Ageing

The most pressing problem of our age

Thomas B L Kirkwood

The increasing proportion of elderly people in Western populations has focused attention on the ageing process. Professor Kirkwood discusses what we know about ageing and the reasons for infirmity in old age

University of Newcastle Institute for Ageing and Health, Henry Wellcome Laboratory for Biogerontology Research, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE

Thomas B L Kirkwood
professor of medicine

tom.kirkwood@ncl.ac.uk

BMJ 2003;326:1297

Summary points

Scientific understanding of the ageing process indicates that, instead of being programmed to die, we age because we gradually accumulate a host of minor faults in the cells and tissues of our bodies

Genes affect longevity, probably by regulating the efficiency of maintenance and repair, but they account for only a quarter of what determines length of life

Other factors, such as nutrition, lifestyle, and environment, account for the rest by influencing an individual's exposure to damage and capacity for repair

As knowledge of the root causes of ageing advances, greater insight into why and how ageing makes us infirm will improve our chances of a long and healthy life

Most of us, professionally and privately, find ageing an uncomfortable subject. From a personal perspective, the reason is obvious: none of us particularly relishes the fact of our own mortality or the prospect that before our life is over we can expect its quality to be impaired by a spectrum of age related disabilities and diseases. Professionally, ageing evokes a curious mixture of reactions. For some, it is just too complicated and frustrating a process to take seriously. For others, it represents ultimate failure in a medical model founded on the idea of curing disease. For a growing number, it is the most intriguing biomedical problem of our time.

Is ageing a disease? Surely not; it is a normal part of the life cycle. But if this is the case, what are we aiming for when we do research into the ageing process? Surveys of public opinion about the desirability of extending human life span show that, in spite of our seeming fascination with the "secret of eternal youth," we are deeply ambivalent about making people live longer. We seem to be caught in a trap of our own making. Great creativity and effort have been expended on preventing "premature" death. But now that we have produced conditions in Western countries in which five out of six infants can expect to see their 65th birthdays, we are much less sure what to do about all these older people.

In recent years ageing has risen up the social and political agenda. It has prompted high level attention from the United Nations, with its research agenda on ageing for the 21st century.[1] There have been many individual actions by governments, and in Britain these include the introduction of the national service framework for older people[2] and the multidisciplinary Foresight review.[3] However, the issues boil down to two main challenges. Firstly, what can we do to meet the social and medical challenges of a world in which a large (and still increasing) fraction of the population is living to an age when intrinsic biological constraints take their toll on health and quality of life? Secondly, what is research likely to reveal about the ageing process that might alter the situation yet further in the years to come?

What makes us age?

One of the strangest things about the ageing process is that, despite its near universality among higher organisms, it is something of an artefact. In the wild, aged organisms are extremely rare because most animals die young. Because old age in nature is a rarity, any idea that the ageing process has been actively favoured through natural selection—such as by evolving "death genes"—to keep population size under check, is almost certainly false. Put simply, we are not programmed to die. Quite the reverse; our bodies are programmed for survival. Even at the last moments of life, nearly every function in every cell of our bodies is still working to keep us alive. To be sure, there is a process of programmed cell death (apoptosis), and we do see cells in the adult body sometimes "committing suicide" by this means, but programmed cell death in adults is almost entirely associated with survival of the organism, such as by deleting damaged cells that might otherwise pose a risk of malignancy.

This apparent paradox—that we are programmed for survival but must face ageing and death as surely as taxes—is resolved when we recognise that it is only in the past 200 years that human life expectancy has risen much above 40 years. Before that, when life generally

was "nasty, brutish and short," there was little evolutionary pressure for our genes to invest in survival mechanisms that could keep the human body in good shape for much longer than about half a century.

These considerations are the basis of the disposable soma theory of ageing, which suggests that the biological determinants of human ageing lie in the fact that our cell maintenance and repair systems evolved when human life expectancy was only half what it is today.[4 5] The theory predicts that ageing results from a gradual accumulation of faults in the cells and tissues of the body. Current research on the mechanisms underlying ageing and age related diseases is focused on understanding the kinds of damage that affect cells and tissues and on the cell maintenance and stress response systems that protect us. One clear conclusion is that there is no single mechanism of ageing. A large number of maintenance and repair systems collectively provide the network of cellular defence mechanisms that keep us going as long as we do. It is the weak links in this network that may predispose us to specific age related disorders, and it is to this network that we must look if we wish to enhance the body's capacity to reach old age in good health.

Research on basic cellular ageing can throw light on age related diseases as well as on the "normal" ageing process. Many of the important diseases of old age—including Alzheimer's disease, osteoporosis, osteoarthritis, and even cancer—show interaction and overlap with normal ageing. For example, the bone loss that causes osteoporosis in susceptible individuals is seen to some degree in all older people. Similarly, the amyloid plaques and neurofibrillary tangles that characterise Alzheimer's disease may be found at autopsy in people aged 70 years and above even if there was no clinical evidence of dementia.

The individuality of ageing

One of the curious features of ageing is its unpredictability at the individual level. Even when there is genetic predisposition for an age related disorder—as in people who carry two copies of the epsilon 4 allele of the gene for apolipoprotein E and are thus at increased risk of developing Alzheimer's disease—there is only a shift in the statistical odds of developing dementia. One of the vital questions for research is therefore to understand the interplay of genetic and lifestyle factors that predispose to the development of age related disease or, conversely, increase the likelihood of remaining in good health. Although there are no genes specifically for ageing, it is clear from twin studies, for example, that there is a noticeable heritable component to human longevity. Estimates suggest that genes account for about 25% of what determines length of life, and progress is being made in identifying some of the genetic factors that may be involved.[6–8]

The fact that genes explain only 25% of individual variability in ageing means that 75% must be accounted for by other factors. These include lifestyle variables, such as nutrition and exercise, as well as the powerful effects of environment. Environment can have enabling or disabling impacts on older age, with unsupportive environments (poor transport and housing, crime, etc) discouraging an active lifestyle and social participation, which in turn results in inactivity and isolation, accelerating physical and psychological decline. These complex interactions between genes, nutrition, exercise, and environment can all be accommodated quite readily within a model of the ageing process as one that is driven, ultimately, by an accumulation of random molecular and cellular damage.

Healthier ageing on the horizon

The positive message from this research is that human ageing is malleable and can be improved by either reducing exposure of the body's cells and organs to damage or by enhancing cell maintenance and repair. Comparative studies have shown that long lived animal species accumulate damage at slower rates than short lived species and that their cells have greater intrinsic resistance to a range of stressors, such as the damaging reactive oxygen free radicals that are produced as a byproduct of the body's requirement for oxygen.[9] Certain short lived species, such as fruit flies and nematodes, are readily amenable to the study of mutants with altered life spans. These studies have consistently shown that increased cell maintenance and stress resistance are associated with increased life span, and vice versa.[5] Although ageing in humans is considerably more complex than in these simple models, identifying the primary mechanisms that protect against cellular damage may yield clues to slowing aspects of the ageing process.

The idea that science should aim to postpone disabling conditions such as Alzheimer's disease without necessarily extending life itself is a concept commonly known as compression of morbidity. Whether it may prove feasible to postpone age related diseases without postponing ageing itself will depend on the extent to which we can separate ageing and disease. It may be that, in order to delay these diseases in humans, we need to delay the build up of several types of damage, including processes as fundamental to ageing as oxidative damage.

Already, our understanding of ageing highlights some key issues. Since ageing is caused by lifelong accumulation of damage, it begins early. We need to recognise this "continuum of ageing" and design lifelong approaches to healthy ageing. We need to confront issues of personal choice (how to exercise and preserve it). We need to target biological and psychological barriers to independence in older age. We should engage in realistic discussion about what we want from research on ageing, including issues on the end of life. Above all, we should celebrate the longevity revolution; it has been hard won, and we must make the most of it.

Competing interests: None declared.

1 United Nations. *Research agenda on ageing for the 21st century*. Geneva: UN, 2002. www.un.org/esa/socdev/ageing/ageraa.htm (accessed 31 May 2003).
2 Department of Health. *National service framework for older people*. London: DoH, 2001. www.doh.gov.uk/nsf/olderpeople/docs.htm (accessed 31 May 2003).
3 Foresight. *Healthcare and ageing population panels. Joint Taskforce on Older People*. London: Department of Trade and Industry, 2000.
4 Kirkwood TBL. *Time of our lives: the science of human ageing*. London: Weidenfeld and Nicolson, 1999.
5 Kirkwood TBL, Austad SN. Why do we age? *Nature* 2000;408:233-8.

6 Cournil A, Kirkwood TBL. If you would live long, choose your parents well. *Trends Genet* 2001;17:233-5.
7 Muiras ML, Muller M, Schachter F, Burkle A. Increased poly(ADP-ribose) polymerase activity in lymphoblastoid cell lines from centenarians. *J Mol Med* 1998;76:346-54.
8 Perls T, Kunkel LM, Puca AA. The genetics of exceptional human longevity. *J Mol Neurosci*. 2002;19:233-8.
9 Kapahi P, Boulton ME, Kirkwood TBL. Positive correlation between mammalian life span and cellular resistance to stress. *Free Radic Biol Med* 1999;26:495-500.