease and accidents, age changes that may never have been experienced in the wild will be unmasked. The resulting greater longevity is not caused by the expression of new genes but by the protection provided by human intervention. The finding of old feral animals usually results from the enormous increase in the human population and the consequent disturbance of many ecological niches (for example, death of predators).

Most animals do not die immediately after reproductive success because it is prohibitively costly in terms of energy to evolve such a system. The class of animals generally referred to as 'big bang animals', represented by the Pacific salmon and the marsupial male rat, may seem to be an exception to this notion. However, it is more likely that the deaths that occur in these animals after reproductive success result from their unique expenditure of enormous amounts of energy that precedes mating[5]. Whether age changes occur is uncertain because the unusual rapidity of the events that precede death is unique and the fact that there is no necessity for death to be preceded by age changes.

Box 2
How long will we live?

There is no evidence to support the many outrageous claims of extraordinary increase in human life expectancy that might occur in our lifetime or that of our children. Based on the US Census Bureau Middle Series, life expectancy in 2050 will be about 82 years for both sexes in the United States[14]. The US Social Security Administration anticipates a life expectancy of 78.1, 80.4 and 83.5 years for both sexes in 2066 based on three alternative assumptions about decreases in mortality rates[15]. The G7 industrialized countries project life expectancy at birth in 2050 to range from a high of 83.5 in France to a low of 80.5 in the United States[16]. In a more recent analysis, in which it was assumed that future decline in mortality rates will follow the exponential decline that has occurred during the past 50 years, Tuljapurkar *et al.* forecast that life expectancy at birth in 2050 will vary from a high of 90.9 in Japan to a low of 82.9 in the United States[16].

More than 75% of all human deaths in developed countries now occur in those over the age of 75. If the causes of these deaths are resolved we will not become immortal but we will have revealed how death occurs in the absence of disease. What will be found is that the underlying cause of these deaths is the inexorable loss of physiological capacity in the cells of vital organs — the hallmark of ageing.

Ageing and longevity determination

If ageing research is to advance, it will not only be necessary to distinguish biogerontology from geriatric medicine but it will also be necessary to distinguish ageing from longevity determination.

Ageing is a stochastic process that occurs after reproductive maturation and results from the diminishing energy available to maintain molecular fidelity. This disorder has multiple aetiologies including damage by reactive oxygen species. Longevity determination, on the other hand, is not a random process. It is governed by the excess physiological capacity reached at the time of sexual maturation that, through natural selection, was achieved to better guarantee survival. For this reason, the question "Why do we live as long as we do?" might be more appropriate than "Why do we age?".

Species survival depends on a sufficient number of members living long enough to reproduce and, if necessary, to raise progeny to independence. Natural selection favours animals that have greater survival skills and, especially, redundant physiological reserve in vital organs beyond the minimum needed to survive the damage that might be exacted by predators, disease, accidents or environmental extremes. The amount of excess physiological capacity, like the amount of redundancy engineered into space vehicles, provides the potential for continued function beyond the primary goal[4,5].

Energy is better spent on guarantying reproductive success than it is for increasing individual longevity. Consequently, age-weakened individuals living beyond reproductive success have diminishing value for the survival of a species and will be culled by natural selection. The genome that governs molecular synthesis and integrity from conception to sexual maturation is incapable of maintaining fidelity indefinitely. After reproductive success the energy available to maintain orderliness diminishes so that continued survival is determined only indirectly by the genome. Increasing systemic molecular disorder, or ageing, occurs in spite of the action of normal repair processes, because these too incur disorder.

Genes do not govern ageing

Ageing is not a programmed process governed directly by genes. Studies in lower animals that have led to the identification of genes that are involved in ageing have not shown a reversal or arrest of the inexorable expression of molecular disorder that is the hallmark of ageing. Those studies are more accurately interpreted as showing that certain genes impact on longevity determination because the results alter physiological capacity and occur before the ageing process begins.

Further evidence that genes do not have a direct role in the ageing process is that individual animals do not age at the same rate nor are the patterns of age changes identical. This results in the variations found in age of death. The quantitative and qualitative disorder of age changes stand out in stark contrast to the ordered changes that occur during genetically driven embryogenesis and development. The variability in the manifestations of ageing differs greatly from animal to animal but the variability in developmental changes differs trivially. Humans from conception to adulthood are virtually identical in respect to the stages and timing of biological development but from about thirty on, age changes make humans much more heterogeneous. Just as a blueprint is vital for manufacturing a complex machine and contains no information to cause its ageing, the genome is vital for biological development but contains no instructions for ageing.

Longevity determination in higher animals has been a profoundly neglected area of research. One class of animals that may provide insight into the mechanisms determining longevity are those animals that do not reach a fixed size in adulthood, and age either undetectably slowly or not at all. Animals of this class include some tortoises, many sport and cold water deep-sea fish, some amphibians and the American lobster. Whether these animals age at all, and the reasons for this, remain to be determined. They are not immortal because, like animals that do age, there is a constant threat of disease, predation and accidents[6] (see Box 1). The time is long overdue for more intense study of the phenomenon of negligible ageing. Telomerase expression, for example, which is a hallmark of immortal cells in tissue culture, has been found at extraordinarily high levels in the cells of negligibly ageing animals such as the American lobster and the rainbow trout[7,8].

Is tampering with the ageing process desirable?

Life expectancy is the average total number of years that a human expects to live. This is fundamentally different from life span, which is the maximum number of years that a human can live.

The human life span has remained unchanged for the past 100,000 years at about 125 years[4,5]. What has changed is life expectancy at birth, which has increased in the United States and other developed countries from about 49 years in 1900 to about 76 years in 1997[9] (and is projected to continue increasing; see Box 2). This 27-year increase in life expectancy is equivalent to the increase in life expectancy that occurred from the time of ancient Rome until the year 1900. The increase has been caused by the substantial elimination of infectious diseases that occur in youth through better hygiene and the discovery of antibiotics and vaccines (see Box 3). It is the chronic diseases — cardiovascular disease, stroke and cancer — that remain unresolved and that dominate today as the causes of death in the elderly. Twenty-one of the 27-year increase in life expectancy that occurred during the twentieth century took place during the first 70 years. Only a six-year increase in life expectancy has occurred in the past 27 years[10].

To know what the future societal impact might be of a 15-year increase in life expectancy, one might consider the changes that have occurred from 1931 until the present, which spans a period of time in which an approximate 15-year increase in life expectancy has occurred[11]. Of the many observations that could be made, three are: the increase in the proportion of older people, the greater time spent in frailty and dependency in old age, and the political and economic consequences that both have had[12].

Despite the likelihood that biological ageing is inexorable and inevitable, is the power to manipulate the human ageing process a desirable goal?

Box 3

Ageing as an artefact of civilization

Ageing is a phenomenon unique to the human species because it is a consequence of our advancing knowledge of hygiene and biomedicine. The resulting increase in the numbers of older people in developed countries is, to a large extent, an unintended consequence of these advances and an artefact of human civilization[4,5,10].

Humans, and the animals we choose to protect, are the only species in which large numbers experience ageing. Furthermore, old humans, or old animals, are not essential for the survival of any species, and there seems to be no selective advantage favouring the survival of old individuals. The evidence for this is that prehistoric human remains have never revealed individuals older than about 50 years of age, and humans had a life expectancy at birth of 30 years or less for more than 99.9% of the time that we have inhabited this planet.

Members of exotic feral animal species, who for millions of years have not experienced ageing (see Box 1), reveal those changes when protected by humans as pets or in zoos. It would be difficult to explain how evolution could have selected for a process like ageing that could be made to appear in all members of a species after, perhaps, millions of years of suppression.

Because modern humans, unlike feral animals, have learned how to escape death long after reproductive success, we have revealed a process that, teleologically, was never intended for us to experience.

The pill

As an exercise to explore what would occur if tampering with the ageing process became possible, one might imagine the simplest method: a pill that either stops or temporarily arrests human ageing. The first concern is that those involved in the discovery and the rich and powerful will have earliest, or depending on availability, even the only, access. It is questionable whether these would be the most important to be favoured first, or at all. Presumably, the pill would also become available to the antisocial killers, tyrants and those guilty of genocide along with those who contribute to, or benefit, human civilization.

Of the many predicaments that could be imagined, one is: when in life would one choose to take the pill? Before making the decision to administer it in youth one should be aware of the fact that many people in their seventies and later will say that this is the happiest time of their lives, and to have had their ageing processes arrested at an earlier age would have denied them the happiness of retirement, travel, freedom from child-rearing responsibilities and unlimited time to pursue their interests.

Furthermore, at what age would one choose to have one's ageing arrested or retarded if one had not yet arrived at a sufficiently mature age to reach an informed decision? Would we be able to reverse the ageing process to return to an age that, with hindsight, had been our happiest? Is it not likely that the circumstances that had contributed to an earlier period of perceived happiness would no longer exist should one be able to return to that age?

We interact with each other to a large extent as a function of our perceptions of relative age. The destruction of such interpersonal relationships would be likely to have enormous negative personal and societal consequences. One of the many bizarre scenarios that could be imagined would be to find families in which children who chose not to take an anti-ageing pill would find themselves to be biologically older than their parents, who did.

It is possible that replacing all old body parts with new ones might circumvent ageing. But our brains could not be replaced without a loss of self-identity and memory. Scenarios in which the information content of an ageing brain could be uploaded onto a computer and then downloaded onto a new 'erased' brain remain the province of science fiction.

The goal of arresting the ageing process might be viewed in the same light that we view the arrest of our physical or mental development in childhood — as a serious pathology. We should also bear in mind that arresting ageing is not likely to be an attractive option for the substantial part of the world's population who find themselves poor, oppressed, sick or all three.

Would the least imperfect scenario be a future society in which everyone lived to their 100th birthday in good physical and mental health, then to die on the stroke of midnight?

Future possibilities

As yet, we know of no way in which the human ageing process can be slowed. Caloric restriction is a probable exception which, although observed in many species, has yet to be demonstrated conclusively in humans[13]. Even so, a near-starvation diet is unlikely to be acceptable to those of us who value quality of life above quantity of life.

It is likely that a natural increase in the human life span is presently occurring but so slowly that our ability to detect it will only be made after millennia of careful record keeping. This belief is based on persuasive evidence in the fossil record that indicates that the life spans of most animals increase as evolution proceeds[5].

As some civilizations have, our society must learn that ageing and youth should be valued equally if for no other reason than the youth in developed countries have an excellent chance of experiencing the phenomenon that they may now hold in such low esteem. Then, the misplaced passion for cosmetic surgery, anti-ageing nostrums and similar snake oil remedies touted to arrest ageing will be recognized for what they truly are — at best, a cover-up for an irreversible and inexorable process and, at worst, a delusion and waste of money by the uninformed.

If the main goal of our biomedical research enterprises is to resolve causes of death, then every old person becomes a testimony to those successes. Biogerontologists have an obligation to emphasize that the goal of research on ageing is not to increase human longevity regardless of the consequences, but to increase active longevity free from disability and functional dependence. □

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