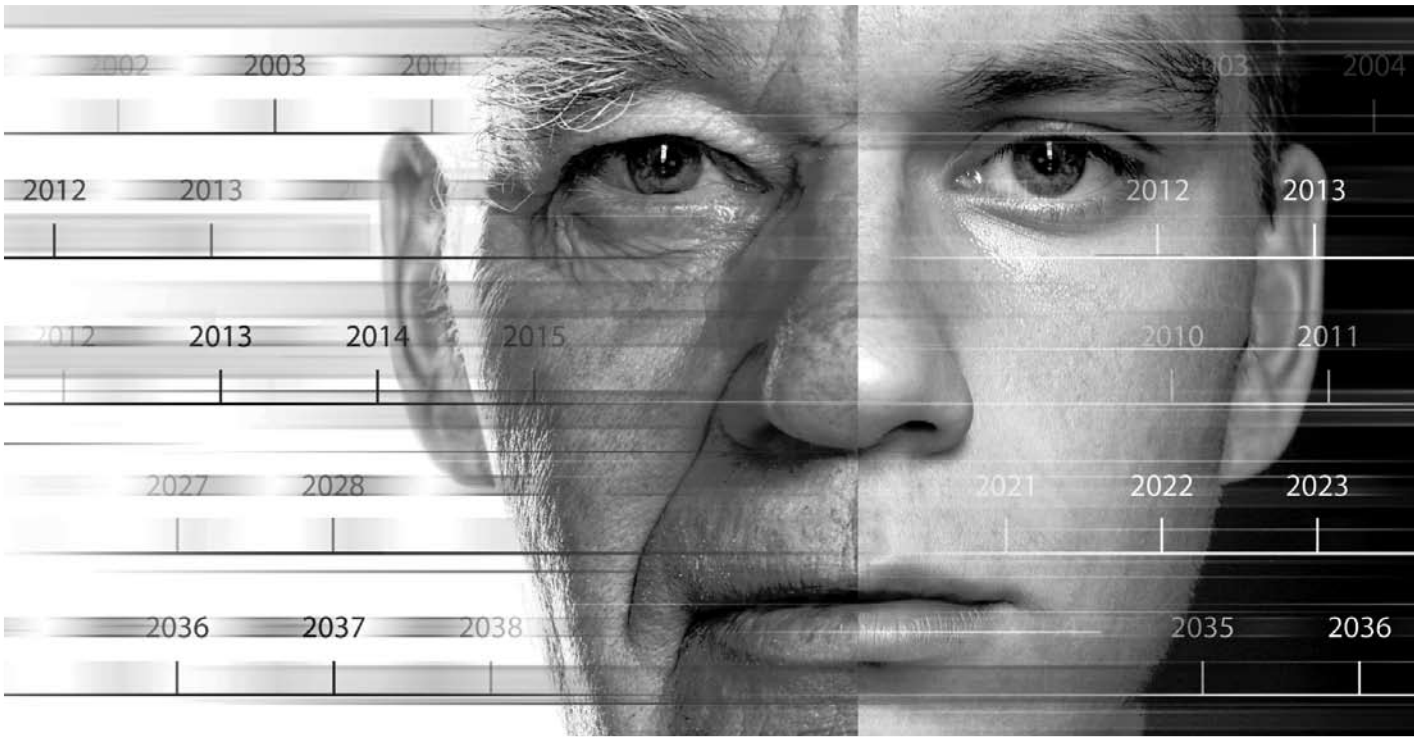
The Academy of Medical Sciences



Rejuvenating ageing research

September 2009

The Academy of Medical Sciences

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Rejuvenating ageing research

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This report is published by the Academy of Medical Sciences and has been endorsed by its Officers and Council. Contributions by the committee were made purely in an advisory capacity. The members of the committee participated in producing this report in an individual capacity and not as representatives of, or on behalf of, their affiliated hospitals, universities, organisations or associations. Their participation should not be taken as endorsement by these bodies.

Contents

Summary

Over the past 150 years, improvements in standards of living and advances in medical science have doubled lifespans in much of the world. Today, average life expectancy in the UK is increasing at more than five hours a day, every day. This rising life expectancy, combined with low birth rates, means that the populations of the UK and world are ageing.

The continuing increase in life expectancy represents a remarkable achievement of humankind. Yet recent debate has been dominated by concerns that rising longevity will be accompanied by an increasing burden of chronic disabling disease – that our living longer represents a threat to the health and wealth of our society. For this reason it is important to focus on *healthy* life expectancy, whereby the 'added years' of life are ones of relatively good health. The provisional evidence indicates that healthy life expectancy is increasing at least as quickly as life expectancy. If this trend is borne out, then increasing longevity becomes an opportunity rather than a threat, with more people enjoying longer, healthier lives that allow them to contribute more to society. Greater efforts are needed to ensure these positive messages from medical research are reflected in public perceptions of ageing and older people.

Nevertheless, the demographic shifts characterised by an ageing population will have profound impacts that by 2050 are likely to cost advanced economies around nine times more than the current economic downturn. Securing increases in healthy lifespan will therefore require a mobilisation of resources that puts our best scientists, engineers, social scientists and policymakers to work on this challenge. The focus of this report is the creation, maintenance and development of the thriving medical research base that must be at the heart of this agenda.

Our understanding of the biological processes of ageing has become increasingly sophisticated in recent years. Ageing is no longer thought of as just a pre-programmed, biological 'self-destruct' mechanism. Rather, ageing is now understood to be a deleterious side effect of biological processes, in particular the limited capacity of natural selection to remove gene effects that cause harm in later life. Ageing is the consequence of damage caused by the gradual accumulation of a complex, diverse and tissue-specific array of faults in molecules, cells and organs that leads to loss of function, frailty and vulnerability to disease and death.

Age is the single biggest risk factor for many life-threatening diseases, including heart failure, cancer and dementia. In the past, the complexity of the biological changes associated with ageing was presumed to mean that it is not determined by a single, underlying mechanism. However, remarkable recent experiments in laboratory animals have shown that quite simple interventions can substantially extend lifespan, improve overall health and slow the onset of age-related diseases. What is more, studies of human participants have demonstrated that ageing is highly malleable, so is in principle open to intervention. Medical research is making the once solid conceptual boundary between the mechanisms of ageing and age-related diseases ever more porous. In short, these groundbreaking discoveries offer the prospect of simultaneously tackling multiple age-related diseases by targeting the process of ageing itself.

In view of the remarkable increases in human life expectancy, there is a biomedical and social urgency to understand the connection between ageing and ageing-related disease, because the major burden of ill health falls on the older section of society. Yet the full value and potential of ageing research in the UK has still to be harnessed. Despite being a top priority for work between the Research Councils, ageing research in the UK has not flourished. Most notably, the UK's research base in the basic

biology of ageing does not compare favourably with countries such as the USA. Although there are some undoubted centres of excellence in ageing research in the UK, they are too few and too fragmented. Overall, it is difficult to obtain a clear picture about the size of the research base in ageing because funders use the term 'ageing' to describe many quite different kinds of research.

In undertaking this study, we have asked why this state of affairs has occurred, and what can be done to improve the UK's performance and international standing in ageing research. Our findings show that four areas in particular should be prioritised in the immediate future:

- Attracting senior scientists from other specialities to undertake basic biological research into ageing: bringing the brightest minds to work in this area of scientific, economic and health importance.
- Developing more centres of excellence in basic biomedical and clinical ageing research, so providing a critical mass of researchers and resources.
- Emphasising the value of in-depth ageing research within individual disciplines, while also recognising the value of a cross-Research Council focus on interdisciplinary science.
- Clearly identifying what research is being undertaken into ageing in the UK, the current investment in the field and the resources necessary for future success.

Significant barriers also remain to the development of interventions in ageing and age-related diseases. These include:

- Insufficient numbers of older people involved in clinical trials.
- A regulatory framework that focuses on treatments for specific diseases rather than the underlying process of ageing.
- The difficulty of identifying appropriate patient cohorts for clinical trials of potential medicines and interventions.
- The timeframe and expense of developing interventions for ageing.
- Lack of robust markers to measure interventions to promote healthy ageing.

Together these factors discourage the commercial sector from targeting the ageing process as a cause of disease, despite the significant potential health, social and commercial gains.

We argue that understanding and intervening in the ageing process are scientifically tractable challenges that offer truly exceptional health, economic and social returns. We have identified specific priorities for ageing research, mechanisms for investment, measures to build research capacity and means to encourage the development of therapeutic and preventative strategies in ageing. In describing the dramatic recent advances in our understanding of ageing, we call on the Medical Research Council (MRC) and other UK research funders to provide the necessary leadership and focus to translate these advances into health and wealth benefits. We hope that this report marks the beginning of a step change in support for ageing research in the UK, allowing us to build on our successes and see this field flourish as it should.

Recommendations

Our five recommendations focus on:

1. Leadership in ageing research in the UK.
2. Priorities for ageing research.
3. Investing in the future.
4. Building capacity.
5. Developing interventions in ageing and age-related diseases.

1. Leadership in ageing research in the UK

Remarkable new insights into the relationship between the processes that underpin ageing and the causes of age-related pathologies are likely to have a profound impact on current paradigms of health and disease. This new science of ageing offers the opportunity for the MRC to bring renewed leadership and vision to ageing research in the UK, both through promoting excellence in research in individual disciplines and through its role in co-ordinating strategy across the National Institute of Health Research (NIHR) and Office for the Strategic Coordination of Health Research (OSCHR), as well as across the Research Councils. At the heart of this vision should be the integration of research into the biology of ageing with our understanding of age-related diseases, and with the development of policies to promote healthy ageing at the population level. Enhanced support for this revolution in the biomedical science of ageing will help to catalyse further work in the engineering, physical and social sciences.

2. Priorities for ageing research

There is now an opportunity to galvanise key areas of ageing research to advance our knowledge and to promote its application for patient benefit. The goal should be to establish an iterative cycle of ideas between research at the laboratory, clinical and population levels.

We recommend that research efforts should focus on the following priority areas:

1. Developing our understanding of the basic biology of healthy ageing.
2. Integrating knowledge of the processes that underpin ageing and age-related diseases.
3. Understanding the determinants of healthy ageing in older people at a population level.
4. Translating basic science and clinical advances in ageing research into effective interventions to promote healthy ageing.

Further details of opportunities for progress in these priority areas are given in the box at the end of this section.

3. Investing in the future

A step change in the scale and organisation of support for ageing research is required to improve the UK's international competitiveness in this field. Substantial additional, ring-fenced funding for basic and translational research into ageing would allow the UK to realise the considerable scientific opportunities and to reap the consequent health and wealth benefits. A strong funding signal would attract senior scientists from other disciplines into the field and stimulate further support from charitable and industry funders.

In this report we outline a range of mechanisms for investment. In particular, we call for consideration of UK centres of excellence in specific areas of ageing research to increase the quality and scale of research, to build workforce and infrastructure capacity, and to integrate opportunities across laboratory, clinical and population research programmes. It will be important to develop high-quality resources and policies to use electronic healthcare records, and to harness the opportunities of large prospective cohort studies, as well as population-based surveys such as the 2011

census. Much could be gained in the short-term by providing incentives to attract existing academic laboratories of international quality into the field of ageing.

Until now, UK funding initiatives have emphasised co-ordination of multiple funders across research disciplines. However, the value of in-depth ageing research within individual disciplines must be recognised. A balance must be struck, and administrative structures both between and within research funders must ensure that the best research proposals receive support. Funders should therefore ensure that their internal mechanisms do not systematically disadvantage ageing research. A thorough audit of ageing research in the UK, both across and within disciplines, is urgently required to gauge the resources available and to guide future funding decisions.

4. Building capacity

There is an urgent need to build ageing research capacity across the spectrum from basic biology to clinical medicine. Ageing research projects are often inherently long-term. Therefore bespoke mechanisms of support are needed, particularly in developing animal models of ageing and age-related disease, and in establishing long-term patient cohorts. With regard to human capacity, it will be particularly important to attract senior researchers from other fields who will bring fresh ideas and help to build capacity at speed. In particular, we recommend:

- A five-year post-doctoral fellowship programme and targeted research grant funding in ageing research to train new researchers and to attract existing investigators from other fields.
- Programmes to engage clinical academics in research into the processes that underpin ageing to drive further work on age-related diseases.

5. Developing interventions in ageing and age-related diseases

There is now a strong need to incentivise strategic alliances among industry, academia and the NHS to promote the development of interventions that target the ageing process and associated age-related diseases. Central to the mission of these collaborations should be clinical research that involves older people, which considers the way in which medicines are used in routine medical practice. Urgent action is also needed to ensure that regulatory pathways for clinical and population research, and the testing of new medicines, do not hinder these efforts.

Research priorities

The Academy recommends that medical research efforts in ageing focus on the priority areas given below. The topics have been identified because of their scientific tractability and timeliness, as well as their health, social and economic value.

1. Developing our understanding of the basic biology of healthy ageing

- Determining the biochemical, cellular, homeostatic and signalling processes that are altered to produce the extension of healthy lifespan in model organisms and humans.
- Resolving the types of molecular and cellular damage that can be ameliorated to reduce the negative impacts of ageing.
- Establishing whether the effects of signalling mechanisms on lifespan are separable from their many other biological effects and, if so, at what level in signalling, and in which tissues, this separation occurs.
- Ascertaining which mechanisms that confer healthy ageing and longevity are evolutionarily conserved across species, including humans, particularly in terms of biochemical and cellular function or damage.
- Determining the role of cellular senescence in ageing, particularly with stem cells as tools to understand the process of ageing.
- Determining the value of stem cells in restoring function in ageing tissues.
- Considering the role of epigenetics in ageing and how such changes might explain phenotypic differences between genetically similar organisms.
- Correlating gene and protein expression with the mechanisms that regulate ageing and the ageing phenotype.
- Understanding and manipulating neuronal cell death and survival.

2. Integrating knowledge of the processes that underpin ageing and age-related diseases

- Defining the healthy ageing phenotype in model organisms and humans at different chronological ages, to identify aspects of health and function that decline at similar or differing rates, including functional, structural and biological dimensions.
- Understanding the relationship between extension of lifespan and preservation of health in model organisms and humans.
- Exploring the increasingly porous boundary between ageing and age-related diseases in people, particularly the sub-clinical manifestation of the diseases of ageing, to determine common pathways of age-related diseases in different organs and physiological systems.
- Dissecting the relationship between cellular and molecular markers of ageing and the age-related decline in function of specific physiological systems.
- Evaluating the role of epigenetic mechanisms during critical periods of early human development in establishing risk of later decline in physical and cognitive function.
- Developing a better taxonomy of age-related diseases to understand how they relate to the underlying process of ageing.
- Understanding the relationship between phenotype and the determinants of ageing at the molecular, cellular, tissue, organ, system, individual and population levels.
- Integrating recent advances in our understanding of genetics, epigenetics and developmental programming with the processes of ageing and age-related diseases.

- Investigating the effects and interactions of contemporary major challenges to public health, such as obesity, diabetes, environmental toxins or new infections, with the processes of ageing and age-related diseases.
- Understanding the common biological mechanisms that underpin ageing and cancer.
- Studying the relationship between the *APOE* gene, the process of ageing and age-related diseases such as Alzheimer's and age-related macular degeneration (AMD).

3. Measuring and understanding the determinants of healthy ageing in older people at a population level

- Capitalising on the rich resource for research into healthy ageing presented by patient data from the NHS and other databases.
- Establishing new, and building on existing, cohorts and populations suitable for the study of normal and pathological ageing and age-related diseases, and establishing biobanks and datasets on these populations, including outbred cohorts and genetic isolates.
- Understanding the relationship between population trends in healthy life expectancy and trends in absolute life expectancy using long-term clinical studies and high quality routine clinical data.
- Understanding the contributions of genetic and environmental determinants of frailty and age-related decline, such as malnutrition and physical activity in the musculoskeletal system and cognition, at different stages in the life course.
- Determining whether a particular disease in young or middle age has similar pathogenesis to the same disorder in older people.
- Understanding the demographic and geographic variations in life expectancy and healthy ageing.
- Determining the impact of imminent changes in retirement age on the biology of ageing and the diseases with which it is associated.
- Learning about healthy ageing from natural experiments and how these might be modified by interventions.
- Understanding the relationship between changes in average human lifespan and maximum human lifespan.
- Developing a conceptual framework for integrating the disparate social and economic factors that generate inequalities in health and longevity with the biological processes of ageing and age-related diseases.
- Identifying robust ageing genotype–phenotype associations through family-based linkage studies, candidate gene association analyses and genome-wide association studies (GWAS).
- Developing more objective measures of functional health that can be related to subjective perception of health as well as to disease and mortality endpoints.

4. Translating advances in the basic biological science of ageing into effective interventions to promote healthy ageing

- Developing and validating easy to measure biomarkers and batteries of biomarkers for ageing in humans and model organisms. These would provide standardised information on biological age across the life course, as well as predicting remaining lifespan, major future health events and the outcome of age-sensitive experimental tests in widely diverse experimental arenas.

- Undertaking more research into the use of interventions in clinical practice that benefit older people, giving particular attention to people who have several diseases, or who take several medicines, or both.
- Identifying and surmounting the barriers to implementation of interventions that target the underlying processes of ageing to the provision of healthcare.
- Building an evidence-based understanding of the determinants of well-being in older people and interventions that might encourage this state.
- Determining whether existing medical interventions slow ageing, particularly at middle or older ages.
- Developing predictive markers of drug toxicity in older people.
- Characterising and evaluating early interventions that might reduce frailty and improve the quality of life of older people.
- Determine the relationship between the processes that underpin ageing and age-related disease that contribute most to the burden of age-related disease in the UK, such as cardiovascular disease (CVD), cancer, dementia, osteoporosis, respiratory disease and arthritis.

1 Objectives and scope of this report

1.1 Background and objectives

In spring 2008 the Academy initiated a working group on ageing research. The project was stimulated by a range of previous Academy work, including reports on 'Restoring neurological function' and 'Brain science, addiction and drugs', as well as our submission to the 2005 House of Lords Science and Technology Committee inquiry into the scientific aspects of ageing.[1,2,3] The Academy had also been approached by the MRC for independent guidance on strategic directions for UK ageing-related research – one of the MRC's six priority areas.

The **terms of reference** of the working group, chaired by Professor Dame Linda Partridge CBE FRS FRSE FMedSci, were to:

- Provide a broad overview of the key challenges for ageing research in the UK.
- Identify strategic priorities and shape future research directions.
- Offer a 'road map' to guide how these priorities might be achieved.

1.2 Scope

Ageing research encompasses a wide range of disciplines across the medical, biological, engineering and social sciences. The focus of this report lies in the medical and biological sciences, but it also considers their implications for the wider research agenda. This report sets out the compelling case for investment in ageing research, describes how recent scientific advances in our understanding of the ageing process can be applied to healthcare, and sets out how capacity in ageing research in the UK can be strengthened to harness fully the opportunities in this field.

This report will be of interest to the MRC and other research funders, industry, Government, regulatory authorities, universities, NHS Trusts and patient groups, as well as the public.

1.3 Process

The membership of the working group includes Academy Fellows and external experts. Members have expertise in basic biology, geriatrics, biogerontology, psychology, psychiatry, epidemiology, engineering, social science, clinical medicine, neuroscience, pathology, ophthalmology and industry. The Chair and members of the group were appointed as individuals and not as representatives of their affiliated organisations.

Although this study was sponsored by the MRC, members of the working group were completely independent in their work and in reaching their conclusions. Further details on the preparation of this report, including biographies of the working group and the process of review, are given in Annex I.

1 Academy of Medical Sciences (2004). *Restoring neurological function*.http://www.acmedsci.ac.uk/p99puid19.html
2 Academy of Medical Sciences (2008). *Brain science, addiction and drugs.*http://www.acmedsci.ac.uk/p48prid47.html
3 House of Lords (2005). *Scientific aspects of ageing*. The Stationery Office, London.

2 Introduction

2.1 The ageing population

The phenomenon of the 'ageing population' has been widely reported in recent years. Over the past 150 years, life expectancy in the more developed world has doubled, and most countries in the developing world are now experiencing sustained increases in longevity. Ever increasing life expectancy, low birth rates and the ageing of the 'baby boom' generation mean that the population of the UK is getting older. Boys born in the UK in 1901 could expect to live for around 45 years and girls for around 49.[4] By 2006, baby boys could expect to live for 77 years and girls for 81. Today, average life expectancy for people in the UK is increasing at **more than five hours a day, every day** – and it is likely that this trend will continue, at least in the medium-term.[5]

Before 1800, average life expectancy in Europe had changed little since the days of the Roman Empire, but by the mid-nineteenth century it had begun to increase. Between 1840 and 1950, advances in the control of infectious disease – including better sanitation, housing, nutrition, vaccination, clean water and antibiotics – led to a dramatic reduction in mortality among younger people.[6,7] Since 1950, improvements in life expectancy in the developed world have been primarily due to a reduction in mortality among older people, in part through improvements and innovations in medical care.[8]

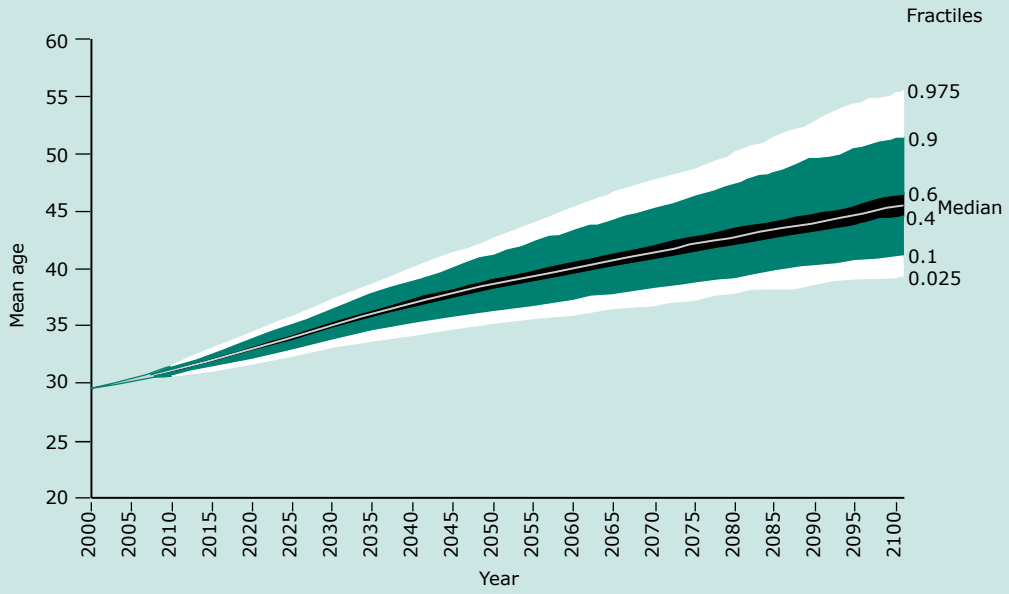
Changes in life expectancy are part of a wider demographic transition from high birth rates and high mortality to low birth rates and low mortality.[9,10] Changes in birth rate have tended to lag behind changes in mortality, creating a period of high birth rate and low mortality that result in population growth. As countries have gone through this demographic transition, so the world population has grown: in 1804 it stood at around one billion; by 2000 it had reached six billion.[11]

If the 20th Century was one of population growth, then the 21st Century will be one of population ageing (see figure 2.1). The Population Division of the United Nations Department of Economic and Social Affairs has projected that, between 2005 and 2050, half of the increase in the world population will be accounted for by a rise in the number of people aged 60 years or over.[12] Furthermore, in more developed global regions, the population aged 60 or over is expected nearly to double, whereas the number of persons under age 60 will probably decline.

4 Allen J (2008). *Older people and wellbeing*. Institute for Public Policy Research, London.
5 Ageaction (2007). *Changing expectations of life*. http://ageaction.ncl.ac.uk/AgeAction_book.pdf
6 Vaupel J (2004). *The plasticity of longevity*. http://www.sagecrossroads.net/webcast21
7 McKeown T (1976). *The modern rise of population*. Academic Press, London.
8 Bunker J (2001). *Medicine matters after all: measuring the benefits of medical care*. Nuffield Trust, London.
9 Thompson WS (1929). *Population.* American Sociological Review **34(6)**, 959–975.
10 Notestein FW (1945). *Population — the long view*. In Schultz TW ed (1945). *Food for the world*. University of Chicago Press, Chicago.
11 United Nations (1999). *The world at six billion*. http://www.un.org/esa/population/publications/sixbillion/sixbillion.htm
12 United Nations (2006). *World population, the 2006* revision. http://www.un.org/esa/population/publications/wpp2006/wpp2006.htm

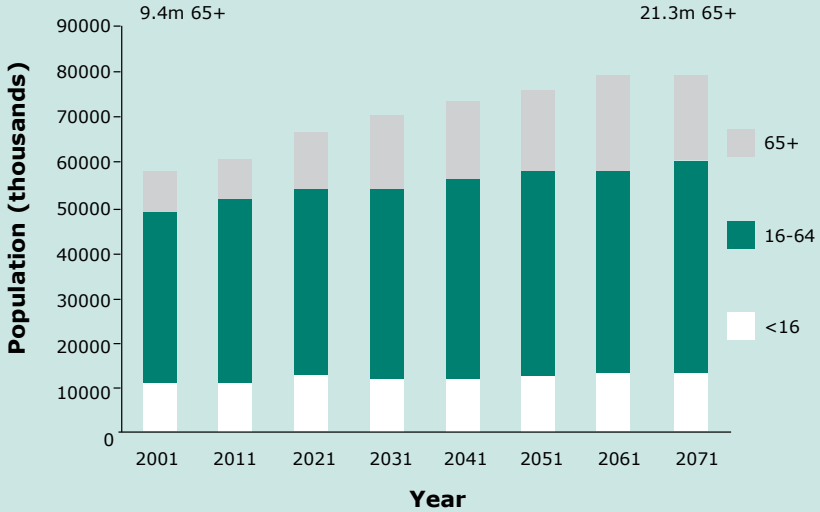
Figure 2.1 Projected mean age of the world human population[13]

The different coloured bands represent the predicted chance of the occurrence of a particular range of mean ages for the world population. The darker the colour, the greater the chance the projection will occur.



Ageing is of particular importance to the UK and Europe, where the size of the population is expected to peak and then decline earlier than in much of the rest of the world.[14] Like many countries, the UK experienced a period of high birth rates after the Second World War (the 'baby boom'), followed by a period of lower birth rates. This has produced the unusual situation where the current generation is smaller than its predecessor. The 'baby boom' generation is now beginning to reach the traditional age of retirement, with significant implications for public policy. It is the combination of increasing life expectancy, low birth rates and the proportion of people who are entering retirement that is so noteworthy. Projections for the UK population categorised by age are shown in figure 2.2.

Figure 2.2 Projection of the age composition of the UK population[15]



13 With kind permission from Professor Wolfgang Lutz, Professor Warren Sanderson and Dr Sergei Scherbov.
14 Lutz W, Sanderson W & Scherbov S (2008). *The coming acceleration of global population ageing*. Nature **451**, 716–719.
15 With kind permission from Foresight. This figure is adapted from Foresight (2008). *Mental capital and wellbeing*. The Stationery Office, London and based on Office for National Statistics, National population projections 2008.

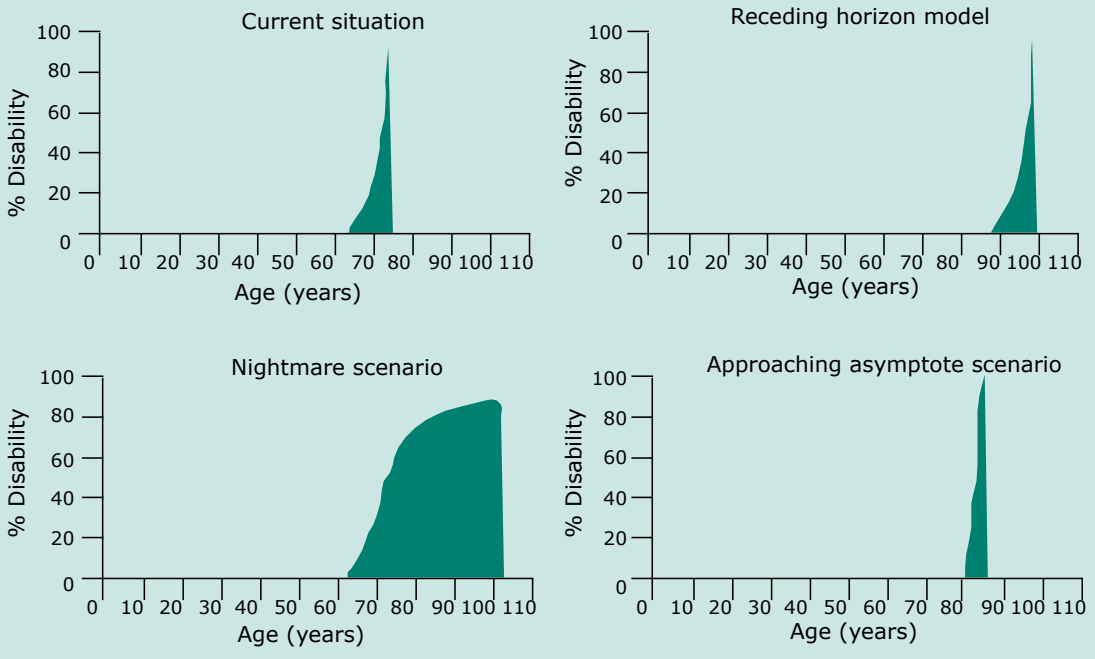
2.2 Promoting healthy life expectancy

The dramatic improvements in longevity described in the previous section could be considered an astonishing feat of human advancement, but this has not always been the case.[16] Some of the most frequently cited concerns include the perceived burden of chronic disabling illness (morbidity) that is thought to accompany increased longevity, and the associated costs of healthcare.

2.2.1 Trends in healthy life expectancy

As argued in the 2005 House of Lords Science and Technology Committee report, increases in life expectancy are to be welcomed only if the 'added years' are ones of relative good health.[17] It is therefore important to distinguish between life expectancy and **healthy** life expectancy. Some of the possible futures for old age are illustrated in figure 2.3. The current situation in the UK is illustrated in the first graph: people tend to live relatively healthy lives until their late sixties whereupon chronic illness and disability start to accumulate until death. The second graph shows a 'receding horizon model', where both morbidity and death are postponed. A third possibility is the 'nightmare scenario', where life expectancy increases but healthy life expectancy does not. Without significant investment in the right sort of research, this scenario remains a worrying possibility, particularly because of neurodegenerative disorders.[18] Finally, there is the 'approaching asymptote scenario', where chronic disease is postponed until much closer to death. The aim of research into ageing is to improve people's health as they age: it is this final scenario that is the ideal goal.

Figure 2.3 The possible futures of old age[19]



16 Tallis R (2003). *Is the ageing population a threat to sustainable health care?* British Association for the Advancement of Science. http://www.cardi.ie/userfiles/ageing_and_health_care.pdf
17 House of Lords (2005). *The scientific aspects of ageing*. The Stationery Office, London.
18 Foresight (2008). *Mental capital and wellbeing*. The Stationery Office, London.
19 With kind permission from Tallis R (2004). *Hippocratic oaths. Medicine and its discontents.* Atlantic, London.

Although it is likely that both life expectancy and the mean age of the population will increase in the future, the status of healthy life expectancy is more uncertain.[20] Evidence about changes in healthy life expectancy in the UK is limited, because surveys of morbidity did not gain momentum until the second half of the 20th Century. The situation should become clearer when the results of ongoing research, such as the English Longitudinal Study on Ageing (ELSA), are reported.[21]

There is some evidence of an increase in chronic disease in the UK over the past 20 years. However, although people may live longer with chronic disease, they suffer fewer disabilities thanks to earlier diagnosis, better treatment and improved assistive devices.[22] The House of Lords inquiry into the scientific aspects of ageing highlighted an apparently widening gap between life expectancy and healthy life expectancy in the UK, although it was noted that this may be due to difficulties in defining healthy life expectancy.[23] In some countries, such as Japan, increases in life expectancy have not led to increased morbidity.[24]

Disability is a powerful indicator of health status and future outcomes.[25] The General Household Survey and other studies indicate that the proportion of older people who are disabled in the UK has remained the same, or has been decreasing, since 1995.[26,27] For instance, the proportion of men aged over 85 able to bathe, feed themselves and get to the toilet without help rose from 69% to 79% between 1980 and 1991; the proportion of women rose even faster from 64% to 80% over the same period.

Box 2.1 Reversing the gains in life expectancy

Some predictions suggest that the rising prevalence of obesity means that today's generation of children might be the first for over a century for whom healthy life-expectancy will fall.[30] Even though obesity is only weakly associated with life expectancy in older people, it is strongly associated with increased morbidity.[31]

The obesity 'epidemic' has been prevalent for longer in the USA than the UK. Nevertheless, figures for 2004 suggest that in the preceding year the average weight of people in the USA fell for the first time.[32] Even if people are getting a little thinner in America, it will be many years before the country solves the health problems caused by half a century of rising obesity, and across much of the rest of the world people are still gaining weight. It will be important to track changing levels of obesity and their impact on longevity in the years to come.

Populations may also show fragmentation, with healthy life expectancy continuing to rise among richer groups, but remaining static or even falling among poorer sections of society. Studies in the USA have shown that, from 1980 to 2000, people in higher socio-economic groups experienced larger gains in life expectancy than those in more deprived groups.[33] People from poorer socio-economic groups are more likely to smoke, to consume excess alcohol, to eat unhealthy food and not to take physical exercise.[34] In many cases it is relative, rather than absolute, economic and educational deprivation within societies that matters most.[35] Migration may also have a significant impact on demographic changes, especially because a transition to Western diets and low levels of exercise have adverse effects on health.[36]

20 Robine JM & Michel JP (2004). *Looking forward to a general theory on population ageing*. Journal of Gerontology **59A(6)**, 590–597.
21 Further details are available from http://www.natcen.ac.uk/elsa/
22 Franco OH, *et al*. (2007). *Ten commandments for the future of ageing research in the UK: a vision for action*. BMC Geriatrics **7(10)**, 1–17.
23 House of Lords (2005). *The scientific aspects of ageing*. The Stationery Office, London.
24 *Ibid*.
25 Guralnik J, Fried LP & Salive ME (1996). *Disability as a public health outcome in the ageing population.* Annual Review of Public Health **17**, 25–46.
26 Office of National Statistics (2006). *General household survey*. Office of National Statistics, London.
27 Tallis R (2003). *Is the ageing population a threat to sustainable health care?* British Association for the Advancement of Science. http://www.cardi.ie/userfiles/ageing_and_health_care.pdf

Data from the USA, where the most extensive research into healthy ageing has taken place, show that the prevalence of chronic morbidity and disability has declined by 6% per decade over the course of the 20th Century.[28] Further evidence from the USA suggests that, between 1935 and 2000, health quality increased faster than life expectancy, resulting in reduced morbidity.[29] The same data indicate that 24–41% of the long-term disability decline was due to innovations in medical care that ameliorated symptomatic consequences of chronic disease. However, as discussed in box 2.1, continuing rises in life expectancy and healthy life expectancy are not a foregone conclusion.

In summary, if healthy life expectancy does not increase as quickly as life expectancy, then the ageing population might indeed present significant health and social challenges. However, preliminary evidence, such as recent data from the UK Office of National Statistics, indicates that healthy life expectancy in the UK is increasing at least as quickly as life expectancy.[37] We may therefore have much less to fear from the ageing population than some anticipate. Indeed, if healthy life expectancy increases rapidly enough, then the ageing population becomes an economic and social opportunity rather than a challenge.

2.2.2 Healthcare costs and the ageing population

Much of the debate about the implications of the ageing population has been dominated by fears of its impact on the cost of healthcare. However, ageing is only a modest component of increasing national healthcare costs, which are mostly driven by demand from patients and expensive improvements in medical treatment (in part owing to increased regulatory demands on the discovery, development and licensing of medicines).[38,39,40] For instance, the median cost of cancer drugs approved by the US Food and Drug Administration more than quadrupled between 1980 and 2005.[41]

For most people, most healthcare costs are associated with the last few months of life. The proposition that healthcare for older people should be restricted because older patients have already used their fair share of resources has now been robustly challenged.[42] In general, older people merely defer drawing upon their major share of healthcare resources until later in life. Research also indicates that exceptional longevity does not result in excessive levels of disability.[43] Quite the contrary: very old people tend to be more frail, so die more quickly and experience shorter periods of disability. Moreover, because most young people can now expect to attain old age, then they in turn will enjoy the benefits of investments to promote healthy ageing.[44]

The picture becomes more complicated if the costs of healthcare at the population and individual levels are disaggregated. Individual healthcare costs may decline owing to rises in healthy life expectancy, but national healthcare costs may increase because older people make up a greater proportion of the population.[45] For instance, research by Help the Aged indicated that, although people have never lived for so long and in such good health, the overall prevalence of disabling diseases is set to rise substantially by 2025, because older people will

28 Manton, *et al*. (2007). *Labour force participation and human capital increases in an ageing population and implications for US research investment*. Proceedings of the National Academy of Sciences of the USA **104(26)**, 10802–10807.
29 *Ibid*.
30 House of Commons Health Select Committee (2004). *Obesity*. The Stationery Office, London.
31 Reynolds SL, Saito Y & Crimmins EM (2005). *The impact of obesity on active life expectancy in older American men and women.* The Gerontologist **45**, 438–444.
32 The Economist (2003). *The shape of things to come*. The Economist, December 11.
33 Singh GK & Siahpush M (2006). *Widening socioeconomic inequalities in US life expectancy*. International Journal of Epidemiology **35(4)**, 969–979.
34 Wanless D (2004). *Securing good health for the whole population.* The Stationery Office, London.
35 Marmot M (2004). *Status syndrome*. Bloomsbury, London.
36 Daar AS, *et al*. (2007). *Grand challenges in chronic non-communicable diseases*. Nature **450**, 494–496.
37 Smith M, Edgar G & Groom G (2008). *Report: health expectancies in the United Kingdom, 2004-06*. Health Statistics Quarterly **40**, 77–80.
38 Turner A (2005). *Pensions commission second report*. The Stationery Office, London.
39 Shapiro R (2008). *Futurecast 2020*. Profile Books, London.
40 Association of the British Pharmaceutical Industry (2008). *The prioritisation of research and the pharmaceutical industry*. Association of the British Pharmaceutical Industry, London.
41 Bach PB (2009). *Limits on Medicare's ability to control rising spending on cancer drugs*. New England Journal of Medicine **360**, 626–633.
42 Himsworth RL & Goldacre MJ (1999). *Does time spent in hospital in the final 15 years of life increase with age at death? A population study*. British Medical Journal **319(7221)**, 1338–1339.
43 Christensen K, *et al*. (2008). *Exceptional longevity does not result in excessive levels of disability*. Proceedings of the National Academy of Sciences of the USA **105(36)**, 13274–13279.
44 Ageaction (2007). *Changing expectations of life*. http://ageaction.ncl.ac.uk/AgeAction_book.pdf
45 Manton KG, *et al.* (2007). *Labour force participation and human capital increases in an ageing population and implications for US research*

make up a greater fraction of the population.[46] This argument applies in other areas where an ageing population may have an impact, such as social care.[47]

2.2.3 Perceptions of the social and economic impacts of the ageing population

The 2005 House of Lords Science and Technology report described '… *a pervasive but often unrecognised ageist attitude of the public and the media towards disease prevalent in old age* …'[48] For example, the focus of recent debates on individual responsibility for disease can result in older people being unfairly blamed for the consequences of ageing, many of which are driven by environmental and biological factors beyond individual control.[49]

Ageism has a negative impact on the lives of older people. It prevents society from taking full advantage of the continuing economic and social contributions that older people can make as a result of improved health. A common misconception about ageing is that older workers are less economically productive than their younger counterparts. Although the research base in this area is relatively small, existing studies show that this idea is mostly unfounded. For instance, research conducted by the Mannheim Institute for the Economics of Ageing indicates that older workers are not significantly less productive, nor more expensive, nor on sick leave more frequently than younger workers.[50] Although it is not appropriate to extrapolate the results of one set of studies to all working environments, these results do indicate that an ageing population is not necessarily less productive.

The impact of ageing is likely to be less significant as jobs move from heavy industry to the less physically demanding service sectors. Older workers can make a particularly valuable contribution through their experience and reliability. Increasing healthy life expectancy offers the potential to build reserves of 'mental capital' in the population, which the Government's Foresight programme has recently identified as being significantly under-used.[51] Of particular relevance to this are efforts to slow cognitive decline that is not overtly associated with explicit pathology.[52] There may also be opportunities for older people to contribute to society through activities that are sometimes overlooked in conventional economic analyses, such as childcare and participation in voluntary organisations.

Brief mention should also be given to the fact that many of the perceived challenges of the ageing population are purely social constructs. The welfare systems of many industrialised countries are based upon social reforms introduced by the German Chancellor Otto von Bismarck in 1883. At the end of the 19th century a retirement age of 65 gave a few people a handful of work-free years before death. Today most people expect to live well past that age. Even age-associated disability can be seen as arising from an 'ecological gap' between what an individual can do and what the environment demands. This gap can be closed by changing both the capabilities of the individual and the limitations of the environment.[53] For instance, wheelchair users are less disadvantaged if there is adequate provision of ramps and lifts. Although discussion of both the age of retirement, employment and provisions for those with disabilities are beyond the scope of this report, it is important to recognise that some consequences of ageing are driven by society rather than biology. More needs to be done to ensure the positive messages from medical research are reflected in public perceptions of ageing and older people.

investment. Proceedings of the National Academy of Sciences of the USA **104(26)**, 10802–10807.

46 Help the Aged (2008). *Help the Aged warns that age-related long term illness is the single greatest health issue facing the UK*. http://press.helptheaged.org.uk/_press/Releases/_items/_Help+The+Aged+Warns+That+Age-Related+Long+Term+Illness+Is+The+Single+Greatest+Health+Issue.htm

47 Wanless D (2006). *Securing good care for older people: taking a long-term view*. The King's Fund, London.

48 House of Lords (2005). *The scientific aspects of ageing*. The Stationery Office, London.

49 Ageaction (2007). *Changing expectations of life*. http://ageaction.ncl.ac.uk/AgeAction_book.pdf

50 Borsch-Supan A & Weiss M (2008). *A discussion paper on productivity and the age composition of work teams: evidence from the assembly line*. MEA, University of Mannheim, Germany.

51 Kirkwood T, *et al.* (2008). *Foresight mental capital and wellbeing project. Mental capital through life: future challenges*. The Government Office for Science, London.

52 Deary IJ & Gow AJ (2008). *Mental capital and welling being: making the most of ourselves in the 21st century. State-of-science review E14: determinants of normal cognitive ageing: implications for mental capital*. The Government Office for Science, London.

2.3 The biology of ageing

2.3.1 Theories of ageing

In biological terms, ageing can be described as *'a progressive, generalised impairment of function that results in a loss of adaptive response to stress and an increasing probability of death'*.[54] In the natural world, ageing is characterised by an increase in mortality and decrease in fertility. Ageing is a consequence of damage, through the gradual accumulation of faults in molecules, cells and organs, leading to loss of physical, cognitive and immune function, and increased frailty and vulnerability to age-related diseases (see chapter 3).

Ageing has sometimes been viewed as a programmed process driven by a biological 'self-destruct mechanism'. However, this idea has now been discredited.[55,56] As far as we know, no genes have evolved by natural selection to cause decline in function and death. Instead, ageing is now understood to be a deleterious side effect of other processes, in particular the limited capacity of natural selection to remove gene effects that cause harm in later life.[57] The theories for the evolution of ageing that underpin this conclusion are summarised below.

Mutation accumulation theory was proposed by Sir Peter Medawar OM CBE FRS in 1952.[58] Medawar first pointed out that the force of natural selection declines at later ages, because of the impact of external hazard. As a result, deleterious mutations that take effect later in life can accumulate because the force of natural selection on them declines.

The pleiotropy theory was proposed by Professor George Williams in 1957 and builds on Medawar's idea of the declining force of natural selection with age.[59] It suggests that a gene with beneficial effects early in life may, as a side effect, cause a more rapid rate of ageing later in life, but will nevertheless be selected because the force of natural selection operates more strongly earlier in life. This could occur, for instance, if costly processes, such as reproduction, compete for nutrients with cellular maintenance and repair, hence compromising somatic maintenance and ultimately lead to ageing. This is known as the disposable soma theory.[60]

It should be noted that these theories are not mutually exclusive. The main difference between the mutation accumulation and pleiotropy theories is that, in the former, ageing evolves as a side effect of mutation pressures, whereas in the latter it evolves as a side effect of an earlier benefit, such as early reproduction.

These theories for the evolution of ageing are supported by evidence from experiments and from the natural world. As postulated by Medawar, there is a general association between a low impact of external hazard and a slow intrinsic rate of ageing. For instance, bats, which are to some extent protected from environmental hazards by their ability to fly, are capable of living much longer than their terrestrial mammalian relatives, and birds can generally outlive mammals of similar body size.[61] Laboratory research on fruit-flies and guppies has also shown that changing environmental conditions and selective pressures can induce rapid changes in longevity over just a few generations.[62]

Support has been found for these theories on the evolution of ageing: an early beneficial effect can be linked with subsequent ageing through the widespread 'cost of reproduction'. Another possible route is the association between the proliferative capacity of cell

53 Grimley-Evans J (2005). *Scientific aspects of ageing: a lordly report.* Journal of the Royal Society of Medicine **98(11)**, 482–483.
54 Maynard Smith J (1962). *The causes of ageing*. In *Review Lectures on senescence*. Proceedings of the Royal Society of London series B **157**, 115–127.
55 Kirkwood T (2008). *A systematic look at an old problem*. Nature **451**, 644–647.
56 Partridge L & Gems D (2002). *Mechanisms of ageing: public or private?* Nature Review of Genetics **3(3)**, 165–175.
57 Williams GC (1957). *Pleiotropy, natural selection, and the evolution of senescence*. Evolution **11**, 398–411.
58 Medawar PB (1952). *An unsolved problem of biology*. H.K. Lewis, London.
59 Williams GC (1957). *Pleiotropy, natural selection, and the evolution of senescence.* Evolution **11**, 398–411.
60 Kirkwood TBL (1977). *Evolution of ageing.* Nature **270**, 301–304.
61 Brunet-Rossinni AK & Austad SN (2004). *Ageing studies on bats: a review*. Biogerontology **5(4)**, 211–222.

lineages during growth and tissue repair, and the later vulnerability to cancer.[63,64,65,66]

Some animals either age very slowly or do not age at all. Consistent with evolutionary theories of ageing, these animals all have life histories that result in a slow or absent decline in the force of natural selection with age. For instance many fish, amphibians and reptiles increase in fecundity with age and show little or no increase in mortality rate; these organisms generally start reproduction before growth is completed, and the increasing body size is associated with an increase in fecundity.[67] Some sea anemones and species of *Hydra*, where the germ line separates from somatic cell lineages later in life, seem not to age at all.[68,69] In contrast, humans and most laboratory model organisms all start reproduction when growth is more or less complete, segregate their germ lines early in development, and therefore age.

2.3.2 Malleability of ageing

As well as showing considerable diversity as a result of evolutionary change, the ageing of individual organisms is a highly malleable process that is open to intervention.[70,71] For instance, dietary restriction, where an organism is allowed to eat only a proportion of its preferred intake, extends lifespan in most cases where it has been tested (for further details see chapter 3).[72] Temperature, exercise and the genetic make-up of individuals can also alter rates of ageing.[73]

Human mortality and ageing are also highly malleable. An often-cited example is the change in mortality that occurred after the reunification of West and East Germany in 1989–1990; in just over a decade, mortality in the East, especially among older people, declined to levels similar to those in the West.[74] Moreover, the risk of death for elderly smokers who quit falls within a couple of years to a lower level than that for individuals who continue to smoke.[75]

Longevity in human populations has been shown to vary according to many environmental factors such as wealth, education, exposure to childhood infection and geography, all of which can be modified (see chapter 3). For example, the difference in life expectancy between the most and least deprived areas of Glasgow is around 28 years.[76] The study of rare genetic disorders, such as Werner's syndrome, that result in conditions that resemble accelerated ageing provides further evidence that ageing is to some extent plastic and may help us understand the normal ageing process. Intriguingly, although our average lifespan has increased dramatically over the past 150 years, maximum lifespan has not risen. If we are to understand better the process of ageing, then this phenomenon requires further investigation.

2.3.3 Ageing and disease

Age is the single biggest risk factor for many life-threatening diseases, such as heart failure, cancer and dementia.[77] For example, a tumour is 100 times more likely to occur at the age of 65 than at 35.[78] In view of the remarkable increases in human life expectancy, there is a biomedical and social urgency to understand the connection between ageing and ageing-related disease, because the major burden of ill health falls on the older section of society.

As indicated in the previous section, ageing is driven by accumulation of damage, a factor

62 Kenyon C (2005). *The plasticity of ageing: insights from long-lived mutants*. Cell **120**, 449–460.
63 Hughes KA & Reynolds RM (2005). *Evolutionary and mechanistic theories of aging*. Annual Review of Entomology **50**, 421–445.
64 Partridge L, Gems D & Wither D (2005). *Sex and death: what is the connection?* Cell **120(4)**, 461-472.
65 Williams GC (1966). *Natural selection, the cost of reproduction, and a refinement of Lack's principle.* American Naturalist **100**, 687–690.
66 Campisi J & Sedivy J (2009). *How does proliferative homeostasis change with age, what causes it and how does it contribute to aging?* Journal of Gerontology series A: Biological and Medical Sciences, **64A(2)**, 164-166.
67 House of Lords (2005). *The scientific aspects of ageing*. The Stationery Office, London.
68 Vaupel JW, *et al*. (2004). *The case for negative senescence*. Theoretical Population Biology **65(4)**, 339–351.
69 Baudisch A (2005). *Hamilton's indicators of the force of selection.* Proceedings of the National Academy of Sciences of the USA **102(23)**, 8263–8268.
70 Vaupel JW (2004). *The biodemography of ageing*. Population and Development Review **30** (supplement), 48–62.
71 Partridge L & Gems D (2002). *Mechanisms of ageing: public or private?* Nature Reviews **3,** 165–175.
72 Mair W & Dillin A (2008). *Aging and survival: the genetics of lifespan extension by dietary restriction*. Annual Review of Biochemistry **77**, 727–754.
73 Fontana L, *et al*. (2007). *Calorie restriction or exercise: effects on coronary heart disease risk factors. A randomized, controlled trial*. American Journal of Physiological and Endocrinological Metabolism **293(1)**, E197–E202.
74 Vaupel JW, Carey JR & Christensen K (2003). *It's never too late.* Science **301**, 1679–1681.
75 Doll R, *et al*. (2004). *Mortality in relation to smoking: 50 years' observations on male British doctors*. British Medical Journal **328(7455)**, 1519–1528.
76 World Health Organization (2008). *Report of the commission on the social determinants of health*. http://www.who.int/social_determinants/thecommission/finalreport/en/index.html
77 Green S & Mills R (2008). *Burden of disease in the UK scoping study*. The Stationery Office, London.

that is also implicated in many age-associated diseases.[79] Consequently, there is considerable overlap in the underlying pathways that contribute to both ageing and ageing-related disease. For example, in cases of 'normal' brain ageing, where an older person's cognition remains essentially intact, the extent of neurofibrillary tangles and amyloid plaques that build up in the brain are more similar to those seen in patients with Alzheimer's disease than might be expected if ageing and Alzheimer's disease were totally distinct.[80]

Common factors, such as oxidative stress, are implicated in both 'normal' ageing and multiple age-associated diseases. For instance, an accumulation of dysfunctional mitochondria can give rise to a decline in energy production, which in turn can lead to a decline in efficacy of cell maintenance systems such as protein turnover, resulting in pathogenic protein aggregates and so on. This may explain, for example, the association between mitochondrial DNA mutations and neuronal death in the substantia nigra of the brains of patients with Parkinson's disease.

As our understanding of the fundamental biological processes of ageing progresses, the sharp distinction between ageing and ageing-related disease is becoming more blurred. This presents challenges for our concepts of 'normal' ageing, and what aspects of ageing can, and should, be subject to medical intervention. It may be that healthy ageing – i.e. ageing in the apparent absence of disease – is indistinguishable at some fundamental molecular or cellular level from diseases that have yet to become clinically apparent. Instead these sub-clinical diseases may manifest themselves as frailty. What is clear is that research into the basic biology of ageing is likely to have a profound impact on our understanding of ageing-related diseases.

2.4 Reaping the rewards of medical research into ageing

The economic gains from medical research into ageing and ageing-related diseases could be substantial. For example, several studies have quantified the impact of research into medicines for CVD (see box 2.2).

The study of the economic benefits of medical research is still a nascent field, and more work is needed to improve the assumptions and data on which these studies were based. However, even by cautious estimates, the economic returns on medical research are substantial and make a compelling case for investment.

2.5 Conclusion

Ever-increasing life expectancy, low birth rates and the ageing of the baby boom generation mean that on average the UK population is getting older. Unfortunately, these changes are still seen by some as a failure rather than as one of humankind's great successes. Many fear that the ageing of the population will be accompanied by rising numbers of people with chronic illness who will place unsustainable pressure on our economy and systems of health and social care.

However, there is some evidence to indicate that healthy life expectancy is increasing at least as quickly as life expectancy. If this trend is verified and continues, then the ageing population becomes an opportunity rather than a challenge as more people enjoy longer, healthier lives that allow them to contribute more to society. The primary objective of research into ageing should therefore be to improve health during ageing and hence promote healthy life expectancy.

78 Kenyon C (2005). *The plasticity of ageing: insights from long-lived mutants.* Cell **120**, 449–460.
79 Kirkwood T (2008). *A systematic look at an old problem.* Nature **451**, 644–647.
80 Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (2001). *Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales*. Lancet **357**, 169–175.

Public investment into ageing research offers truly exceptional health, economic and social returns. Ageing is a malleable process that is open to interventions that could in turn help mitigate many diseases. Clearly there is now a strong scientific, health, economic and social case for research into healthy ageing and well-being in older people.

Box 2.2 Exceptional returns from medical research into cardiovascular disease

A US study 'Exceptional Returns', published by the Lasker Foundation in 2000, examined the economic value in the reduction in deaths from CVD that occurred in the USA between 1970 and 1990. Further details are available from: http://www.laskerfoundation.org/advocacy/econimpact.htm. The top-line findings of the study were dramatic and include:

- Increases in life expectancy of US citizens from 1970 to 1990 were worth around US$2.8 trillion per year.
- The reduction in deaths from CVD alone was worth roughly US$1.5 trillion per year.
- Assuming that only a third of the reduction in CVD deaths could be attributed to medical research, spending on research yielded an annual 20-fold rate of return.

In 2003, the Australian Society for Medical Research used a similar methodology to the US work to show that the returns on Australian research were also 'exceptional': the total return on the investments in CVD research in the year 1998–99 was estimated to be as high as 788%.[81]

More recent work, commissioned by the Academy of Medical Sciences, MRC and Wellcome Trust, showed that the health and economic gains derived from UK public and charitable investments in CVD research (over the period 1975–1992) is equivalent to an annual rate of return of around 39%.[82] In other words, a £1.00 investment in public/charitable CVD research produced a stream of benefits equivalent to earning £0.39 per year in perpetuity. This figure of 39% adds together an annual rate of return of 30% in gains in gross domestic product (i.e. direct returns to the UK economy) and an annual rate of return of 9% in health gains (arising from new preventative and therapeutic interventions for disease).

81 Access Economics (2003). *Exceptional return: the value of investing in health R&D in Australia.* http://www.accesseconomics.com.au/publicationsreports/showreport.php?id=33&searchfor=2005&searchby=yearearlier

82 Wellcome Trust, Medical Research Council and Academy of Medical Sciences (2008). *Medical research: what's it worth?* http://www.acmedsci.ac.uk/p99puid137.html

3 The science of ageing

In this chapter we consider some of the recent groundbreaking advances in ageing research including:

- *The insulin and insulin-like growth factor-1 (IGF-1) signalling pathway*
- *Dietary restriction*
- *Sirtuins*
- *Oxidation*
- *Cellular senescence*
- *Stem cells*
- *Glucocorticoids*
- *Genetics of ageing*
- *Developmental origins of ageing and age-related disease*
- *Social determinants of ageing*

We then consider some of the tools and methods used to obtain this knowledge, such as:

- *Animal models*
- *Biomarkers*
- *Population-based research: epidemiology and population genetics*
- *Clinical trials*

Finally we argue that research can reveal opportunities for medical interventions that systematically target the process of ageing and can therefore address many age-related diseases at once.

3.1 Advances in research into ageing

The advances outlined in this section represent a sample of the progress that has been made in our understanding of ageing. By highlighting some of these developments, we show that not only is ageing is a scientifically tractable problem, but that harnessing the opportunities presented by this exciting field could lead to real and significant progress in improving human health and tackling disease.

Genetic mutations and environmental interventions that increase lifespan are particularly informative to understanding the ageing process. This is because mutations that shorten lifespan, while of importance in specific contexts, are often of less relevance for understanding ageing because they result in novel pathology, rather than acceleration of the normal ageing process. The major breakthrough in ageing research has been the discovery of single gene mutations that: increase lifespan; show evolutionary conservation; and increase health during ageing. Nutrient-sensing pathways, such as insulin/IGF-1 and TOR (target of rapamycin), currently best fulfil these criteria, and these and other candidate mechanisms are considered below.

3.1.1 The insulin and insulin-like growth factor-1 (IGF-1) signalling pathway

The first evidence that single gene mutations could increase lifespan came from mutagenesis screens in the nematode worm *Caenorhabditis elegans*.[83,84,85] This first experiment isolated long-lived strains that were mutant for the gene *age-1*; subsequent screens produced a further long-lived strain mutant for the gene *daf-2*. One of these mutant strains of *C. elegans* was shown to live five times longer than its wild-type counterparts.[86]

The genes *daf-2* and *age-1* have been revealed as components of the insulin and IGF-1 signalling pathway. This pathway controls many functions, including multiple and diverse downstream genes that act together in a cumulative fashion to influence ageing.[87] Among the products of these downstream genes are molecules that detoxify lipophilic

83 Friedman DB & Johnson TE (1987). *A mutation in the age-1 gene in* Caenorhabditis elegans *lengthens life and reduces hermaphrodite fertility*. Genetics **118(1)**, 75–86.
84 Morris, *et al*. (1996). *A phosphatidylinositol-3-OH kinase family member regulating longevity and diapause in* Caenorhabditis elegans. Nature **382**, 536–539.
85 Klass M & Hirsh D (1976). *Non-ageing developmental variant of* Caenorhabditis elegans. Nature, **260(5551)**, 523–525.
86 Kuningas M, *et al*. (2008). *Genes encoding longevity: from model organisms to humans*. Ageing Cell **7**, 270–280.
87 Kenyon C (2005). *The plasticity of ageing: insights from long-lived mutants.* Cell **120**, 449–460.

endobiotic and xenobiotic compounds, and factors that reduce protein synthesis.[88] The insulin/IGF-1 pathway is also involved in biological functions such as reproduction, stress resistance, growth, nutrition and metabolism, although increases in longevity can be uncoupled from many, or possibly all, of these other functions.[89]

The insulin/IGF-1 pathway in *C. elegans* is also involved in a process called dauer formation.[90] In a benign environment, *C. elegans* develop through four larval stages cumulating in adulthood. Under harsh conditions, such as food scarcity or overcrowding, the worms enter an alternative state, called dauer. This is a non-reproductive, non-feeding, stress-resistant condition adapted for long-term survival; during dauer, ageing is halted. The dauer state allows worms to survive difficult times, postponing reproduction until the environment is more amenable. Importantly, the post-dauer lifespan is not affected by a prolonged dauer stage.

It was thought for a time that the role of the insulin/IGF-1 pathway in longevity might be specific to worms, through re-expression in the adult worm of genes that make the dauer larva long-lived. However, it subsequently transpired that at least some of the components of the insulin/IGF-1 mechanisms, and their influence on ageing, are evolutionarily conserved across species. For example:[91,92]

- Mutation of the insulin receptor InR in fruit-flies (the orthologue of the *daf-2* receptor in worms), as well as mutation of chico, the single insulin-receptor substrate in the fly, extends their lifespan.[93]
- Unlike worms or fruit-flies, rodents and mammals have separate insulin and IGF-1 receptors, and mice have been shown to live longer if either their insulin or IGF-1 signals are disrupted.[94]
- There is evidence that long-lived humans have **decreased plasma IGF-1 levels** and **preserved insulin action**, whereby resistance to insulin increases more slowly with age. This indicates that insulin/IGF-1 responsiveness may influence ageing in people.[95]
- In worms, flies and rodents, **forkhead transcription factors** that act downstream of insulin/IGF-1 receptors have been shown to affect ageing.[96, 97]
- Studies in dwarf mutant mice have shown that deficiencies in **pituitary hormones**, including growth hormone, reduce plasma IGF-1 and extend lifespan.[98]
- Over-expression of a newly discovered hormone, **Klotho**, has been shown to extend lifespan in mice, probably through regulation of mechanisms downstream of the insulin and IGF-1 receptors.[99] Klotho-deficient mice exhibit a syndrome that resembles accelerated human ageing. A haplotype allele, KL-VS, has recently been associated with Klotho expression in humans and is under-represented in elderly people.[100]
- Single-gene mutations that affect the related, nutrient-sensing **TOR pathway** can extend lifespan in budding yeast, *C. elegans* and *Drosophila*, and pharmacological interventions have recently been found to increase healthy lifespan in mice.[101,102]

88 Piper MDW, *et al*. (2008). *Separating cause from effect: how does insulin/IGF signalling control lifespan in worms, flies and mice.* Journal of Internal Medicine **263**, 179–191.
89 Partridge L & Gems D (2002). *Mechanisms of ageing: public or private?* Nature Reviews **3**, 165–175.
90 Kuningas M, *et al*. (2008). *Genes encoding longevity: from model organisms to humans.* Ageing Cell **7**, 270–280.
91 Russell SJ & Kahn CR. (2007). *Endocrine regulation of ageing*. Nature Reviews Molecular Cell Biology **8(9)**, 681–691.
92 Taguchi A & White MF (2008). *Insulin-like signalling, nutrient homeostasis, and lifespan*. Annual Review of Physiology **70**, 191–212.
93 Piper MDW, *et al*. (2008). *Separating cause from effect: how does insulin/IGF signalling control lifespan in worms, flies and mice.* Journal of Internal Medicine **263,** 179–191.
94 Geesaman BJ (2006). *Genetics of ageing: implications for drug discovery and development*. American Journal of Clinical Nutrition **83** (Supplement), 466–469.
95 Kuningas M, *et al*. (2008). *Genes encoding longevity: from model organisms to humans*. Ageing Cell **7**, 270–280.
96 *Ibid*.
97 Partridge L & Brüning JC (2008). *Forkhead transcription factors and ageing*. Oncogene, **27**, 2351–2363.
98 James Martin Institute (2006). *Tomorrow's people: the challenges of technologies for life extension and enhancement. Longer?* http://www.martininstitute.ox.ac.uk/JMI/Forum2006/Forum+2006+Webcast.htm
99 Bartke A (2006). *Long-lived Klotho mice: new insights into the roles of IGF-1 and insulin in ageing*. Trends in Endocrinology and Metabolism **17(2)**. 33–35.
100 Kuningas M, *et al*. (2008). *Genes encoding longevity: from model organisms to humans*. Ageing Cell **7**, 270–280.
101 Smith ED, *et al*. (2008). *Quantitative evidence for conserved longevity pathways between divergent eukaryotic species*. Genome Research **18(4)**, 564–570.
102 Harrison DE, *et al*. (2009). *Rapamycin fed late in life extends lifespan in genetically heterogenous mice*. Nature **10**, doi:10.1038/nature08221.

Altering the activity of the insulin/IGF-1 signalling pathway has an effect on lifespan that shows evolutionary conservation, opening up the prospect of using the simpler invertebrates to make initial discoveries of genes and mechanisms that can then be extrapolated to mice and humans. The invertebrates also act as a relatively quick and simple testing ground for the effects of genes that are discovered through gene expression profiling or population-genetic association studies in humans. The use of model organisms is a powerful research approach that has proved successful for understanding other biological processes, such as development and the functioning of the nervous system, and is now rapidly progressing our understanding of the ageing process.[103,104]

3.1.2 Dietary restriction

Dietary restriction, where dietary intake retains sufficient micronutrients but is reduced below normal consumption, was first discovered to extend lifespan in rodents in 1935.[105] Until the 1970s, it was the only mechanism known to delay ageing in diverse organisms, including yeast, worms, fruit-flies and rodents, and, as has been shown recently, primates.[106,107,108] Some experimental studies have also shown health benefits from dietary restriction in humans, but there is not yet any evidence that it can extend human lifespan.[109,110]

Despite its widespread effects, it is not yet known whether dietary restriction extends lifespan by similar mechanisms in different organisms, or whether instead there is evolutionary convergence, where a particular trait evolves independently and by different mechanisms in different lineages. Nor are the precise mechanisms by which dietary restriction exerts its effects understood in particular species.[111] Some studies have implicated roles for the classic nutrient sensing insulin/IGF-1 and the related TOR pathways, whereas other studies have implied that dietary restriction extends lifespan through mechanisms that are to some extent distinct from these pathways.[112]

Recent research in *C. elegans* and fruit-flies implies that sensory perception, specifically chemosensation, may be an important component in detecting nutritional status and could therefore be implicated in the changes in longevity that accompany dietary restriction.[113] The metabolic consequences of dietary restriction, such as increased insulin-sensitivity and lowered inflammation (although apparently not lowered adiposity) are also probably important in mediating lifespan extension.[114] As with the insulin/IGF-1 pathway, the major challenge is to understand the chain of events by which a reduction in nutrient intake can lead to extended lifespan, and to determine the extent of evolutionary conservation of these mechanisms.

3.1.3 Sirtuins

Over expression of the evolutionarily conserved family of enzymes known as silent information regulatory proteins, or sirtuins, has been shown to extend lifespan in worms and flies, and to extend replicative lifespan in yeast.[115] Increased activity of SirT1, a mammalian

103 The C. elegans Sequencing Consortium (1998). *Genome sequence of the nematode* Caenorhabditis elegans. *A platform for investigating biology*. Science **282**, 2012–2018.
104 Kennedy BK, Steffen KK & Kaeberlein M (2007). *Ruminations on dietary restriction and ageing*. Cellular and Molecular Life Sciences **64(11)**, 1323–1328.
105 McCay C, Crowell M & Maynard L (1935). *The effect of retarded growth upon the length of life and upon ultimate size*. Journal of Nutrition **10**, 63–79.
106 Ingram DK, *et al*. (2006). *The potential for dietary restriction to increase longevity in humans: extrapolation from monkey studies*. Biogerontology **7(3)**, 143–148.
107 Anderson RM, Shanmuganayagan D & Weindruch R (2009). *Caloric restriction and aging: studies in mice and monkeys*. Toxicological Pathology **31(1)**. 47–51.
108 Colman RJ, *et al*. (2009). *Caloric restriction delays disease onset and mortality in rhesus monkeys*. Science **325**, 201–204.
109 Weiss EP, *et al*. (2006). *Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial*. American Journal of Clinical Nutrition **84(5)**, 1033–1042.
110 Shanley DP & Kirkwood TBL (2006). *Caloric restriction does not enhance longevity in all species and is unlikely to do so in humans.* Biogerontology **7**, 165–168.
111 Mair W & Dillin A (2008). *Aging and survival: the genetics of lifespan extension by dietary restriction.* Annual Review of Biochemistry **77**, 727–754.
112 Partridge L & Gems D (2002). *Mechanisms of ageing: public or private?* Nature Reviews Genetics **3**, 165–175.
113 Gems D & Partridge L (2001). I*nsulin/IGF signalling and ageing: seeing the bigger picture.* Current Opinion in Genetics and Development **11(3)**, 287–292.
114 Kennedy BK, Steffen KK & Kaeberlein M (2007). *Ruminations on dietary restriction and ageing*. Cellular and Molecular Life Sciences **64(11)**, 1323–1328.
115 Kuningas M, *et al*. (2008). *Genes encoding longevity: from model organisms to humans*. Ageing Cell **7**, 270–280.

sirtuin, can promote regrowth of nerve axons after injury.[116] The mechanism of the protective action of SirT1 on nerve cells is not yet fully understood, but if it is found to apply more generally it may also protect cells from neurodegenerative diseases.

Some studies have reported that polyphenols, particularly resveratrol, can increase activity of SirT1 and therefore potentially slow ageing, although these findings have not always proved robust.[117,118,119] Resveratrol is a naturally occurring chemical that is produced in several plants when they are attacked by pathogenic bacteria or fungi. Although sirtuins are now being studied as possible targets for interventions in ageing, there is still much debate about their role in ageing both in model organisms and people.[120]

3.1.4 Oxidation

As outlined in section 2.3, a dominant model of ageing implicates the action of oxygen free radicals, which are a by-product of normal metabolic processes that can react with a range of cellular constituents and can cause cumulative damage over the lifetime of an organism.[121] Many correlative studies have found that oxidative damage does increase with age and is lowered by interventions such as dietary restriction that extend lifespan.[122] However, the experimental evidence for a key role of oxidative damage in causing normal ageing is relatively weak.[123]

A low oxygen environment has been shown to lengthen the lifespan of *C. elegans*, whereas high oxygen environments reduce longevity.[124] More recently, changes in the rate of mitochondrial respiration, which generates free oxygen radicals, have been implicated in ageing. For instance, RNA interference directed at sections of the *C. elegans* mitochondrial electron transport chain during the development of the worm increases lifespan by about 40%.[125] Further research has demonstrated that lifespan is increased in worms by mutations in the *clk-1* gene, which encodes an essential component of the electron transport chain known as ubiquinone.

There are indications that cell signalling pathways are again involved in mediating the effects of oxidative stress on the ageing process. For instance, the mammalian $p66^{shc}$ adaptor protein, which connects surface receptors to the ras signalling pathway (involved in cell division), may be associated with longevity by conferring increased resistance to oxidative stress.[126] However, none of these findings provide conclusive evidence that oxidative damage is key to the ageing process.

More direct evidence about the role of oxidative damage in ageing comes from experiments where antioxidant systems have been experimentally manipulated.

Superoxide dismutase (SOD) removes superoxide free radicals and converts them to hydrogen peroxide, which is then broken down by the enzyme catalase. Evidence from model organisms on the effect of these enzymes has provided few data in support of a key role for oxidative damage. For instance, manipulation of antioxidant defence systems in *C. elegans* can increase levels of resistance to oxidative damage without increasing lifespan and can increase levels of oxidative damage without reducing lifespan.[127] Similarly, naked mole rats are known to have exceptionally high levels of oxidative damage yet are relatively long-lived compared with other rodents.

116 Kenyon C (2005). *The plasticity of ageing: insights from long-lived mutants*. Cell **120**, 449–460.
117 Howitz KT, *et al*. (2003). *Small molecule activators of sirtuins extend* Saccharomyces cerevisiae *lifespan*. Nature **425 (6954)**, 191–196.
118 Wood JG, *et al*. (2004). *Sirtuin activators mimic caloric restriction and delay aging in metazoans*. Nature **430 (7000)**, 686–689.
119 Bass TM, *et al*. (2007). *Effects of resveratrol on lifespan in* Drosophila melanogaster *and* Caenorhabditis elegans. Mechanisms of Ageing and Development **128(10)**, 546–552.
120 Kennedy BK (2008). *The genetic of ageing: insight from the genome-wide approaches in invertebrate model organisms*. Journal of Internal Medicine **263**, 142–152.
121 Harman D (1956). *Aging: a theory based on free radical and radiation chemistry*. Journal of Gerontology **11(3)**, 298–300.
122 Schulz TJ, *et al*. (2007). *Glucose restriction extends* Caenorhabditis elegans *life span by inducing mitochondrial respiration and increasing oxidative stress*. Cell Metabolism **6(4)**, 280–293.
123 Muller FL, *et al*. (2007). *Trends in oxidative aging theories*. Free Radical Biology & Medicine **43(4)**, 477–503.
124 Cohen E & Dillen A (2008). *The insulin paradox: ageing, proteotoxicity and neurodegeneration*. Nature Reviews Neuroscience **9**, 759–767.
125 Dillin A, *et al*. (2002). *Rates of behavior and aging specified by mitochondrial function during development*. Science **298**, 2398–2401.
126 Migiaccio E, *et al*. (1999). *The p66shc adaptor protein controls oxidative stress response and lifespan in mammals*. Nature **402**, 309–313.
127 Kuningas M, *et al*. (2008). *Genes encoding longevity: from model organisms to humans*. Ageing Cell **7**, 270–280.

There is also no evidence so far that dietary supplementation with antioxidants (such as some vitamins) reduces mortality in otherwise healthy human populations.[128,129] Free radical spin traps, another potential intervention that targets oxidative mechanisms, block or reverse damage associated with various diseases in model organisms, but have not been shown to increase longevity in mice.[130] The precise nature of the association between respiratory metabolism, oxidation and ageing requires clear elucidation, and is likely to be complex. Indeed, the complexity of the ageing process, which involves the synergistic action of many types of cellular and molecular damage, suggests that research in this area might benefit from a systems approach that seeks to understand how the individual components of whole biological systems interact in time and space.[131] This was explored in a 2007 report from the Academy of Medical Sciences and Royal Academy of Engineering that highlighted systems biology as a groundbreaking new approach to scientific research and called for more support for research at the intersection of engineering and medicine to ensure the UK remains competitive.[132]

3.1.5 Cellular senescence

One of the earliest experimental systems for the study of ageing arose from the discovery in 1961 that normal, differentiated cells, such as fibroblasts, have a limited division potential in culture before undergoing so-called 'replicative senescence'.[133] The maximum number of replications that such cells can undergo is around 50 and is termed 'the Hayflick limit' after one of the investigators who discovered the phenomenon. This means that normal cells eventually stop dividing, in contrast to malignantly transformed cells, which can divide indefinitely and can cause cancer.

In human cells, the difference between finite and infinite division potential of cells in culture is largely due to the presence or absence of telomerase, an enzyme that maintains telomeres. Telomeres are regions of repetitive, non-coding DNA at the end of chromosomes that protect them from destruction. During cell division, the enzymes that replicate DNA cannot continue all the way to the end of the chromosome. Telomeres therefore act as 'disposable buffers' that are consumed during cell division; every time cells divide the telomeres are shortened until they reach a critically short length when the cell cycle becomes permanently arrested.

The link between repetitive telomere erosion and loss of cell division potential suggests that normal cells may be programmed to undergo senescence, perhaps as protection against tumour formation. However, if cells are programmed, the programming is loose, because there is variation in the rates of senescence of individual cells within the population.[134] The idea that telomere loss, through the end-replication problem, is a mechanism to 'count' cell divisions (acting as a cellular 'clock') does not provide a full explanation. Stress-induced DNA damage appears to be more important than the end-replication problem for determining the rate of telomere erosion.[135] Recently, it was shown that mitochondrial defects appear to be important for generating the variation in intrinsic levels of oxidative stress that account for the pronounced cell-to-cell heterogeneity in replicative potential.[136]

Although telomere erosion appears not to represent a strict cellular counting mechanism, telomere length has been found to serve as a valuable predictor of future survival and

128 Bjelakovic G, *et al* (2007). *Mortality in randomised trials of antioxidant supplements for primary and secondary prevention*. Journal of the American Medical Association **297**, 842–856.
129 Kirkwood T (2008). *A systematic look at an old problem*. Nature **451**, 644–647.
130 Vijg J & Campisi J (2008). *Puzzles, promises and a cure for ageing*. Nature **454**, 1065–1071.
131 Kuningas M, *et al*. (2008). *Genes encoding longevity: from model organisms to humans*. Ageing Cell **7**, 270–280.
132 Academy of Medical Sciences and the Royal Academy of Engineering (2007). *Systems biology: a vision for engineering and medicine*. http://www.acmedsci.ac.uk/p48prid4.html
133 Hayflick L & Moorhead PS (1961). *The serial cultivation of human diploid cell strains*. Experimental Cell Research **25**, 585–621.
134 Smith JR & Whitney RG (1980). *Intraclonal variation in proliferative potential of human diploid fibroblasts: stochastic mechanism for cellular aging*. Science **207**, 82–84.
135 von Zglinicki T(2002). *Oxidative stress shortens telomeres*. Trends in Biochemical Sciences **27**, 339–344.
136 Passos J, *et al*. (2007). *Mitochondrial dysfunction accounts for the stochastic heterogeneity in telomere-dependent senescence*. PLoS Biology **5**, e110.

morbidity. The relationship between telomere length and disease risk was first demonstrated by von Zglinicki T *et al*.[137] The shortening of telomeres is accelerated in CVD and in the presence of risk factors such as obesity and high blood pressure.[138] The enzyme telomerase reverse transcriptase acts to replenish telomeres and so prevent shortening. Moreover, activation of this enzyme has been shown to extend the lifespan of cultured human cells.

The relationship between ageing and telomeres is complex and involves many drivers. For instance, mice have longer telomeres than people yet age more rapidly. Indeed, senescence can also be triggered by a wide array of other cellular stresses such as de-repression of the cyclin kinase-dependent inhibitor 2a (*CDKN2a*), also known as *INK4a* or *ARF*.[139] The *CDKN2a* locus encodes three proteins, p16INK4a, p19ARF and p15INK4b, which are major tumour suppressors and globally increase longevity independently of their influence on cancer.[140] This is probably achieved by promoting cellular quiescence and preventing unnecessary cellular proliferation. Two important mediators of these processes are the well-known tumour suppressors retinoblastoma protein-1 and the p53 protein.

Details of the mechanism of the de-repression of *CDKN2a* are beginning to emerge and involve highly conserved genes from the polycomb group that epigenetically regulate chromatin structure and gene expression.[141] For example, the levels of *BMI-1* expression, which regulates the p16INK4a and p19ARF in specific cell types, have been reported to change as mice age.[142] This may in turn have a direct effect on levels of tumour suppressor gene expression, or of genes involved in stem cell self-renewal, both of which could contribute to the ageing process in mammals.

The link between tumour suppressor genes and longevity points to a biological mechanism common to ageing and cancer. However, this relationship is complicated and influenced by many factors including shortening of the telomeres, de-repression of *CDKN2a*, genomic instability, metabolism and autophagy - the regulated process for the removal of damaged proteins and organelles from cells. In some circumstances, such as the shortening of telomeres, mechanisms that protect against cancer seem to hasten ageing. In others, such as genomic instability or autophagy, ageing and cancer seem to share common causes. Further research would help discern how these phenomena interact.

3.1.6 Stem cells

As tissues age, so their regenerative potential declines. Much of the body's ability to regenerate is conferred by stem cells; unspecialised cells that have the ability to proliferate indefinitely, producing both more stem cells (a process called self-renewal) and cells that commit to a pathway of differentiation into specialised cell types.[143] Stem cells occur in many different tissues and at different stages of development – from the early embryo to the adult organism.

Tissue-specific stem cells are involved in tissue maintenance and repair and have therefore been implicated in ageing. For instance, research using mouse models has demonstrated that loss of stem cell function in response to DNA damage correlates with at least some aspects of normal ageing.[144] The function of stem cells from the intestines of mice demonstrably declines with age and the frequency of dysfunctional mitochondria increases with age in stems cells in the epithelium of the human colon.[145,146,147] There is also some evidence that mechanisms to

137 von Zglinicki T, *et al*. (2000). *Short telomeres in patients with vascular dementia: an indicator of low antioxidative capacity and a possible risk factor?* Laboratory Investigations. **80**, 1739–1747.
138 Major S (2009). *Unravelling the secrets of ageing*. British Medical Journal **338**. 136–138.
139 Finkel T, Serrano M & Blasco MA (2007). *The common biology of cancer and ageing*. Nature **448**, 767–774.
140 Matheu A, *et al*. (2009). *Anti-ageing activity of the Ink4/Arf locus*. Ageing Cell **8**, 152–161.
141 Finkel T, Serrano M & Blasco MA (2007). *The common biology of cancer and ageing*. Nature **448**, 767–774.
142 Chatoo W, *et al*. (2009). *The polycomb group gene Bmi1 regulates antioxidant defences in neurons by repressing p53 pro-oxidant activity*. Journal of Neuroscience **29(2)**, 529–542.
143 Smith A (2006). *A glossary for stem-cell biology*. Nature **441**, 1060.
144 Ruzankina Y & Brown EJ (2007). *Relationships between stem cell exhaustion, tumour suppression and ageing*. British Journal of Cancer **97**, 1189–1193.
145 Martin K, *et al*. (1998). *Age changes in stem cells of murine small intestinal crypts*. Experimental Cell Research **241**, 316–323.
146 Martin K, *et al*. (1998). *Altered stem cell regeneration in irradiated intestinal crypts of senescent mice*. Journal of Cell Science **111**, 2297–2303.
147 Taylor RW, *et al*. (2003). *Mitochondrial DNA mutations in human colonic crypt stem cells*. Journal of Clinical Investigation **112**, 1351–1360.

suppress cancer may contribute to a decline in stem cell function that may inadvertently affect ageing.[148]

Stem-cell research can improve our understanding of the basic biological processes of ageing. For instance, changes associated with the senescence of stem cells derived from bone marrow may provide clues about the cellular process of ageing.[149] It would be interesting to determine whether the decline during ageing in the ability of stem cells to replace cells lost by normal wear and tear could be due to factors intrinsic to the stem cells, which limit their self-renewal, or to accumulating damage to their surrounding niches.[150]

A better understanding of stem cells may also contribute to the development of interventions in the ageing process. Although stem cells remain dormant in older tissues, transplantation to younger tissue causes them to behave more like younger stem cells.[151] Theoretically this suggests the presence of some sort of reversible factor, perhaps epigenetic rather than genetic, which could be harnessed to enhance stem cell function, allowing these cells to continue to maintain and repair older tissue. Furthermore, transplantation of stem cells combined with tissue engineering and activation of those already present in the body could make it possible to repair tissues that have become damaged or diseased with age and so improve quality of life.

3.1.7 Glucocorticoids

Glucocorticoids are a class of steroid hormones that regulate a range of crucial physiological processes. They are principally involved in restoring physiological homeostasis after stress, but also play key roles in intermediary metabolism, development, central nervous system function and immune responses.

Stress and elevated glucocorticoid levels have been associated with accelerated ageing, most notably in the brain.[152] Glucocorticoid responses to stress in adult life are determined by an individual's genetic makeup, by early life events (particularly through developmental programming that often acts through epigenetic mechanisms – see section 3.1.8), and by the adult environment and experience (see section 3.1.10). Glucocorticoids might also play a direct role in chromatin remodelling and gene expression. The reactivation of genes during ageing, such as those on the inactive X chromosome in females, further suggests that epigenetic mechanisms are relevant.[153]

The glucocorticoid system and its controls are amenable to manipulation. Thus, blocking a brain enzyme that normally increases glucocorticoid levels inside neurons protects mice from memory decline with ageing.[154] Early clinical trials suggest enzyme inhibitory drugs produce memory improvements in otherwise healthy older people and those with type 2 diabetes.[155] This sort of research offers another facet to the complex relationship between the processes of ageing and age-related disease.

3.1.8 Genetics of ageing

Heritable variation between individuals accounts for around a quarter of what determines the length of life, and healthy life, in humans, with the remainder attributable to non-heritable influences that can begin in early life.[156] Detailed analysis of genetic effects on human longevity has only recently begun. It remains to be seen whether genetic variants that affect longevity primarily do so through processes that generate ageing-related damage or processes that protect against it, and to what extent the effects are disease-specific.

148 Tyner SD, *et al*. (2002). *P53 mutant mice that display early ageing-associated phenotypes*. Nature **415**, 45–53.
149 Ho AD, Wagner W & Mahlknecht U (2005). *Stem cells and ageing*. EMBO Reports **6**, S35–S38.
150 Rando TA (2006). *Stem cells, ageing and the quest for immortality*. Nature **441**, 1060.
151 *Ibid*.
152 Hibberd C, Yau JLW & Seckl JR (2000). *Glucocorticoids and the ageing hippocampus*. Journal of Anatomy **197**, 553–562.
153 Bennett-Baker PE, Wilkowski J & Burke DT (2003). *Age-associated activation of epigenetically repressed genes in the mouse*. Genetics **165**, 2055–2062.
154 Seckl JR (2006). *Glucocorticoids, enzymes and memory impairments with ageing*. Endocrine Abstracts **11**, S15.
155 Sandeep TC, *et al*. (2004). 11*ß-Hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics*. Proceedings of the National Academy of Sciences of the USA **101(17)**, 6734–6739.
156 McGue M, *et al* (1993). *Longevity is moderately heritable in a sample of Danish twins born 1870–1880*. Journal of Gerontology **48(6)**, B237–B244.

As discussed, searching for mutations that can increase lifespan in laboratory animals has often implicated cellular signalling pathways, particularly those that respond to nutrient levels and to stress. These pathways can exert co-ordinated regulation of large numbers of maintenance and repair systems. Preliminary indications suggest that similar processes may also affect human lifespan.[157,158,159] Moreover, studies of human populations have provided insight into the heritability of ageing and age-related diseases.

Twin and family studies show a moderate heritability of longevity in people, although thus far the genes responsible have mostly proved elusive. One such gene is *APOE*, although there are likely to be many others with small effects.[160] The *APOE* gene encodes the protein apoe, a ligand of the low-density lipoprotein receptor and related receptors, which alters circulating levels of cholesterol. The *Apoε4* gene variant has repeatedly been associated with increased risk of CVD and Alzheimer's disease, whereas the *Apo2* gene variant has been shown to protect against these diseases.[161,162]

Although the mechanism remains uncertain, the association of APOE with Alzheimer's disease is one of the strongest associations of any genetic variant with a complex disease. Teasing out an effect of *APOE* variation in longevity independent of disease, given that both of the disorders associated with APOE variation shorten life, is self-evidently difficult. Nonetheless this is an important task; not least as APOE becomes a target for therapies.

The strength of association of APOE with Alzheimer's disease is matched, even exceeded, by the association of variation in complement factor H (CFH) with another disorder of ageing – AMD.[163] Intriguingly AMD is also associated with APOE and is, like Alzheimer's, a disorder with Aβ pathology.[164,165] This association is mirrored by the observation that Alzheimer's is a disorder with CFH abnormalities and may also be associated with CFH variation.[166,167,168,169] This tells us that CFH and APOE are both linked to two of the commonest disorders of later life and may reflect a common pathological mechanism of ageing.

3.1.9 Developmental origins of ageing and age-related disease

There is growing evidence that many of the events that cause ageing and age-related diseases take place over the whole life course.[170] If ageing is the result of imperfect maintenance and repair of the body, then differing levels of exposure to sources of damage over a lifetime are likely to underlie some of the wide variation in biological ageing and age-related diseases.

Over 20 years ago it was demonstrated that low birth weight is associated with coronary artery disease.[171] This has been replicated in different studies, in different countries, and cannot be explained by confounding variables, such as continued exposure to some environmental factor before and after birth, nor as a consequence of premature birth. One study demonstrates that incidence of coronary heart disease among men would be reduced by 40%

157 Kuningas M, *et al*. (2007). *Haplotypes in the human Foxo1a and Foxo3a genes; impact on disease and mortality at old age*. European Journal of Human Genetics **15(3)**, 294–301.
158 Lunetta KL, *et al*. (2007). *Genetic correlates of longevity and selected age-related phenotypes: a genome-wide association study in the Framingham Study*. BMC Medical Genetics **8**(Supplement 1), S13.
159 Willcox BJ, *et al*. (2008). *FOXO3A genotype is strongly associated with human longevity*. Proceedings of the National Academy of Sciences of the USA **105(37)**, 13987–13992.
160 Christenson K, Johnson TE & Vaupel JW (2006). *The quest for genetic determinants of human longevity: challenges and insights*. Nature Reviews Genetics **7**, 436–448.
161 Hulette CM, *et al*. (2007). *Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers*. Neurology **68(6)**, 68.
162 Beffert, U, *et al*. (2006). *ApoE receptor 2 controls neuronal survival in the adult brain*. Current Biology **16**, 2446–2452.
163 Thakkinstian A, *et al*. (2006). *Systematic review and meta-analysis of the association between complementary factor H Y402H polymorphisms and age-related macular degeneration*. Human Molecular Genetics **15(18)**, 2784–2790.
164 Swaroop A, *et al*. (2007). *Genetic susceptibility to age-related macular degeneration: a paradigm for dissecting complex disease traits*. Human Molecular Genetics, R174–R182.
165 Luibl V, *et al*. (2006). *Drusen deposits associated with aging and age-related macular degeneration contain nonfibrillar amyloid oligomers*. Journal of Clinical Investigation **116(2)**, 378–385.
166 Hye A, *et al*. (2006). *Proteome-based plasma biomarkers for Alzheimer's disease*. Brain **129(11)**, 3042–3050.
167 Finehout EJ, *et al*. (2005). *Complement protein isoforms in CSF as possible biomarkers for neurodegenerative disease*. Disease Markers **21(2)**, 93–101.
168 Strohmeyer R, *et al*. (2002). *Association of factor H of the alternative pathway of complement with agrin and complement receptor 3 in the Alzheimer's disease brain*. Journal of Neuroimmunology **131(1–2)**, 135–146.
169 Zetterberg M, *et al*. (2008). *Association of complement factor H Y402H gene polymorphism with Alzheimer's disease*. American Journal of Medical Genetics series B **147B(6)**, 720–726.
170 Gluckman PD, *et al*. (2008). *Effect of in utero and early-life conditions on adult health and disease*. New England Journal of Medicine **359**, 61–73.
171 Barker DJ & Osmond C (1986). *Infant mortality, childhood nutrition and ischaemic heart disease in England and Wales*. Lancet **1(8489)**, 1077–1081.

if they were all as large as the largest third of babies at birth and had more stable growth rates in infancy.[172]

It is now known that low birth weight is also associated with other age-related diseases, such as type 2 diabetes, chronic obstructive pulmonary disorder and osteoporosis, as well as general markers of ageing, such as thinner skin, hearing loss and reduced grip strength.[173] For instance, low weight at birth and during infancy predicts low adult bone size, mineral content and density, which are risk factors for diseases such as osteoporosis.[174]

Developmental drivers of ageing and age-related diseases extend beyond nutrition. For instance, the children of mothers with broad hips are at increased risk of cancer apparently because their mother's sex hormones cause genetic instability in the stem cells of the breast, ovary or prostate.[175] Events that drive ageing and age-related diseases also take place outside the womb. Research indicates that during infancy, the tempo of growth is more important to future health than particular weight. When under-nutrition during foetal life is followed by improved postnatal nutrition, rapid compensatory growth may take place, although this comes at the cost of reduced lifespan.[176] It is interesting to note that under-nutrition in early life is associated with more rapid ageing, whereas dietary restriction in later life is associated with longevity (see section 3.1.2).[177]

The biological basis of the associations between birth weight, ageing and ageing-related diseases seems to rest in developmental plasticity, which has been defined as *'... the ability of a single genotype to produce more than one alternative form, structure, physiological state or behaviour in response to environmental conditions.'*[178] This enables the generation of different phenotypes that are more suited to their environment than would be the case if the same phenotype were produced regardless of prevailing environmental conditions.

Developmental plasticity is a key element of the 'developmental origins of disease' hypothesis, which proposes that certain diseases associated with ageing originate through developmental plasticity in response to under-nutrition during foetal life and infancy.[179] If the energy available to the foetus or infant is constrained because of under nutrition, then certain developmental processes, such as brain growth, are favoured over others, such as tissue repair. Thus smaller infants who received less energy *in utero* manage growth, but at the expense of health in later life.

At the level of cells and molecules there is growing interest in the role of epigenetic regulation of transcription – heritable but reversible changes in phenotype or gene expression – as a mechanism for adaptation to different environments.[180] For instance, it has been demonstrated that altering intrauterine nutrition can influence epigenetic programming in a manner that can be passed between generations in humans and animals.[181]

Another molecular mechanism under investigation that might help explain the relationship between early life nutrition, ageing and age-related diseases are defects in production of adenosine triphosphate (ATP), the body's energy carrier. Retarded intrauterine growth can lead to increased production of reactive oxygen species that can lead to a

172 Barker DJP, *et al*. (2002). *Foetal origins of adult disease: strength of effects and biological basis*. International Journal of Epidemiology. **31**, 1235-1239.
173 Sayer AA, Cooper C & Barker DJP (1997). *Is lifespan determined in utero?* Archives of Disease in Childhood. **77**, F161–F162.
174 Oliver H, *et al*. (2007). *Growth in early life predicts bone strength in late adulthood: the Hertfordshire cohort study*. Bone **41(3)**, 400-405.
175 Barker DJP, *et al*. (2007). *A possible link between the pubertal growth of girls and breast cancer in their daughters*. American Journal of Human Biology **20(2)**, 127–131.
176 Barker DJP & Bagby SP (2005). *Developmental antecedents of cardiovascular disease: an historical perspective*. Frontiers in Nephrology **16**, 2537–2544.
177 Sayer AA, Cooper C & Barker DJP (1997). *Is lifespan determined in utero?* Archives of Disease in Childhood **77**, F161–F162.
178 Sayer AA & Cooper C (2007). *Ageing, sarcopenia and the life-course*. Reviews in Clinical Gerontology **16**, 265–274.
179 Barker DJP & Bagby SP (2005). *Developmental antecedents of cardiovascular disease: an historical perspective*. Frontiers in Nephrology **16**, 2537–2544.
180 Burdge GC, *et al*. (2007). *Epigenetic regulation of transcription: a mechanisms for inducing variations in phenotype (foetal programming) by differences in nutrition in early life?* British Journal of Nutrition **97**, 1–11.
181 Lillycrop KA, *et al*. (2007). *Induction of altered epigenetic regulation of hepatic GR in the offspring of rats fed a protein restricted diet during pregnancy suggests that reduced Dnmt1 expression is involved in impaired DNA methylation and changes in histone modification*. British Journal of Nutrition **97(6)**, 1064–1073.

cycle of cellular and molecular damage (see section 3.1.4).[182] This may in turn lead to age-related diseases such as type 2 diabetes, since pancreatic beta cells, which control insulin, are particularly dependent on ATP, making them vulnerable to defects in production of this chemical.

The relationship between developmental determinants, numerous age-related diseases and markers of ageing adds clinical evidence to the wealth of basic biological research that indicates that there are a limited number of common, malleable pathways that underpin ageing and the diseases with which it is associated. For instance, loss of grip strength in people due to sarcopenia (muscle loss) with age is associated with increased mortality and morbidity from multiple diseases.[183] This complements genetic and biological studies of age-related sarcopenia in the worm *C. elegans*, which leads to decline in motility and serves as a marker of increased mortality.[184] Mutations affecting the *age-1* gene, which slows ageing in worms, results in significant delays in the development of sarcopenia, suggesting a direct causal relationship between ageing and sarcopenia.

3.1.10 Social determinants of ageing

The social and economic conditions in which people live contribute substantially to their longevity and health. A boy born in Japan in 2006 had a life expectancy of over 79 years, whereas a boy born in the Russian Federation in the same year had a life expectancy of less than 60 years.[185] There is a corresponding gulf in longevity between neighbouring communities. Life expectancy falls by around one year for every station travelled eastward from Westminster to Canning Town on the Jubilee underground line in London.[186] Migration studies demonstrate that these distinctions cannot be attributed solely to genetics: members of the Luo tribe in Kenya had low blood pressure when living in rural environments but high blood pressure when they moved to urban Nairobi.[187,188] Rapid changes in environment, such as the reunification of Germany discussed in section 2.3.2, also indicate that differences in mortality are no wholly determined by genetics.[189]

The dramatic impact of social and economic forces on longevity is reflected in the biological process of ageing and age-related disease. Around three-quarters of life expectancy can be ascribed to non-heritable factors, some of which are determined by social and economic conditions.[190] On average, poorer people in the UK become ill and die five to ten years earlier than their more privileged counterparts, in effect 'ageing' more quickly.[191] Indeed, it has been suggested that those of higher socio-economic and educational status age more healthily.[192]

Social and economic inequalities in longevity are complex phenomena with many interacting causes. Absolute poverty is certainly harmful to health. More than a billion people in the world live on less than a dollar a day and their health suffers because of the consequent malnutrition, poor housing and unsanitary conditions.[193] Although some of this illness can be attributed to causes such as suicide, violence and accidents, which are not directly related to the underlying process of ageing, the association between material deprivation and many age-related diseases is well established.[194]

Absolute deprivation cannot, however, explain the significant differences in life expectancy within richer countries, where even the poorest citizen is relatively wealthy. The Whitehall study

182 Jones RH & Ozanne SE (2009). *Foetal programming of glucose-insulin metabolism*. Molecular and Cellular Endocrinology. **297(1-2)**, 4–9.
183 Sayer AA & Cooper C (2007). *Ageing, sarcopenia and the life-course*. Reviews in Clinical Gerontology **16**, 265–274.
184 Fisher AL (2004). *Of worms and women: sarcopenia and its role in disability and mortality*. Journal of the American Geriatric Society **52**, 1185–1190.
185 World Health Organization (2006). *Life tables for WHO member states*. http://apps.who.int/whosis/database/life_tables/life_tables.cfm
186 Marmot M (2009). *Overview of the review of health inequalities post 2010 in England*. http://www.ucl.ac.uk/gheg/marmotreview
187 Vaupel JW (1988). *Inherited frailty and longevity*. Demography **25(2)**, 277–287.
188 Poulter NR, *et al*. (1990). *The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure*. British Medical Journal **300**, 967–972.
189 Vaupel JW, Carey JR & Christensen K (2003). *It's never too late*. Science **301**, 1679–1681.
190 House of Lords (2005). *The scientific aspects of ageing*. The Stationery Office, London.
191 Perlman RL (2008). *Socioeconomic inequalities in ageing and health*. Lancet **372**, S34–S39.
192 Fries JF (1980). *Ageing, natural death and the compression of morbidity and health in the elderly*. New England Journal of Medicine **313**, 407–428.
193 United Nations (2006). *Fast facts: the faces of poverty*. http://www.unmillenniumproject.org/documents/3-MP-PovertyFacts-E.pdf
194 World Health Organization (2008). *Social determinants of health*. http://www.who.int/social_determinants/en/

of UK civil servants demonstrated a nine-year difference in life expectancy between those with higher and lower status jobs.[195] Studies in the USA, Sweden and Australia produced similar findings, which indicate that the phenomenon is not idiosyncratic to the UK.[196] Although early life plays an important role in determining longevity, it does not account for all of the observed disparities; nor do unhealthy behaviours, poor healthcare or people having lower status because of their poor health.[197]

There is evidence that many of the health inequalities in rich countries can be attributed to differences in social status; a steeper social gradient therefore generates greater health inequalities. One explanatory mechanism is that low social status stifles social participation and autonomy.[198] This harms health by inducing chronic biological stress responses, such as release of the hormone cortisol that diverts the body's resources away from mechanisms that protect and repair such as the immune system (see section 3.1.7).[199]

Life expectancy and health are strongly influenced by the way in which we live our lives. Those who avoid smoking, regularly eat fruit and vegetables, drink alcohol in moderation and are not overweight live up to 14 years longer than those who do otherwise.[200] Although small changes in lifestyle can have a major role in preventing disease, it can be difficult for people to change their habits and for others to convince them to do so.[201] This is particularly true for those from lower socio-economic classes who often have the least healthy lifestyles.[202]

Tantalising links exist between the social determinants of health, the underlying biological processes of ageing and age-related diseases. Improved nutrition and appropriate exercise can help to reduce many age-related diseases like osteoporosis and CVD, although the mechanisms are not well understood.[203,204,205] These beneficial behaviours have intriguing similarities to the broad spectrum improvements in health and life expectancy observed in model organisms using simple biological interventions. It has also been proposed that those who live in better social and economic conditions experience less somatic biological damage so age more slowly.[206] Clearly there is a strong need for a conceptual framework for integrating the disparate social and economic factors that generate inequalities in health and longevity with the biological processes of ageing and age-related disease.

3.2 Research resources

To tackle the scientific challenge of ageing it will be necessary to harness a wide array of research resources: the methods, subjects and tools that support research. In the following sections, four of these resources are discussed: animal models, biomarkers, population-based research and clinical trials. Efforts should be made to ensure that the UK draws upon its rich complement of research resources to investigate ageing.

3.2.1 Animal models

Biopsies, post-mortem samples and tissue cultures of humans have told us much about ageing in humans but studying ageing directly in humans is challenging, because of our long lifespan and the difficulties of experimental intervention. Animal models will therefore continue to be an essential part of

195 Marmot M, *et al*. (1978). *Employment grade and coronary heart disease in British civil servants*. Journal of Epidemiology and Community Health **32**, 244–299.
196 Marmot M (2004). *Status syndrome*. Bloomsbury, London.
197 Marmot M (2005). *Social determinants of longevity and mortality*. http://sagecrossroads.net/webcast26
198 *Ibid*.
199 *Ibid*.
200 Khaw KT, *et al*. (2008). *Combined impact of health behaviours and mortality in men and women: the EPIC Norfolk prospective population study*. PLoS Medicine **5(1)**, 39–47.
201 Academy of Medical Sciences (2004). *Response to the Department of Health's consultation on Choosing Health*. http://www.acmedsci.ac.uk/p100puid33.html
202 Academy of Medical Sciences (2004). *Calling time: the nation's drinking as a major health issue*. http://www.acmedsci.ac.uk/p99puid20.html
203 Clarke MSF (2004). *The effects of exercise on skeletal muscle in the aged*. Journal of Musculoskeletal Neuronal Interaction **4(2)**, 175–178.
204 Rivlin RS (2007). *Keeping the young-elderly healthy: is it too late to improve our health through nutrition?* American Journal of Clinical Nutrition **86**, 1572S–1576S.
205 Wanless D (2004). *Securing good health for the whole population*. The Stationery Office, London.
206 Perlman RL (2008). *Socioeconomic inequalities in ageing and health*. Lancet **372**, S34–S39.

the infrastructure required for fundamental research into ageing and age-related disease. A particular challenge for such work is determining the extent to which results in one species apply to others, and to humans. We also need to learn more about the value of animal models for developing medicines for age-related diseases, such as stroke or neurodegenerative disorders, which can manifest differently in animals and people.[207]

Model laboratory organisms with relatively short lifespans, such as the single-celled budding yeast *Saccharomyces cerevisiae*, the nematode *C. elegans*, the fruit-fly *Drosophila melanogaster* and the mouse, have the potential to provide significant insights, as long as their ageing processes are sufficiently similar to those of humans.[208] The research value of the invertebrate model organisms is augmented by their low cost, relative simplicity, well-characterised biology, completely sequenced genomes and the development of advanced genetic tools. These could inform further mammalian model studies; for some topics, such as epigenetics and stem cells, higher animals can be more appropriate.

Important areas that will involve animal models include further research into:

- Signalling pathways.
- The biochemical processes that generate and protect against damage.
- Genetics and epigenetics.
- The role of stem cells and cellular senescence.
- Systemic aspects of ageing and the ways in which the ageing process acts as a risk factor for age-related diseases.

As discussed previously, an inherent problem in ageing research is the time it takes: even for short-lived species, it is necessary to wait for animals to get old. This is a particular challenge for PhD students who undertake three- or four-year studies that only offer a relatively short window of opportunity for their investigations.[209] A system for providing aged rodents would help to address this problem for mammalian studies. There can also be a more general problem with research funding for work on longer-lived species such as rodents and particularly non-human primates. Funding structures to support ageing research are considered further in chapter 4.

3.2.2 Biomarkers

We are used to thinking about age in chronological terms, i.e. the length of life measured in time. However, the age of organisms can also be expressed in biological terms, i.e. as a point along the curve of rising mortality caused by the build up of biological damage. Differences in genetic make-up and the impact of environmental factors mean that biological age does not always correspond to chronological age. From the perspective of medical science, biological age is particularly important because it is more indicative of current and future health. However, biological age is much more difficult to measure in a standardised way.

A biomarker is a measurable phenotype that can be used as an indicator of some physiological state. Biomarkers usually represent characteristics that can be measured or evaluated as indicators of normal function, pathogenic processes or responses to pharmaceutical interventions. Biomarkers allow more standardised assessments of complex physiological processes such as ageing, and could therefore potentially be used to measure biological age and to diagnose or predict age-related disease. Identifying and validating biomarkers for ageing will be a key step in developing interventions that might slow or prevent the underlying processes that cause ageing. These may help to reduce the time taken for ageing research by providing indicators of underlying biological processes before their clinical manifestation.[210]

Some biomarkers for age-related diseases are already well established. For instance, cholesterol levels act as a biomarker for CVD.

207 Cheng YD, Al-Khoury L & Zivi JA (2004). *Neuroprotection for ischemic stroke: two decades of success and failure*. NeuroRx **1(1)**, 36–45.
208 Partridge L & Gems D (2002). *Mechanisms of ageing: public or private?* Nature Reviews Genetics **3**, 165–175.
209 Miller RA (2002). *Extending life: scientific prospects and political obstacles*. Millbank Quarterly **80 (1)**, 1–20.
210 House of Lords (2005). *The scientific aspects of ageing*. The Stationery Office, London.

Other examples, such as the relationship between oxytocin and positive mental health, remain more controversial.[211,212] No biomarkers have yet been validated in humans as indicators of the underlying process of ageing itself. A single biomarker for ageing is unlikely to be found. Instead, a battery of biomarkers will be needed to reflect the complexity of the ageing process across a multitude of cellular and physiological systems.

Past efforts to identify biomarkers were not successful, but more recently there has been a resurgence of interest.[213] For instance, the Innovative Medicines Initiative (IMI), a Europe-wide programme to promote collaboration between academia and industry, has sought to encourage the development of biomarkers for Alzheimer's disease, and the MRC 'Lifelong Health and Wellbeing' initiative is providing welcome support for the development of biomarkers for ageing.[214] The significant scientific and technological advances that have occurred in the two decades since the last attempt are likely to make the identification of biomarkers more feasible.[215] For example, our understanding of the genome has improved significantly, and modern sequencing methods allow tens of thousands of genes to be screened simultaneously (see section 3.2.3). This makes biomarkers a tractable challenge that may lead to a better understanding of the process of ageing and age-related diseases and to practical methods for documenting health and disease over a life course.

3.2.3 Population-based research: epidemiology and population genetics

Research in the fields of demography, epidemiology and population genetics will greatly increase our understanding of the determinants of healthy ageing. Although the UK has been traditionally strong in these fields, the potential for large-scale research in these areas has not yet been fully realised.
As discussed in previous sections, understanding the factors that influence ageing requires consideration of the whole life course. Since early life events and parental (perhaps even grandparental) life details may have a strong bearing on the ageing process of current generations, it will be important to conduct studies of a very long-term nature. Prospective, long-term studies of human cohorts and epidemiological research using health records represent powerful research tools in this regard. This opportunity has been recognised by the USA, where substantial resources are being provided to stimulate the use of electronic patient records.[216]

UK systems such as the General Practice Research Database (GPRD) and Connecting for Health offer globally unique resources for ageing research, but only if operational and regulatory frameworks are developed that allow medical research to proceed effectively in a way that maintains public trust and confidence. Care should also be taken to ensure routinely collected clinical data are of sufficient quality for research. A more detailed discussion of this issue is provided in the Academy of Medical Sciences' 2006 report 'Personal data for public good: using health information in medical research'.[217,218,219,220,221]

The UK, with its traditional strength in long-term cohort studies, and with the new UK Biobank and Generation Scotland projects, is uniquely placed to exploit scientific and

211 Horvat-Gordon M, *et al*. (2005). *Oxytocin is not a valid biomarker when measured in saliva by immunoassay*. Physiology and Behaviour **84(3)**, 445–448.
212 Ryeff CD, Singer BH & Love GD (2004). *Positive health: connecting wellbeing with biomarkers*. Philosophical Transactions of the Royal Society of London series B **359**, 1383–1394.
213 Sprott R (2008). *Biomarkers of ageing: what came out of the National Institute of Ageing's biology of aging program?* http://www.sagecrossroads.com/sagecast45
214 Lovestone S, Francis P & Strandgaard K on behalf of the Addneuromed Collaborative Group (2007). *Biomarkers for disease modification trials – the Innovative Medicine Initiative and AddNeuroMed*. Journal of Nutrition, Health and Ageing **11(4)**, 359–361.
215 Academy of Medical Sciences (2004). *Cancer biomarkers and imaging*. http://www.acmedsci.ac.uk/index.php?pid=45&evid=2
216 Anon (2009). *Health highway*. Nature **458**, 259–260.
217 Academy of Medical Sciences (2006). *Personal data for public good: using health information in medical research.* http://www.acmedsci.ac.uk/index.php?pid=99&puid=62
218 Academy of Medical Sciences (2006). *Report of proceedings at the legal symposium*. Academy of Medical Sciences, London.
219 Academy of Medical Sciences (2007). *Response to the House of Commons Health Committee consultation on electronic patient records*. http://www.acmedsci.ac.uk/p100puid111.html
220 Academy of Medical Sciences (2008). *Response to the Ministry of Justice data sharing review*. http://www.acmedsci.ac.uk/p100puid121.html
221 Academy of Medical Sciences (2009). *Response to the Department of Health consultation on disclosure of information for research purposes*. http://www.acmedsci.ac.uk/p100puid145.html

technological developments to characterise a healthy ageing phenotype, as well as its trajectory and determinants. This will enable a more profound understanding of the ageing process and of ways in which decline in health and function with age can be postponed or ameliorated.

New imaging technology now enables non-invasive and safe assessment and quantification of structural changes in humans. For instance dual X-ray absorbimetry (DEXA) has been used to understand the musculoskeletal system and magnetic resonance imaging (MRI) has been used to study nutrition in older people.[222,223] High-throughput biochemistry and genotyping platforms enable characterisation of biological (including metabolic, hormonal and inflammatory) and genetic markers, which may provide new insights into mechanisms of ageing. The ability to assess more precisely environmental and behavioural exposures throughout the life course using these more accurate instruments allows a better understanding of factors that influence the ageing trajectory.[224,225]

The sequencing of the human genome and the growing understanding of its function are providing powerful new research tools for identifying genetic variants associated with complex diseases and traits.[226] However, most of the focus so far has been on disease-related studies and less emphasis has been placed on studies to identify genes associated with healthy ageing. A critical step before the design of such studies is to define a healthy ageing phenotype. Phenotypes of particular value for genetic research are those with high heritability and close relationships to gene products or pathways, preferably with minimal or at least measurable environmental influences. Most importantly, definitions of healthy ageing phenotypes need to be standardised to allow comparisons across studies. This requires study designs to identify robust ageing genotype–phenotype associations through family-based linkage studies, candidate gene association analyses and genome-wide association studies (GWAS).

Advances in genotyping and sequencing technologies, and the generation of the human haplotype map database, now allow the cost-effective investigation of the very large sample sizes needed for GWAS in unrelated individuals.[227] Compared with a hypothesis-driven candidate gene approach, GWAS can identify new susceptibility genes without making any *a priori* biological assumptions. GWAS are therefore very powerful tools to identify genetic contributors to ageing-related phenotypes.[228] There are several challenges associated with the interpretation and translation of such studies, including:[229]

- Assessing the potential for bias and confounding variables.
- Determining the clinical validity and utility of findings proposed for wider application.
- Ethical and social consequences such as for life insurance.

These challenges were discussed in a recent report from the Academy's FORUM, and are outlined in the Academy's submission to the House of Lords Science and Technology inquiry into genomic medicine.[230]

The UK is particularly rich in long-term population based studies that will help to identify the determinants of healthy ageing, to ascertain the relationship between experiences in early life and health in older age and to

222 Reid KF, *et al*. (2008). *Lower extremity muscle mass predicts functional performance in mobility-limited elders*. Journal of Health Nutrition and Ageing. **12(7)**, 493–498.
223 Nakamura H, *et al*. (2006). *A longitudinal study on the nutritional state of elderly women at a nursing home in Japan*. Internal Medicine **45(20)**, 1113–1120.
224 Bingham S, *et al*. (2007). *Epidemiologic assessment of sugars consumption using biomarkers: comparisons of obese and nonobese individuals in the European prospective investigation of cancer Norfolk*. Cancer Epidemiology and Biomarker Prevention **16**, 1651.
225 Prentice RL, *et al*. (2002). *Research strategies and the use of nutrient biomarkers in studies of diet and chronic disease*. Public Health Nutrition **5(6a)**, 977–984.
226 The Wellcome Trust Case Control Consortium (2007). *Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls*. Nature **447**, 661–669.
227 McCarthy MI, *et al*. (2008). *Genome-wide association studies for complex traits: consensus, uncertainty and challenges*. Nature **9**, 356–367.
228 Kronenberg F (2008). *Genome-wide association studies in aging-related processes such as diabetes mellitus, atherosclerosis and cancer*. Experimental Gerontology **43(1)**, 39–43.
229 McCarthy MI & Hirschhorn JN (2008). *Genome-wide association studies: potential next steps on a genetic journey*. Human Molecular Genetics **17(2)**, R156–R165.
230 Academy of Medical Sciences (2009). *Genome wide association studies: understanding the genetics of common disease*. http://www.acmedsci.ac.uk/download.php?file=/images/page/GWASWEBF.pdf

evaluate prospectively the effectiveness of interventions to promote healthy ageing. Examples of such investigations are given in box 3.1.

Prevention of disability and maintenance of functional health are clearly critical, but many population studies have been limited in their ability to address this issue for several reasons. Many prospective studies ascertain mortality by cause, but lack the capacity to address non-fatal disease incidence and disability. Self-reported questionnaires on functional health are difficult to assess, owing to potential variability and bias in self-reports and changes in perception over time. There is a need for more objective measures of functional health that can be related to subjective perception of health as well as to disease and mortality endpoints.

We need more detailed understanding of the biological and physiological processes involved in ageing and of how they translate into specific aspects of functional health, such as physical performance. We also need a better understanding of how cognitive performance and sensory function, such as vision and hearing, relate to well-being, and how they can be modified.

Emphasis must be placed on including older people in future population and cohort studies wherever possible, and on identifying opportunities to 'piggyback' research into the determinants of ageing onto other investigations such as the Million Women Study. It is likely that many future prospective cohort studies investigating environmental, genetic and disease interactions will be

Box 3.1 Long-term population studies that may help identify the determinants of ageing

- The MRC National Survey of Health and Development, the oldest of the British birth cohort studies, is unique in having data from birth to age 60 years on the health and social circumstances of a representative sample of over 5,000 men and women born in Britain in March 1946.[231]
- The English Longitudinal Study of Ageing is an interdisciplinary data resource on health, economic position and quality of life as people age, with the aim of exploring the dynamic relationships between health, functioning, social networks and economic position.[232]
- The Department of Twin Research and Genetic Epidemiology at King's College London encompasses the biggest UK adult twin registry of 11,000 twins used to study the genetic and environmental aetiology of age-related complex traits and diseases.[233]
- The MRC-funded Newcastle 85+ Study, which is examining in close detail the complex array of biological, clinical and psychosocial factors associated with trajectories of health in very old individuals.[234]
- The European Prospective Investigation into Cancer and Nutrition study in Norfolk, a large multi-centre study looking at determinants of health in middle and later life, with a focus on modifiable lifestyle and biological factors.[235]
- The Avon Longitudinal Study of Parents and Children followed the health of more than 14,000 mothers in detail who were enrolled during pregnancy in 1991 and 1992.[236]
- The Million Women Study of women's health involving more than one million women aged over 50.[237]

231 Further details are available from http://www.nshd.mrc.ac.uk/
232 Further details are available from http://www.ifs.org.uk/elsa/
233 Further details are available from http://www.twin-research.ac.uk/
234 Collerton J, *et al*. (2007). *The Newcastle 85+ study: biological, clinical and psychosocial factors associated with healthy ageing: study protocol*. BMC Geriatrics **7**, 14.
235 Khaw KT, *et al*. (2008). *Combined impact of health behaviors and mortality in men and women: the EPIC-Norfolk prospective population study*. PLoS Medicine **5(1)**, 39–47.
236 Further details are available from http://www.bristol.ac.uk/alspac/
237 Further details are available from http://www.millionwomenstudy.org/introduction/

Box 3.1 Long-term population studies that may help identify the determinants of ageing (Continued)

- The Breakthrough Generations Study is the largest study into the causes of breast cancer and includes over 100,000 women from the UK.[238]
- The Disconnected Mind Study aims to combat the threat of cognitive declines and dementia by comparing the results of people who took an intelligence test, the Scottish Mental Survey, in 1947 with the same test taken today.[239]
- The Oxford Vascular Study, a community-based incidence study of acute stroke and acute myocardial infarction in a population of 200,000, mainly based in Oxfordshire.[240]

based in primary care settings. It is therefore crucial that the potential contribution from community-based sites is better harnessed for ageing research. The Academy will shortly be publishing a report of a workshop on medical research and general practice that is relevant to this discussion. Support also needs to be directed to systems-based approaches so that basic biologists are given incentives to collaborate with population scientists to establish links between the biology of ageing and how ageing affects the UK population.

Ultimately, the purpose of the research is to translate findings into effective interventions to improve health and well-being. A fruitful approach would involve translational iteration between laboratory and epidemiological studies, so that promising biological associations could be tested in populations and risk factors identified that might cast light on basic biological mechanisms. The UK, with its strong links between research and practice in public health centres of excellence, and Academic Health Science Centres, is well placed to develop effective clinical and public health interventions for changing population-level diet and physical activity with specific programmes aimed at working age and retirement age adults.

3.2.4 Clinical trials

Older people often take many different medications (polypharmacy) and experience several medical conditions at once (co-morbidities). For instance, around 20% of people over 70 take five or more drugs.[241] In older people, medicines often have different pharmacodynamics (the effects of a drug on the body) and pharmacokinetics (how the body metabolises a drug) to those in younger people. Pharmacodynamics and pharmacokinetics reflect age-related differences in renal clearance, liver size, lean body mass, hepatic enzyme activity and the influence of age-related diseases. Physiological variation between individuals also increases significantly with age, perhaps because environmental factors and disease have had the chance to play a bigger role in determining individual phenotypes.

Despite recent efforts by the MRC and others, the co-morbidities and polypharmacy that occur with greater frequency in older people often exclude them from participation in clinical trials. Moreover it is too often incorrectly assumed that older people will not benefit from interventions so should not participate in studies of their effects.[242,243] Older people, especially those who are frail or over 75, are therefore generally under-represented in clinical trials of treatments for which they are often the major consumers and from which they potentially have the most to gain. Furthermore, information on the effects of potential treatments on co-morbidities and interactions with other drugs is extremely important to inform pragmatic decision-making around pharmaceutical licensing and

238 Further details are available from http://www.breakthroughgenerations.org.uk/index.html
239 Further details are available from http://www.disconnectedmind.org.uk/Home.aspx
240 Further details are available from http://www.stroke.ox.ac.uk/research/oxvasc.htm
241 Milton JC, Hill-Smith I & Jackson S (2008). *Prescribing for older people*. British Medical Journal **336**, 606–609.
242 Mant J, *et al*. (2007). *Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial*. Lancet **370(9586)**, 493–503.
243 Beckett NS, *et al*. (2008). *Treatment of hypertension in patients 80 years of age or older*. New England Journal of Medicine **358(18)**, 1887–1898.

prescription.[244] This means many clinical studies are not as externally valid as decision-makers might wish.[245]

Clinical trials involving older people bring significant resource implications in terms of time and financial cost: the increased variability, polypharmacy and co-morbidities present in older cohorts require larger sample sizes and more stratification of patient groups to determine accurately the effects of interventions. Clinical trials involving older people require very careful study design, and it will be important to harness the expertise and experience of those involved in geriatric medicine.

Improvements in the availability and detail of clinical trial data will be useful in gaining a better understanding of age-related effects on new medicines; better access to this information allows the type of sub-group analysis that is necessary to generate hypotheses about the determinants of responses in older people.[246] There are also opportunities to initiate more systematic efforts within the public sector to investigate outcomes of new medicines in older patients at the post-marketing stage.

However, at present, groups conducting clinical trials, most often within the commercial sector, have few incentives to undertake externally valid research involving older people. This is in part because such research is often impractical before drug licensing; it offers little commercial benefit and is not required by the regulatory authorities. There is an urgent need for research funders, industry and regulators, such as the Medicines and Healthcare products Regulatory Agency (MHRA), to consider how this issue can be addressed, including consideration of the potential impact of regulations that require new drugs to be trialled on older people if they are the therapeutic target group

3.3 Conclusions

Medical science has tended, understandably, to focus on intervening in specific, age-related diseases, rather than tackling the ageing process itself.[247] The mechanisms of ageing are complex, with the accumulation of a diverse and tissue-specific array of damage and pathology.[248] For instance, research in model organisms and human populations has shown that multiple forms of molecular and cellular damage accumulate during ageing, including:[249]

- Somatic mutations of DNA in the cell nucleus and mitochondria.
- Dysregulation of gene expression.
- Oxidative stress and damage.
- Adducts on macromolecules.
- Misfolding and aggregation of proteins.
- Erosion of the telomeres at the tips of chromosomes.
- Failure of processes for repair and turnover of damaged macromolecules.
- Cellular senescence and loss of stem cells.

Indeed, it could be deduced that there is no single ageing process underlying this complex set of changes. If this were true, the prospect of experimental analysis of, or medical intervention into, the ageing process would be poor. Rather, each age-related medical problem would have to be tackled independently, in a piecemeal approach. Since the chance of experiencing disease increases exponentially with age, curing or preventing one age-related deficiency would provide only marginal benefit to overall health, because other deficiencies would continue unabated.

A major finding of recent years, however, has been that not only can quite simple interventions extend lifespan in laboratory animals, but that when they do so they produce a broad-spectrum improvement in health (see sections 2.3.3, 3.1.1 and 3.2.1). Moreover,

244 Academy of Medical Sciences (2007). *Identifying the environmental causes of disease: how should we decide what to believe and when to take action?* http://www.acmedsci.ac.uk/index.php?pid=99&puid=115
245 Cartwright N (2007). *Are RCTs the gold standard?* Biosciences **2**, 11–20.
246 Academy of Medical Sciences (2007). *Optimizing stratified medicines R&D: addressing scientific and economic issues.* http://www.acmedsci.ac.uk/download.php?file=/images/page/stratifi.pdf
247 Kim S (2003). *Molecular biology of ageing*. Archives of Surgery **138**, 1051-1054.
248 Martin GM, Partridge L & Kirkwood T. (1999). *Evolution, senescence, and health in old age*. In Stearns SC Ed. (1999). *Evolution in health and disease*. Oxford University Press, Oxford.
249 Kirkwood T (2005). *Time of our lives: what controls the length of life?* EMBO Reports **6(S1)** S4–S8.

population-based studies of people show that longevity and health depend partly on environment so are demonstrably malleable.[250] A productive approach would therefore be to target systematically the process of ageing itself.[251,252]

It is important to be clear that this research does not offer the prospect of immortality or even substantial increases in lifespan (see box 3.2). Nor are we calling for modification of human genes.[253] Instead, this work could provide a route to tackling health during ageing and ageing-related disease in a more coherent and efficient way.

Research with model organisms is revealing that, when the ageing process itself is slowed down, so too is the impact of multiple and diverse ageing-related diseases.[256,257] For instance, mice with a null mutation in the gene encoding the insulin receptor substrate 1 live longer. Furthermore, as they age, they maintain their glucose homeostasis, motor function and immune profile better than control mice, and they are protected against osteoporosis, cataract and ulcerative dermatitis of the skin.[258] Invertebrates with greater longevity due to alterations in the insulin/IGF-1 pathway also maintain immune, cardiac and motor function better as they age, and they are protected against the pathology associated with specific genetic models of cancer and Alzheimer's disease.[259,260,261]

Studies in humans have also found links between the IGF-1 pathway, neurodegeneration and ageing. Type 2 diabetes, insulin and ageing have all been closely associated with vascular disease and Alzheimer's.[262,263] Many of the diseases associated with ageing have been shown to share common mechanisms. For example, it is thought that α-synuclein found in the brains of patients with Parkinson's disease might have similar neurotoxic effects to amyloid oligomers found in the brains of patients with Alzheimer's disease.[264] Moreover, there have been reports of associations and potential biological mechanisms by which periodontitis, inflammatory disease of the mouth, can be linked to other diseases of ageing such as rheumatoid arthritis.[265]

Box 3.2: Reasonable expectations for research into ageing

Although ageing is a tractable scientific challenge, it is important to emphasise the limitations of ageing research. Promises of substantial increases in lifespan, reversing ageing or even immortality are unlikely to be fulfilled in the foreseeable future, if at all. Many hypotheses about ageing seem attractive, and even plausible, but most come to nothing when subject to rigorous scientific inquiry. Treating proposals that are not supported by scientific evidence as if they were scientific ideas carries the risk of legitimising spurious ideas.

The recent scientific advances described in this chapter have nothing in common with spurious claims about 'miracle' anti-ageing interventions that are often reported in the media: no such treatments exist.[254] Bogus assertions about anti-ageing medicines that are not supported by evidence can harm genuine scientific research into ageing.[255] The more realistic and justifiable goal put forward by legitimate researchers in the field is to improve healthy ageing and thereby increase healthy life expectancy. The provision of timely, evidence-based information on medicines for ageing and age-related disease remains important.

250 Marmot M (2008). *Closing the gap in a generation: health equity through action on the social determinants of health*. WHO, Geneva.
251 Butler, *et al*. (2008). *A new model of health promotion and disease for the 21st century*. BMJ **337**, 339.
252 Holliday R (1984). *The ageing process is a key problem in biomedical research*. The Lancet **2**, 1386-7.
253 Butler RN, *et al*. (2008). *A new model of health promotion and disease for the 21st century*. British Medical Journal **337**, 339.
254 Olshansky SJ, *et al*. (2003). *In pursuit of the longevity dividend: what should we be doing to prepare for the unprecedented aging of humanity*. http://www.lifestarinstitute.org/files/library/Longevity_Dividend.pdf
255 Warner H, *et al*. (2005). *Science fact and the SENS agenda*. EMBO Reports **6(11)**, 1006–1008.
256 Kenyon C (2005). *The plasticity of ageing: insights from long-lived mutants*. Cell **120**, 449–460.
257 Mair W & Dillin A (2008). *Aging and survival: the genetics of lifespan extension by dietary restriction*. Annual Review of Biochemistry **77**,727–754.
258 Selamn C, *et al*. (2008). *Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice*. FASEB Journal **22**, 807–818.

This chapter demonstrates that basic biological insights can reveal potential targets for medical interventions to slow ageing. It may therefore be possible to develop medicines that can target underlying ageing processes and thus address several diseases at once, before or early in their clinical manifestation. To achieve this goal it will be necessary to integrate our growing understanding of the mechanisms of ageing with our burgeoning knowledge about age-related diseases. There is now the chance for the MRC to harness UK potential and strengths by making targeted support and integration of research into ageing a central theme of their research strategy. Areas of ageing research where major progress might be made in the future include:

- Developing a more comprehensive understanding of the basic biology of healthy ageing.
- Better integrating knowledge of the processes that underpin ageing and age-related diseases.
- Measuring and understanding the determinants of healthy ageing in older people at a population level.
- Translating basic science and clinical advances in ageing research into effective interventions.

A more detailed description of ageing research priorities is given at the beginning of this report.

259 Pinkston JM, *et al*. (2006). *Mutations that increase the life span of* C. elegans *inhibit tumor growth*. Science **313(5789)**, 971–975.
260 Pinkston-Gosse J & Kenyon C (2006). *DAF-16/FOXO targets genes that regulate tumor growth in* Caenorhabditis elegans. Nature Genetics **39(11)**, 1403–1409.
261 Cohen E, *et al*. (2006). *Opposing activities protect against age-onset proteotoxicity*. Science, **313(5793)**, 1604–1610.
262 Piper MDW, *et al*. (2008). *Separating cause from effect: how does insulin/IGF signalling control lifespan in worms, flies and mice*. Journal of Internal Medicine **263**, 179–191.
263 Craft S (2009). *The role of metabolic disorders in Alzheimer's disease and vascular dementia: two roads converged*. Archives of Neurology **66(3)**, 300–305.
264 Academy of Medical Sciences (2008). *Response to the Nuffield Council on Bioethics consultation on 'Dementia: ethical issues'*. http://www.acmedsci.ac.uk/index.php?pid=100&puid=128
265 Persson GR (2006). *What has ageing to do with periodontal health?* International Journal of Dentistry **56 (4s1)**, 240–249.

4 Policy measures for ageing research

In this chapter we explore policy measures to encourage ageing research. These will involve providing leadership, strengthening support, establishing an overview of available resources, breaking down barriers, building capacity and centres of excellence, and incentivising the development of interventions that target the processes of ageing and technologies for the wider health needs of older people. Implementation of these measures will help to establish an iterative process of discoveries between research at the laboratory, clinical and population levels that will translate advances in our understanding of ageing into actual benefits for patients and the public.

4.1 Leadership

The public sector is a key funder of research into ageing. One of the consequences of the broad nature of ageing research in the UK is that it falls within the remit of several public funders, including:

- MRC
- The Biotechnology and Biosciences Research Council (BBSRC)
- NIHR
- R&D functions of the four UK health departments
- The Economic and Social Research Council (ESRC)
- The Engineering and Physical Sciences Research Council (EPSRC)
- The Technology Strategy Board (TSB)
- The Regional Development Agencies (RDAs)

Without dedicated support, ageing research could easily fall into the gaps between these bodies, with each failing to recognise ageing as one of their responsibilities for funding. The co-ordinating roles of OSCHR and Research Councils UK (RCUK), particularly through the Cross-Council Committee for Ageing Research (XCAR), are crucial in helping to avoid this trap. A key barrier to medical research into ageing exists at the boundary between medicine and biology. This is important, because so much opportunity for scientific progress lies at this interface.[266] Currently the BBSRC funds research into the basic biology of ageing, but not research into human diseases. In contrast, the MRC has been more inclined to support work on age-related diseases. This structure has discouraged applicants who specifically wish to address the interplay between ageing and ageing-related disease and to study the biological basis of healthy ageing in older people. Currently it is not clear which funder to approach and there is a danger of 'double jeopardy' – where research falls into the gap between the remits of two funders.

In addition, the internal structures of individual funding bodies often inhibit the funding of ageing research. The subject cuts across standing committee structures, because it can address changes in several different tissues, at all levels of biological organisation, in different species or involving more than one disease. Ageing therefore often fails to achieve the necessary level of representation on any one research committee, with no mechanism in place to ensure that applications can compete on a level playing field with other research areas. This is an issue that each of the funding bodies should address with changes to their internal mechanisms for handling this subject area.

Bringing together the disparate bodies responsible for ageing research to focus better their internal efforts and to co-ordinate funding, research outreach and public engagement would provide clearer direction for ageing research in the UK. Historically, however, there has been limited co-ordination between the public funders of research into ageing, and where there has been co-ordination it

266 Butler RN, *et al*. (2008). *A new model of health promotion and disease for the 21st century*. British Medical Journal **337**, 339.

has lacked direction. Despite half a decade of being a priority for work across the Research Councils, ageing research in the UK has yet to fulfil its potential. One challenge has been that ageing is such a large and diverse topic. The recent advances in our understanding of the processes that underpin ageing offer a focus for future activity. The UK Age Research Forum, currently the sole body that represents the whole of ageing research in the UK, plays an important role in preventing overlap and identifying gaps in funding allocations, but it is not mandated to direct research and has no dedicated corporate budget so cannot provide the necessary leadership.[267] Although co-ordination can be beneficial, a diversity of funders should be maintained to ensure that novel ideas in single disciplines have a suitable range of sources from which to obtain support.

One method for co-ordinating ageing research in the UK might be to establish a National Institute for Ageing, similar to those found in the USA and Canada. Although this model is a good first step that has boosted support for research into the processes that underpin ageing in North America, we consider that this would not necessarily be appropriate for the UK, where the structures for funding public sector research are quite different. However, because ageing is a major determinant of many diseases, there is a strong need for an equivalent leadership role in the UK. There is opportunity not only to support the basic biology of ageing but also to go further by encouraging its iterative interaction with research into age-related diseases and translation into improvements in health during ageing.

The MRC currently leads on ageing research for the NIHR/OSCHR and for the Research Councils' 'Lifelong health and wellbeing' initiative. It is also involved with the cross-Council 'New dynamics of ageing' and the Strategic Promotion of Ageing Research Capacity programmes. This comes at a time when medical research into ageing is offering ever-greater opportunities. We believe the MRC should build on the thinking in its strategic plan and seize the chance to provide valuable leadership and co-ordination by putting recent advances in our understanding of the processes of ageing and their relationship with age-related diseases at the heart of both its own ageing research strategy and that of the wider research funders.[268]

4.2 Strengthening support for ageing research

The scientific progress in ageing research discussed in chapter 3 demonstrates that the overall volume of research does not currently match its scientific opportunities. Although information on funding for ageing research is sparse, data show that the US National Institute of Ageing's *Biology of ageing* Programme spent around €111 million in 2006, whereas the European Union (EU) fifth and sixth Framework Programmes spent around €18 million on similar work in the same year.[269] This disparity is surprising because the EU has a similar gross domestic product to the USA, but a more rapidly ageing population. We note that UK support for the biology of ageing has been somewhat greater than some other EU countries, but is still not of the same magnitude as the USA and has not received sufficient attention from medical funders.

It is significant that there is no major research charity that focuses on the underlying process of ageing of similar size to Cancer Research UK, the British Heart Foundation or the Arthritis Research Campaign. This is unfortunate, because we have anecdotal evidence that older people are willing to support research into healthy ageing. The reasons for such an omission, and lack of support for this type of research in general, are considered in box 4.1.

267 Franco O, *et al*. (2007). *Ten commandments for the future of ageing research in the UK: a vision for action*. BMC Geriatrics **7(10)**. doi:10.1186/1471-2318-7-10
268 Medical Research Council (2009). *Research changes lives. MRC strategic plan 2009–2014*. http://www.mrc.ac.uk/About/Strategy/StrategicPlan2009-2014/index.htm
269 Ageaction (2007). *Changing expectations of life*. http://ageaction.ncl.ac.uk/AgeAction_book.pdf

Box 4.1 Challenges to supporting research into the mechanisms that underpin ageing

At the James Martin Institute for Science and Civilisation Forum in 2006 on *Tomorrow's people*, Professor Richard Miller, Professor of Pathology and Associate Director of the Geriatrics Centre at the University of Michigan, offered some reasons why research into the mechanisms that underpin ageing receives such limited support.[270]

A key challenge is that legitimate researchers into the basic biology of ageing suffer stigma because a few high-profile gerontologists promise too much. There are also many misconceptions about ageing that make funders hesitant about supporting research into the area. For instance, many people incorrectly believe that ageing is not a malleable process, leaving little reason to fund research into understanding and potentially intervening in ageing. As we have shown in this report, this is clearly not the case.

Another reason suggested by Professor Miller is that patients and their relatives suffer from specific diseases that present a clear banner around which to rally and engage policymakers. Ageing itself cannot be so neatly categorised and does not provide such an attractive focus for political advocacy.

Finally, bright young researchers are often attracted to fast-moving fields with substantial resource that use high-technology equipment and techniques. Research into the mechanisms that underpin ageing often takes time, does not currently receive substantial resource and does not necessarily rely on sophisticated technology. This is compounded by the commercial disincentives for industry to support research into the processes that underpin ageing (see section 4.7).

The strategic importance and potential of ageing research discussed in previous chapters justify a step change in the magnitude of support to build momentum and critical mass. To ensure this takes place, the MRC should provide significant ring-fenced funding in a manner similar to the way in which it supported research into AIDS.[271] The substantial investment made by the Gates Foundation has helped to revitalise global health research so increased support might do the same for ageing research. Since the financial cost of an ageing population for rich countries between now and 2050 is estimated to be nine times that of the recent global economic downturn, there is a compelling case for greater support for ageing research.[272] Significant public support for research into ageing is also likely to leverage further support from industry and medical research charities, thereby magnifying the impact of the original public investment. Moreover, it will attract the best and brightest scientists from other fields.

When allocating new funds, we urge consideration of a range of mechanisms including centres of excellence, which are discussed further below. Diverse, periodic rounds of funding would generate excitement among researchers, allow flexibility, offer innovative ideas, multiple types of support and provide an initial stimulus to allow researchers investigating ageing to compete for general response mode funding in the future.

270 James Martin Institute (2006). *Tomorrow's people: the challenges of technologies for life extension and enhancement. Longer?* http://www.martininstitute.ox.ac.uk/JMI/Forum2006/Forum+2006+Webcast.htm
271 Grimley-Evans J (2005). *The scientific aspects of ageing: a Lordly report*. Journal of the Royal Society of Medicines **98**, 482–483.
272 IMF staff position note (2009). Fiscal implications of the global economic and financial crisis

4.3 Breaking down the barriers

Many research disciplines are needed to understand and tackle the complex process of ageing. Research into the biological mechanisms that underpin ageing, and research into age-related diseases, have traditionally been performed by distinct communities. One group, including many biogerontologists, focuses on the biological basis of ageing and its underlying mechanisms. The other group, including many medical scientists, clinicians and allied health professionals, concentrate on the problems of the diseases associated with ageing. In the past, there has been little communication and collaboration between these two constituencies. They rarely belong to the same learned societies; they are often supported by different funding agencies, and usually operate in different academic departments.[273] The advances discussed in the previous chapter demonstrate that there would be significant value in greater exchange of ideas and collaboration between these two groups.

For UK research into ageing to realise its potential, close collaboration and co-ordination will be needed between the medical sciences and other disciplines. For instance, the challenge of dementia will require:

- Basic biologists to determine underlying processes of ageing of the nervous system and the ways in which these act as risk factors for neurodegeneration.
- Collaboration between biologists, chemists and others to develop preventative interventions.
- Clinical researchers to test interventions in patients.
- Engineers to develop assistive technologies.
- Social scientists to examine consequences for communities.

Traditional research governance structures, such as the way in which institutes are organised, methods of research assessment, peer-review and career progression, often undervalue this sort of approach.[274] No single measure will ensure that such a multi-faceted process for ageing research will be established. Instead, it will be necessary to use diverse policy levers, both in engaging researchers from the 'bottom-up' and developing the 'top-down' strategies of funders, universities and governing bodies. The objectives of these efforts should be to remove barriers within existing funding structures and cultivate a fertile environment that encourages and rewards effective collaboration between disciplines.

We emphasise that interdisciplinary working should be a vehicle for research success, rather than as an end in itself. It should not be rigidly enforced from above, or distract from assessing the scientific merit of excellent proposals from single disciplines, when making funding decisions. The emphasis should be on excellence and diversity, and the aim should be to ensure that research is judged on its scientific merit rather than being hindered or advantaged by its particular disciplinary nature. Support in the UK so far has emphasised co-ordination among multiple disciplines and funders. However, in-depth ageing research in individual disciplines can contribute much and its importance should be recognised with increased support.

4.4 Establishing an overview of support for ageing research

To develop policies to encourage ageing research it will be important to have a clear overview of the resources that are currently available. The House of Lords Science and Technology Select Committee inquiry into the scientific aspects of ageing estimated that, in 2002, UK public and charitable bodies spent nearly £200 million on ageing research.[275]

273 Ageaction (2007). *Changing expectations of life*. http://ageaction.ncl.ac.uk/AgeAction_book.pdf
274 Academy of Medical Sciences and the Royal Academy of Engineering (2007). *Systems biology : a visions for engineering and medicine*. http://www.acmedsci.ac.uk/p99puid97.html
275 House of Lords (2005). *The scientific aspects of ageing*. The Stationery Office, London.

However, accurate figures are difficult to obtain because:

- Different funders define ageing research in different ways, and generally definitions tend to be over-inclusive.
- Initiatives often span several years so it can be difficult to determine when a particular tranche of money has been spent.
- The way in which funders internally monitor and categorise their funding changes over time.
- Ageing research often cuts across many disciplines.

Publicly available data from funders rarely disentangle support for research into the mechanisms that underpin ageing from support for research into age-related diseases. Consequently, support for research into age-related diseases can simulate the appearance of substantial support for research into the mechanisms that underpin ageing. Moreover, because ageing takes place over the life course, it is possible to include nearly every type of medical research under the rubric of ageing. This is not helpful as some types of medical research are clearly more closely associated with ageing than others. Funders should clearly badge different sorts of ageing research to avoid ambiguity. A thorough audit of all types of ageing research would help guide future funding decisions.

4.5 Building academic capacity in ageing research

The increased scale of ageing research proposed in this report will urgently require increased human capacity. However, it is difficult to get an accurate picture of current UK capacity in this area. For instance, information on the number of basic scientists involved in ageing research is sparse and is complicated by the fact that ageing research cuts across multiple disciplines. Anecdotal evidence and views expressed to the working group suggest that the number of basic scientists working on ageing research around the world is still small compared with more established areas of ageing-related disease, and that critical mass has not yet been achieved.[276] It appears that, all too frequently, researchers who start out in ageing research leave the field because the work involves inherently long lead times and therefore presents difficulties for existing research funding and career-advancement structures.

It is similarly hard to collect evidence on current clinical capacity in ageing research. However, anecdotal evidence indicates that again there are insufficient numbers. We recommend that funders make efforts to determine the number of basic biologists and clinicians who undertake research into ageing in future surveys of academic capacity in the UK.

Building capacity in the basic biological science of ageing is key to the future success of medical research into ageing because it will generate new knowledge that will attract those with clinical backgrounds. This could be achieved both by training new investigators in the basic biology of ageing to research topics such as genetics, epigenetics and environmental interactions, and attracting existing investigators into this field. The latter approach is likely to prove particularly fruitful because it will bring fresh perspectives to existing challenges and will increase capacity more rapidly than training new investigators. Many current successful researchers in ageing began their careers in different fields, thereby demonstrating the power of the multi-disciplinary approach to this complex problem.

A particular challenge when building capacity in basic biology is that experimental research in model organisms and humans takes a long time and requires substantial resource. A competitive post-doctoral fellowship programme in the basic biology of ageing of at least five years in length should therefore be established to train new investigators and attract existing investigators from other fields. The Academy's report 'Freedom to

276 Ageaction (2007). *Changing expectations of life*. http://ageaction.ncl.ac.uk/AgeAction_book.pdf

succeed' provides helpful recommendations on, and principles for, non-clinical fellowship schemes.[277] Grants should include sufficient funding for work in rodents or humans. The fellowships should also include an enforceable takeover clause, where the host institution is required to provide the post-doctoral individual with a permanent position after initial funding has finished, while being generous enough to ensure the host institutions still find the fellowships attractive.

Major progress toward the goal of increased capacity in the basic biology of ageing will be made by:

- Providing support for experimental ageing research in both model organisms and humans to accelerate progress and increase the international competitiveness of UK research.
- Recognising that ageing research involves work at different spatial levels, from cells to populations requiring the involvement of many disciplines. Support should therefore be provided to encourage appropriate collaboration between workers with different kinds of expertise.
- Providing targeted support for studentships to provide a stream of trained PhDs.
- Providing support to encourage leading investigators in other relevant disciplines to undertake work on ageing using funding instruments such as project and programme grants. Collaboration with existing workers in ageing should be encouraged, but not necessarily required.
- Offering clear career pathways.
- Visible role models and leadership.
- Organising meetings on ageing, both in key subject areas with strong research teams that do not currently work on ageing and in important contact zones, for instance between ageing and ageing-related disease.

We believe that there is a strong case for engaging clinical academics in research that brings together age-related diseases and the underpinning processes of ageing in order to translate knowledge between the two and to consider the long-term biological impact of interventions. Clinical capacity in ageing research is likely to come from academic sub-specialties with expertise in particular age-related diseases. Approaches that attract clinical researchers into ageing projects have been successfully pursued in North America, where we believe there has been more success in building clinical research capacity than in the UK. It will be important to include geriatricians to ensure medical advances influence service delivery and to engage older patients with research. Those working in primary care and public health should also be involved, because most older people access healthcare at the community level. Guidance on building academic capacity in clinical specialties can be found in an Academy report on this topic.[278]

Clinical academics would benefit from undertaking their training in centres of excellence to avoid isolation, provide access to infrastructure and encourage interaction with researchers from other fields. The Edinburgh Clinical Academic Track scheme offers one successful model of building capacity in this manner.[279] Support for clinical training fellowships, clinician scientist fellowships and intermediate clinical fellowships would be particularly helpful as researchers often decide the future research direction at this time. It will also be important to draw in experts from other areas, as this sort of 'cross fertilisation' of ideas often generates the most innovative thinking.

Promising pockets of research outside centres of excellence might be encouraged by making ageing research a priority area for general fellowship schemes, as has been the case with other strategically important specialties such as surgery and radiology through the Academy's Clinician Scientist Fellowship scheme. Consideration should also be given to greater emphasis on the biology of ageing in general medical education and training to engage those

277 Academy of Medical Sciences (2005). *The freedom to succeed*. http://www.acmedsci.ac.uk/p99puid2.html
278 Academy of Medical Sciences (2009). *Building clinical academic capacity and the allocation of resources across academic specialties*. http://www.acmedsci.ac.uk/p99puid150.html
279 Further information is available from http://www.ecat.mvm.ed.ac.uk/

involved in health service provision better. Finally, the scientific community should make ageing research a more attractive career path by emphasising how such investigations will benefit health.

4.6 Centres of excellence

A step change is needed in the magnitude and organisation of ageing research in the UK if its potential is to be swiftly realised in full. Centres of excellence offer one important route to achieve this goal. These centres could provide valuable opportunities to:

- Persuade internationally competitive research groups to direct their attention to ageing.
- Attract and recruit the brightest researchers from the UK and abroad.
- Establish a critical mass of researchers.
- Build clinical and non-clinical capacity.
- Encourage and support the most promising strands of research.
- Promote investment in expensive infrastructure such as colonies of aged animals.
- Secure expertise and resources in ageing research in the UK over the long-term.

Much can be learnt from successful existing centres including the Institute for Healthy Ageing at University College London, the Institute for Ageing and Health (IAH) at Newcastle University, the MRC Epidemiology Resource Centre at the University of Southampton and the Oxford Institute of Ageing.[280] These and other examples demonstrate the power of:

- Creating development opportunities for highly imaginative and dynamic scientists to enable them to branch out into a new subject area mid-career.
- Stimulating iterative translation of research between the laboratory and the clinic.
- Promoting networking between academics at all levels of seniority across different disciplines.
- Providing opportunities for researchers from different disciplines to spend time together to encourage informal exchange of ideas.
- Physical co-location and provision of shared infrastructure, particularly of large and expensive pieces of equipment such as MRI scanners.
- Proactively managing integrated working through strong leadership, clear shared goals and mutual understanding of methods of working and definitions of success.
- Bringing together ad hoc interdisciplinary teams to solve particular research challenges.
- Joint supervision of interdisciplinary PhD students by researchers from different disciplines.

Although there are some centres of excellence in the UK, such as three centres recently established as part of the MRC's lifelong health and well-being initiative, these are too few and too fragmented. We now have the chance to scale-up existing facilities to broaden their remit and to establish new centres. This would make them more internationally competitive, of sufficient size to tackle the considerable scientific challenges presented by ageing, involve more disciplines, cover more topics and nurture a critical mass of capacity.

Centres of excellence would need to be outward looking and effectively networked to each other and to smaller initiatives, both nationally and internationally. This would help them avoid isolation and ensure that integrated understanding of the basic biology of ageing and age-related diseases in individuals and populations pervades the thinking of researchers more widely. Applications for the expansion of existing centres or the establishment of new centres should be principally determined on scientific merit. The details of future calls should be determined by funders and the scientific community dependent on circumstance.

280 Further details of these four institutions can be found at http://www.ucl.ac.uk/~ucbtdag/iha/ http://www.ncl.ac.uk/iah/ http://www.mrc.soton.ac.uk/ and http://www.ageing.ox.ac.uk/

4.7 Developing interventions for ageing

Industry is the most important source of the development of new medicines. However, so far, industry research has focused on age-related diseases rather than the common processes of ageing that underpin them. There are several reasons for this, including the way in which diseases are traditionally classified, the significant time and cost required for the development of medicines targeted at the processes of ageing and the challenges of developing medicines that target diseases before they become clinically manifest.

Many of the health consequences of ageing are not formally considered endpoints for clinical trials, despite their clear impact on health. For instance, muscle weakness is common among many older people, and has a negative impact on their lives, but its importance is often not recognised by regulatory authorities or healthcare professionals. Without this acknowledgement, industry has little incentive to develop medicines for sub-clinical ageing deficiencies as it may not be possible to get them licensed. The same is true of the processes underlying ageing and many of its impacts upon health.

Drug discovery and development is expensive and time consuming. The average total development time for a new drug has risen from around 8 years in the 1960s to around 14 years in the 1990s.[281] The Association of the British Pharmaceutical Industry (ABPI) estimates that it now costs around $100 million to bring a single medicine to market.[282] This leaps to over $1 billion if the cost of a particular drug development programme takes into account the cost of failed projects within the portfolio; it rises to over $3 billion if capital costs are also added. Moreover, the resources required to develop medicines that target the processes that underpin ageing are likely to be even greater than for other medicines, given the time it takes to study ageing in humans and animals. Even with new technology platforms, such as biomarkers of ageing, the commercial disincentives are significant.

Another potential barrier is that industry may not be prepared to accept the risks associated with treating the underlying processes of ageing in healthy patients in order to prevent age-related diseases. Preventive medicines are not new: drugs, such as statins, are already used to lower cholesterol and blood pressure in individuals with sub-clinical disease. However, the safety requirements for such medicines are much higher than for medicines used to treat existing illness, and the clinical trials needed to demonstrate their value take a long time. The potential rewards for industry might simply not outweigh the risk of harm and litigation, as well as the costs of more stringent regulatory requirements.

The barriers discussed above mean that industry is less interested in developing medicines that target the processes underpinning ageing, despite the substantial health and social benefits. A strong case can therefore be made for Government to help surmount these hurdles for the long-term public good. Part of the solution will be adjusting the regulatory framework so that it provides incentives for the development of safe, effective medicines that ameliorate ageing. One short-term opportunity for the development of medicines for ageing under the current regulatory system might be to test them in patients with a disease of particular economic and social importance. In the longer term, however, new thinking is required to incorporate such broad-spectrum medicines into the pharmacopeia by developing a new taxonomy of disease based on molecular mechanisms, as well as on clinical symptoms and physiological measurements.[283]

281 Academy of Medical Sciences and the Royal Academy of Engineering (2007). *Systems biology: a vision for engineering and medicine.* http://www.acmedsci.ac.uk/p99puid97.html
282 Association of the British Pharmaceutical Industry (2008). *The prioritisation of research in the pharmaceutical industry.* ABPI, London.
283 Academy of Medical Sciences (2008). *Presidential perspectives.* http://www.acmedsci.ac.uk/p98puid129.html

Opportunities exist to encourage collaborations between industry, academia and the NHS that could:

- Compensate for the lack of incentives for industry to develop medicines for ageing by allowing the risk and cost to be spread among stakeholders.
- Allow the various stakeholders to combine their distinct strengths in fundamental research, drug development and clinical utility.
- Encourage iterative translation of research between the laboratory and clinic.
- Use the opportunities for clinical and epidemiological research offered by the NHS.
- Inform the research agenda through a better understanding of unmet patient need.

There is certainly an increasing appetite for collaboration between individual commercial companies, and between industry and academia.[284] Increasingly, commercial companies are collaborating with academia in 'pre-competitive' research and we are seeing an increasing number of industry researchers forging partnerships with research groups and university departments at more local levels, and in some cases outsourcing research to academic teams.[285] Opportunities to facilitate and promote these types of collaboration in ageing research must be seized.

Such consortia might dovetail with the recently announced MRC 'developmental pathway funding scheme'. This approach seeks to stimulate translational research by encouraging universities to develop medical technologies that address unmet clinical needs through goal-orientated, rather than hypothesis-driven, research.[286] One successful example of the proposed consortium model is the Scottish Translational Medicine Research Collaboration that has been formed to translate medicines from 'bench to bedside' by providing links between discovery and development.

As a minimum, communication between academia, industry and the NHS must be improved. Researchers and clinicians from these constituencies rarely attend the same conferences and meetings, and have few opportunities to come together to discuss their work and objectives. Networks such as the Academy's FORUM with industry can do much to help encourage such collaborations, but industry could take more proactive steps to ensure their representation and visibility at scientific conferences and policy debates.[287]

The recent 'Review and refresh of bioscience 2015' published by the Bioindustry Association reiterated the importance of collaboration between industry, academia and the NHS, and stressed the conclusions of the original report 'Bioscience 2015: improving national health, increasing national wealth'.[288,289] Importantly, both of these reports identified the lack of incentives for industry to undertake research in the NHS, including the slowness of approval for clinical trials and challenges in recruiting patients. Tackling these barriers goes beyond the ageing research agenda, but will be a crucial component in ensuring that potential interventions in ageing are translated into real patient benefits. As discussed in section 3.2.3, there is a particular need to harness the power of NHS health records systems, particularly for post-marketing surveillance of new drugs.[290]

284 Academy of Medical Sciences (2008). *The UK pharmaceutical industry FORUM lecture 2008 – what does the future hold?* http://www.acmedsci.ac.uk/download.php?file=/images/event/2008lec.pdf
285 Anon (2008). *Triple therapy*. http://www.economist.com/research/articlesbysubject/displaystory.cfm?subjectid=531766&story_id=11919385&source=login_payBarrier
286 Further details are available from http://www.mrc.ac.uk/Newspublications/News/MRC005366
287 Further information on the academy's FORUM can be found at http://www.acmedsci.ac.uk/p23.html
288 Bioscience Innovation and Growth Team (2009). *Review and refresh of bioscience*. The Stationery Office, London.
289 Bioscience Innovation and Growth Team (2003). *Bioscience 2015: improving national health, increasing national wealth.* The Stationery Office, London.
290 Academy of Medical Sciences (2005). *Safer medicines*. http://www.acmedsci.ac.uk/p99puid61.html

4.8 Technologies for the wider health needs of older people

The opportunities for industry to address the needs of older people are not limited to pharmaceuticals. They also include the development of nutritional, personal care and lifestyle products that will promote health and well-being.[291] It is surprising that industry has failed to address the enormous potential market that older people represent.[292] Non-pharmaceutical interventions would also benefit from closer liaison between academia and industry, both to assist the translation of research into new products and to ensure new products are clearly based on understanding of the needs of older people.

Assistive technology will be vital in empowering older people to live independently and avoid the consequences of disabling environments. In this regard, the TSB, Department of Health, EPSRC and ESRC have developed the Assisted Living Innovation Platform to advance the UK's technological capability to enable the ageing population and people suffering from long-term chronic conditions to live independently.[293]

Advances in information and communications technologies in particular have much to offer older people who may become gradually limited by physical and cognitive impairment associated with age-related diseases such as Alzheimer's, heart failure, chronic inflammatory diseases, diabetes and lung disease. Such technologies require careful evaluation during their development to ensure they are effective in meeting the complex needs of this population, and to ensure their development is not just driven by technology push, but also by consumer pull. The EPSRC has been particularly active in support of this area through initiatives such as KT-EQUAL, to network research with the beneficiaries of their work and other stakeholders, and as part of two £10 million hubs in digital economy that will focus in particular on information and communication technologies and telemedicine for older people.[294]

There are opportunities to combine online tools with evidence from medical research to provide more accurate and accessible information about medicines for patients with disabilities. The NHS can play a particularly important role in providing pull for this sort of innovation, as exemplified by the collaboration between the Scottish Executive Health Department and Scottish Telemedicine Initiative.[295] Medical devices encompass a wide range of physical diagnostic and therapeutic interventions, such as hip replacements, that have revolutionised life for many older people. There are significant opportunities for UK researchers to fulfil unmet needs in the medical devices market, for instance in non-invasive ultrasound techniques, robotic surgery and medical implants.

As the population ages, the market for these technologies will grow, offering rich opportunities for industry that invests in this field. Although a full discussion of how industry can address the wider health needs of older people is beyond the scope of this report, we emphasise the need for the development of new assistive technologies and medical devices to be informed by the medical and social sciences, to ensure they are evidence-based and targeted at genuine user need. Priority areas for development recently identified by the Royal Academy of Engineering include mobility, independence and safety.[296]

291 Franco OH (2007). *Ten commandments for the future of ageing research in the UK: a vision for action*. BMC Geriatrics **7(10)**. doi:10.1186/1471-2318-7-10.
292 House of Lords (2005). *Ageing: scientific aspects.* The Stationery Office, London.
293 Further details are available from http://www.innovateuk.org/ourstrategy/innovationplatforms/assistedliving.ashx
294 Further details are available from http://www.sparc.ac.uk/about_kt_equal.asp and http://www.epsrc.ac.uk/Content/News/DEHubsAnnouncement.htm
295 Further details are available from http://www.telemedicine.scot.nhs.uk/
296 Royal Academy of Engineering (2007). *The ageing population: challenges for engineering.* http://www.raeng.org.uk/policy/ukfocus/pdf/Ageing_Population.pdf

4.9 Conclusion

Research into the complex processes of ageing requires excellent single discipline and interdisciplinary research, an integrated approach that crosses basic and clinical communities in different disciplines, and must engage academia, industry and the NHS.[297] Recent advances in basic biology, clinical research and population studies are at last providing an understanding of the relationship between the process of ageing and age-related diseases. The discovery of this common framework means medical science should be placed at the heart of the UK's ageing research agenda.

Major progress would be made by:

- New leadership and focus in ageing research in the UK to capitalise on the scientific opportunities.
- Providing additional ring-fenced investment in research into the basic biology of ageing and its translation into clinical practice.
- A thorough audit of resources for ageing research in the UK.
- Establishing a five-year post-doctoral fellowship programme in ageing research to train new researchers and to attract existing investigators from other fields.
- Efforts to engage clinical academics who could integrate research into healthy ageing for the benefit of older people.
- Establishment of new centres of excellence and expansion of existing centres.
- Developing alliances between industry, academia and the NHS.
- Adjusting regulatory mechanisms to remove barriers to the development of medicines for ageing.
- Harnessing opportunities presented by data resources, such as electronic care records and the 2011 census.

297 House of Lords (2005). *The scientific aspects of ageing.* The Stationery Office, London.

Annex I: Report preparation

The working group

This report was prepared by an Academy of Medical Sciences working group. Members participated in a personal capacity and not on behalf of their affiliated organisations. The working group's interests are summarised below.

Chair

Professor Dame Linda Partridge CBE FRS FRSE FMedSci
Weldon Professor of Biometry, University College London
Professor Partridge is Weldon Professor in the Department of Biology at University College London. She earned her PhD from the University of Oxford and undertook postgraduate work at the University of York. Professor Partridge was a recipient of the Sewell Wright Award in 2002 and the Linnaean Society of London's prestigious Darwin-Wallace Medal in 2008. She has been a Fellow of the Royal Society since 1996 and a Fellow of the Academy of Medical Sciences since 2004. She was appointed CBE in 2003 and Dame Commander of the Order of the British Empire in 2009.

Her work uses *Drosophila* (fruit-fly) and mice as models to explore the underlying genes and processes that affect the timing and rate of ageing in all organisms, including humans. By studying some of the most phylogenetically constrained systems among organisms, such as the insulin/IGF-like signalling pathway, as well as other behavioural phenomena such as dietary restriction, stress, and somatic versus reproductive trade-offs, Professor Partridge is piecing together the physiological and genetic factors that could be the keys to altering the inevitable process of senescence. Her research is already suggesting that increasing the potential of the human lifespan is possible. Meanwhile, understanding more about the evolution of senescence could help scientists to educate people on how to live healthier for longer in their later years.

Members

Professor Alastair Buchan FMedSci
Director of the NIHR Biomedical Research Centre, University of Oxford
Professor Buchan has recently returned to Oxford where he did his initial training in medicine and neurology. He completed his training in London, Ontario, with Dr Henry Barnett and with Professor Fred Plum in New York and subsequently held staff positions in London and Ottawa before holding the Heart and Stroke Foundation Professorship in Stroke Research in Alberta. In Oxford, he has now been successful in obtaining funding from the MRC and the Dunhill Foundation to set up an Acute Stroke Programme in collaboration with Professor Peter Jezzard and Professor Peter Rothwell FMedSci. He is the Translational Research Director for the UK Stroke Research Network. He has led the Oxford University bid for a Wellcome Clinical Research facility and has successfully obtained funding for the new Acute Vascular Imaging Centre. He has just been appointed the Director of the Oxford Biomedical Research Centre, one of the five comprehensive centres for the new English NIHR.

Professor Chris Day FMedSci
Pro-Vice Chancellor and Provost of Medical Science, Newcastle University
Professor Chris Day is a consultant hepatologist with an international reputation in medical research, as recently recognised by his election as a Fellow of the Academy of Medical Sciences

and his appointment as one of the first 100 NIHR Senior Investigators. Before this appointment, Professor Day was Head of the School of Clinical Medical Sciences at Newcastle and Academic Head of the Liver Research Group, which is regarded as the largest and most successful group of its kind in the UK. He was the founding Director of the NIHR Biomedical Research Centre in Ageing and Chronic Disease, which is operated jointly by the Newcastle Hospitals NHS Trust and the University of Newcastle. Among his numerous external positions, Professor Day plays an influential role within the MRC and is a member of both its Populations and Systems Medicine Board and its Translational Stem Cell Research Committee. He is also a Trustee of the Alcohol Education and Research Council.

Professor Felicia Huppert
Professor of Psychology, University of Cambridge
Professor Huppert's principal research interest is well-being across the life course. Her work is unusual in that it brings together traditional approaches from cognitive psychology and neuropsychology with a population perspective derived from epidemiology. Working with outstanding colleagues in cognate disciplines (biomedical science, genetics, psychometrics, social science, economics and engineering), she has been able to integrate her work on both well-being and positive ageing with an understanding of underlying physiological mechanisms, gene–environment interactions, and the role of the social context.

Professor Huppert is involved in major population studies including the English Longitudinal Study of Ageing. She is also principal investigator on a project to investigate the life-course antecedents of mid-life flourishing, which involves analysing data from of the longest-running British birth cohort study - a representative sample of those born in 1946.

Dr Eric Karran
Chief Scientific Officer for Neuroscience Research and Early Development, Johnson and Johnson
Dr Karran works in the pharmaceutical industry where his research has concentrated on Alzheimer's disease, the most common cause of dementia. Age is a well-recognised risk factor for Alzheimer's disease, and the demographic change to an increasingly elderly population will cause a substantial increase in the incidence and prevalence of dementia. Currently, there are no therapies available that have been shown to slow or halt the progression of Alzheimer's disease, although there are several potential 'disease-modifying' therapies in late-stage clinical testing. Thus, a perspective on the increasing societal burden of treating and caring for Alzheimer's disease must be part of a strategy for ageing.

Professor Tom Kirkwood CBE FMedSci
Director of the Institute for Ageing and Health, Newcastle University
Professor Kirkwood is Professor of Medicine and Director of the Institute for Ageing and Health at the University of Newcastle. Educated in biology and mathematics at Cambridge and Oxford, he worked at the National Institute for Medical Research, where he formed and led a new research division, until in 1993 he became Professor of Biological Gerontology at the University of Manchester. He has received the Verzar Medal, Lord Cohen Medal and Henry Dale Prize for his work on ageing. He was appointed CBE in 2009.

His research is on the basic science of ageing and on understanding how genes as well as non-genetic factors, such as nutrition, influence longevity and health in old age. He was European President (Biology) of the International Association of Geriatrics and Gerontology, led the project

on 'Mental Capital Through Life' within the recent Foresight programme on Mental Capital and Well-Being, was Specialist Adviser to the House of Lords Science and Technology Select Committee inquiry into 'Ageing: Scientific Aspects' and has served on the Councils of the BBSRC and of the Academy of Medical Sciences. His books include the award-winning 'Time of Our Lives: The Science of Human Ageing', 'Chance, Development and Ageing' (with Caleb Finch) and 'The End of Age' based on his BBC Reith Lectures in 2001.

Professor Kay-Tee Khaw CBE FMedSci
Professor of Gerontology, University of Cambridge
Professor Khaw trained in medicine at Girton College, Cambridge, and St Mary's Hospital, London, and in epidemiology at the London School of Tropical Medicine and Hygiene, with subsequent clinical and academic posts in the University of London and the University of California San Diego. She is currently Professor of Clinical Gerontology in Cambridge and a Fellow of Gonville and Caius College, Cambridge. Professor Khaw is a Fellow of the Academy of Medical Sciences and was a member of the working group that produced the report 'Identifying the environmental causes of disease: how should we decide what to believe and when to take action?'

Professor Khaw is a principal investigator in the European Prospective Investigation of Cancer-Norfolk study (EPIC), which is supported by grants from the MRC and Cancer Research UK. She first became interested in diet and health when investigating reasons for the rise in blood pressure and rapidly changing patterns of CVD in different communities around the world, including Kenya and the Caribbean. The wide geographic, social and secular variations in most chronic diseases associated with ageing including CVD, cancer and osteoporosis suggest a substantial proportion of disabling conditions are potentially preventable. EPIC-Norfolk aims to identify how we can maintain health in the population.

Professor Simon Lovestone FMedSci
Professor of Old Age Psychiatry, Institute of Psychiatry, King's College London
Professor Lovestone is Professor of Old Age Psychiatry at the Institute of Psychiatry, King's College London and Director of the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Trust and the Institute of Psychiatry.

He studied microbiology at Sheffield University and then medicine at Southampton University, and has continued to practice both medicine and molecular science ever since. After working as a junior doctor in medicine and in healthcare of older people, he trained in psychiatry and then obtained a Wellcome Trust fellowship to study the molecular relation between plaques and tangles in Alzheimer's disease. He has an MPhil in psychiatry for his research, while a trainee psychiatrist, on the mental health of new fathers under the supervision of Professor Channi Kumar and a PhD in biochemistry resulting from his Wellcome Trust fellowship supervised by Professor Brian Anderton. He became a senior lecturer and then a reader in old age psychiatry and neuroscience before becoming Professor at the Institute and consultant old age psychiatrist at the Maudsley Hospital. In addition to heading a multi-disciplinary old age psychiatry clinical team, he has clinical interests in the dementias and in genetic counselling.

He is the Director of the NIHR Biomedical Research Centre for Mental Health founded in 2007, Deputy Director of the MRC Centre for Neurodegeneration Research, Chairman of the Scientific Advisory Board of the Alzheimer's Research Trust and has been a member of the Wellcome Trust Neurosciences Panel and part of the MRC College of Experts.

Dr Ruth McKernan
Vice-President for External Research in Europe, Pfizer
Dr McKernan is Vice President of External Research in Europe at Pfizer. She graduated from the University of London with joint honours in biochemistry and pharmacology and gained her PhD studying the mechanism of action of antidepressant drugs. She spent two years at the University of California in San Diego before returning to the UK to join the pharmaceutical company Merck. Her 17 years at Merck included three years as Vice President and Head of the Neuroscience Research Centre. Ruth is a renowned scientist, author of over 120 publications on neuroscience and is a visiting Professor at London's Institute of Psychiatry. Her first book for non-scientists, *Billy's Halo,* was shortlisted for the 2007 MIND awards.

Professor Roger Orpwood
Director of the Institute of Medical Engineering, University of Bath
Professor Orpwood is currently Director of the Bath Institute of Medical Engineering, a design institute run in association with Bath University to develop disability and healthcare equipment. He originally trained as a physiologist and pursued research in neurophysiology, but then retrained as a mechanical engineer and worked in the aerospace industry as a designer. He returned to academia after a few years, doing research in medical engineering and has been involved ever since in the field, with design and development experience of a wide range of technologies, mostly on devices for disabled people. For the past nine years he has been involved in managing the design of assistive technology for people with dementia, including the development of autonomous homes. He is keen to encourage a user-led approach to design, and to ensure the outcome of design work reaches the people who can benefit.

Professor Avan Aihie Sayer
MRC Clinical Scientist and Honorary Professor of Geriatric Medicine,
University of Southampton
Professor Sayer is Professor of Geriatric Medicine and an MRC Clinical Scientist at the MRC Epidemiology Resource Centre, University of Southampton. She leads the interdisciplinary Ageing and Health Group that carries out high-quality integrated clinical, epidemiological, basic and social science research that translates into improving the health of older people. The focus of this research is on the life-course causes, clinical consequences and prevention of sarcopenia and physical frailty using birth cohorts such as the Hertfordshire Cohort Study. A particular area of interest is capacity building in academic geriatric medicine, which is being addressed by the involvement of a growing number of clinical researchers in the group supported by the recent award of an NIHR academic clinical fellowship programme.

Professor Jonathan Seckl FRSE FMedSci
Professor of Molecular Medicine, University of Edinburgh
Professor Seckl undertakes research into the glucocorticoid hypothesis of ageing. This has led to the discovery that drugs that reduce brain sensitivity to glucocorticoids protect against cognitive ageing in brain cells *in vitro* and *in vivo* in ageing rodents and, for the latter, in humans. Professor Seckl was also responsible for the glucocorticoid hypothesis of 'foetal programming' and for characterising cyp7b as a brain-enriched enzyme responsible for activating neurosteroids for neuroprotection with ageing. The approaches taken by Professor Seckl's laboratory span molecular and cellular biology, *in vivo* models and into detailed human investigation. He has additional interests in how peripheral steroid biology affects metabolic, cardiovascular and brain (cognitive and neuroendocrine) function. Professor Seckl led the bid for the 'Centre for the Study

of the Ageing Brain', an interdisciplinary collaboration of experts from across the medical sciences addressing central nervous system ageing and its disorders, which received Scottish Governmental funding; this then led to a series of other major awards in collaboration with colleagues.

Professor Adam Sillito FMedSci
Professor of Visual Sciences, Institute of Ophthalmology University College London
Professor Sillito began his career in the Department of Physiology at the University of Birmingham, during which he also worked at Johns Hopkins University in the USA on a Sir Henry Wellcome Travelling Fellowship. In the early 1980s he moved to the University College Cardiff to become Professor and Head of Physiology. He then moved to become Head of Visual Science at the Institute of Ophthalmology, of which he was then Director from 1990-2005.

Other previous positions include a non-executive directorship of the Moorfields Eye Hospital NHS and Foundation Trust and membership of the Moorfields Eye Hospital Board. He was a Founding Fellow of the Academy of Medical Sciences and a Founding Member of the European Visual Institute. His research focuses on the neural mechanisms in visual processing, the role of feedback systems in sensory processing, and synaptic and pharmacological microcircuitry.

Professor Raymond Tallis FMedSci
Emeritus Professor, University of Manchester
Professor Tallis was Professor of Geriatric Medicine at the University of Manchester until 2006. His major research interests are neurological rehabilitation, stroke and epilepsy in older people. In 2004 he co-authored the Academy of Medical Sciences report 'Restoring neurological function: putting the neurosciences to work in neurorehabilitation'. In 2007 he was awarded the British Society for Research on Ageing Lord Cohen of Birkenhead Gold Medal for outstanding contribution to Research on Ageing.

Professor Andrew Wyllie FRS FRSE FMedSci
Professor of Pathology and Head of the Department of Pathology, University of Cambridge
Professor Wyllie is a Scottish pathologist. In 1972, while working with electron microscopes at the University of Aberdeen, he realised the significance of natural cell death. He and his colleagues Professor John Kerr and Professor Alastair Currie called this process apoptosis, from the use of this word in an ancient Greek poem to mean 'falling off' (like leaves falling from a tree). His works have contributed to the understanding of apoptosis in health and in disease, and he continues to lecture to undergraduate medical and natural sciences students in Cambridge today.

He was made a Fellow of the Royal Society in 1995 and was a Founding Fellow of the Academy of Medical Sciences. He has received several awards including the Bertner Award in 1994, the Hans Bloemendal Award in 1998 and the Gairdner Foundation International Award in 1999.

Observers

Professor David Armstrong CBE
Professor of Medicine and Sociology, Department of General Practice and Primary Care, King's College London

Dr George Sarna (until summer 2008)
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Dr Janet Valentine (from Summer 2008)
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Mr Laurie Smith
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We also thank all other Academy current and former staff including Mrs Mary Manning, Dr Helen Munn, Dr Rachel Quinn, Nick Hillier, Dr Suzanne Candy, Dr Robert Frost and Ellie Pond for providing advice and assistance throughout the study.

Review group

This report was reviewed by a sub-committee of the Academy of Medical Sciences' Council. Reviewers were invited to consider whether the report met its terms of reference and whether the evidence and arguments presented in the report were sound and supported the conclusions. Members participated in a personal capacity and not on behalf of their affiliated organisations.

Professor Ronald Laskey FRS FMedSci (Chair)
Honorary Director of the MRC Cancer Cell Unit, University of Cambridge

Professor John Aggleton FMedSci
Professor of Cognitive Neurosciences, Cardiff University

Professor John Connell FMedSci
Professor of Endocrinology, University of Glasgow

Dr Robin Lovell-Badge FRS FMedSci
Head of the Division of Developmental Genetics, National Institute for Medical Research

Professor Veronica van Heyningen FRS FRSE FMedSci
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Dr Jonathan Reeve FMedSci
Professor Kenneth Rockwood
Professor Peter Rothwell FMedSci
Professor Kent Woods FMedSci

Annex II: Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AMD	Age-related macular degeneration
ATP	Adenosine triphosphate
BBSRC	Biotechnology and Biosciences Research Council
CDKN2a	Cyclin kinase dependent inhibitor 2a
CFH	Complement factor H
CVD	Cardiovascular disease
DEXA	Dual X-ray absorbimetry
ELSA	English Longitudinal Study on Ageing
EPIC	European Propsective Investigation of Cancer'.
EPSRC	Engineering and Physical Sciences Research Council
ESRC	Economic and Social Research Council
GPRD	General Practice Research Database
GWAS	Genome-wide association studies
IAH	Institute for Ageing and Health (University of Newcastle upon Tyne)
IGF-1	Insulin-like growth factor 1
IMI	Innovative Medicines Initiative
MHRA	Medicines and Healthcare products Regulatory Authority
MRC	Medical Research Council
MRI	Magnetic resonance imaging
NIHR	National Institute of Health Research
OSCHR	Office for the Strategic Coordination of Health Research
RCUK	Research Councils UK
RDA	Regional Development Agency
SOD	Superoxide dismutase
TOR	Target of rapamycin
TSB	Technology Strategy Board
XCAR	Cross-Council Committee for Ageing Research

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