Section 1

Background to ageing and demographics

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Chapter 1

Ageing: what is it and why does it happen?

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Introduction

The world faces unprecedented challenges and opportunities from an ageing population. In health care, this is resulting in a transition from the dominance of acute illnesses and infections to that of chronic and degenerative conditions. Clinical recognition of this is hardly new. Hippocrates noted common age-associated medical conditions and Aristotle even offered a theory of ageing based on loss of heat. Remarkably, our current concepts of ageing are also bound up with combustion – cellular respiration. The emergence of old age as the focus of a medical specialty was prompted by the growth of older populations living in urban poverty in Paris[1] and, later, New York and London. Now that the expectation of growing old is commonplace in developed countries and is very rapidly spreading worldwide, it is beginning to influence attitudes and behaviour throughout life. In this chapter we address briefly several issues.

- What is population ageing, and why and how does it occur?
- The genetics and evolution of ageing – has ageing evolved?
- What distinguishes ageing from disease?
- What are the cellular and molecular processes involved with ageing of somatic cells?
- How do germ cells differ from somatic cells?
- How does menopause fit in with evolution of ageing?

Population ageing – why and how?

The demographic transition

The transition from populations with a great preponderance of the young into the current pattern typical of developed countries can be understood as a series of stages. The classic pattern of this demographic transition starts from a steady-state 'young' population with typically high fertility rates and high mortality rates throughout the lifespan. Only a minority of individuals reach old age, so the population shape has a broad base and narrow apex, like a pyramid. The first change is a decline in death rates, particularly in infancy. For example, deaths occurring under the age of 5 years, as a proportion of all deaths occurring in England and Wales, fell from 37% in 1901 to 0.6% by 2000 and, during the same period, death after the age of 75 years rose from

12% to 64%.[2] As a result, a male born in England and Wales in 2006 is estimated to have a 91% chance of reaching age 65 years and a female a 94% chance. The resultant changes in life expectancy since the mid-19th century are shown in Table 1.1. Thus, there are more people from the broad base, the young, that survive into older age. At this stage, the fertility rate remains high. The pyramid retains the broad base but with a wider apex, the population grows and the proportion and absolute numbers of older people increase. Subsequently, fertility rates decline. In England and Wales, for example, the fertility rate remained at over four per woman for the two centuries from 1700 until nearly the start of the 20th century,[3] before falling below two per woman by the 1930s, the rate which currently remains.[4] As a result, the pyramid base narrows and begins to resemble the shape of a broad pillar. Mortality rates continue to decline, so the proportion of older people rises further. However, as the smaller birth cohorts work through, many decades later the absolute numbers of older people may fall again. In this classic model, the new steady state has a higher overall population but lower fertility rates and low death rates throughout the lifespan until advanced ages, and radically changed relative proportions of different age groups.

There are, of course, numerous factors that modify this pattern. The post-World War II 'baby boom' is one example. Most members of this much larger birth cohort are surviving into older age, producing the current rapid rise in the numbers and proportion of older people in the UK. They will be followed by smaller cohorts and therefore there will be a dramatic reduction in the proportion of adults of working age (Figure 1.1). In recent decades, these trends have been further exaggerated by significant improvements in life expectancy for people having already reaching age 65 years, an increase of nearly 4 years for men and women since 1981 (Figure 1.2). In 2008, for the first time, there were more pensioners in the UK than those aged under 16 years. In addition, significant variation exists. The extremes of life expectancy in the UK in 2007 are 83.7 years for residents of Kensington and Chelsea (London) and 70.8 years for their fellow citizens in Glasgow (Scotland). Most of the difference is explicable by socio-economic factors, operating throughout the lifespan.

Worldwide, the most notable variation in this demographic transition is the speed at which it occurs. Demographers encapsulate the rate of population ageing by estimating the years taken for a doubling from 7% to 14% of the number of people aged 65 years or over as a proportion of the total population. In early industrialised European countries, this was typically in the region of 50 years or more. In contrast, this takes about half that time or less in the later developing countries; for example, 21 years from 2011 to 2032 is the current estimate for Brazil.

Table 1.1 Expectation of life at birth for England and Wales, 1838–54 to 2008; data from the Office for National Statistics[32,33]

Year(s)	Males	Females
1838–54	40	42
1901–10	49	52
1950–52	66	72
2007	77	81
2008 (estimate)	76.37	81.46

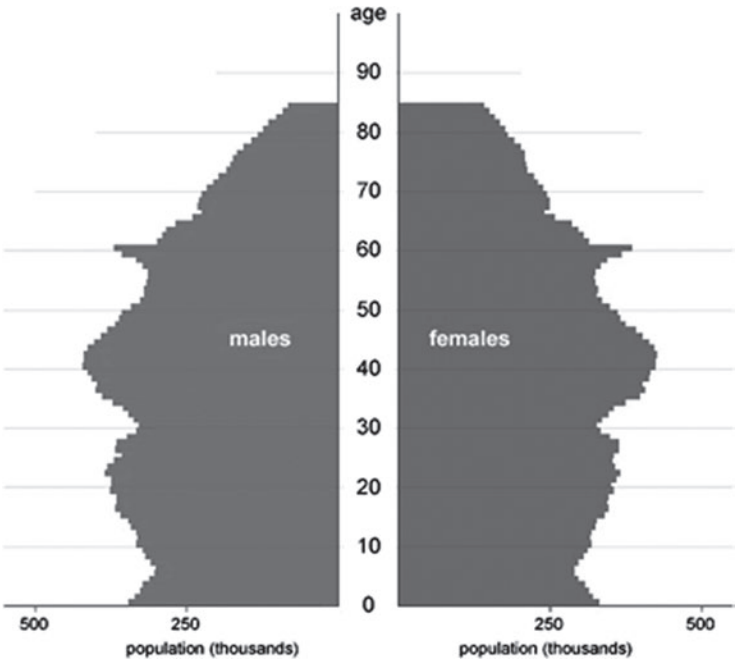

Figure 1.1 Age structure of England and Wales, mid-2007; data from the Office for National Statistics[4]

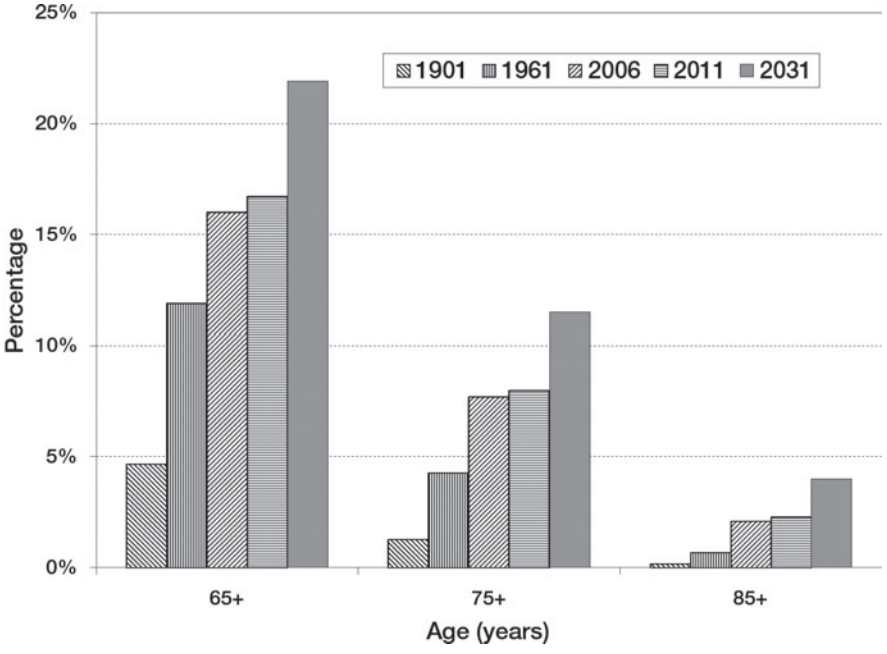

Figure 1.2 Population ageing in England and Wales from 1901 to 1961[34] and projections from 2006 to 2031[35]; data from House magazine[34] and the Government Actuary's Department[35]

Why have mortality rates declined?

The reduction in mortality rates is largely a story of improved public health through increasing availability of clean water, sanitation and adequate foods at key life stages, and through reductions of accidental deaths. Healthier cohorts, related to better gestational nutrition, is a possible mechanism for the continuing improvements in life expectancy as low birth weight is associated with higher rates and earlier onset of cardiovascular diseases, diabetes and hypertension.[5] Post-war improvements in housing, welfare and medical care during old age have also contributed significantly towards the end of this period of transition. The decline in fertility follows falls in mortality rates for socio-economic and cultural reasons, and these may be changing further in modern society.

Implications of ageing populations on the health of older people

The dramatic survival changes in recent decades have prompted debate in the gerontological literature on whether the added years of life would be characterised by increasing age-related disability or whether, conversely, there would also be a delay of the average age of onset of disabling conditions. This idea has been termed the compression of morbidity.[6] Various possible scenarios exist. There may be an increase in the survival rates of sick people, which would result in longer periods of morbidity for individuals and an increased population prevalence of disability. Social and medical advances may control the progression of chronic diseases, thus delaying death but not necessarily the disability resulting from these conditions. Improvement of the health status of new cohorts of older people, associated with more advantageous early life experiences (and perhaps improved health behaviours) would perhaps result in a compression of morbidity. Finally, if age-related frailty is an inevitable development in the absence of specific diseases, there would be the emergence of very old and frail populations, which would result in expansion of morbidity. It is probable that all these factors are operating currently, so projections of healthy life expectancy become problematic. However, evidence from the UK suggests that only about half of the extension of life expectancy for older people in the past two decades has been extra life in good health.

The genetics and evolution of ageing

When low death rates are followed by a sharp acceleration at a stage we have come to regard as 'old age', it produces a rectangularisation of the life survival curve (Figure 1.3). If death occurred randomly from birth onwards, with age (time since birth) playing no part in the likelihood of death, the result would be a life survival curve with an exponential shape. Something like this has probably been the majority situation during animal life on earth. The rectangularisation suggests that we are now observing a 'natural life span', as a result of species-specific longevity. Only in later phases of animal evolution, most particularly with primates and domesticated or farmed animals, have we seen this rectangularisation and thus confronted ageing as a significant issue.

Not all organisms age. A single-cell organism such as *Escherichia coli* reproduces by division without having undergone the range of ageing changes seen in multicellular organisms. As more complex life forms have evolved, ageing has appeared. Although an estimated two-thirds of the genome have some effect on ageing changes, a number of factors point to the central role of relatively few genes in the determination of

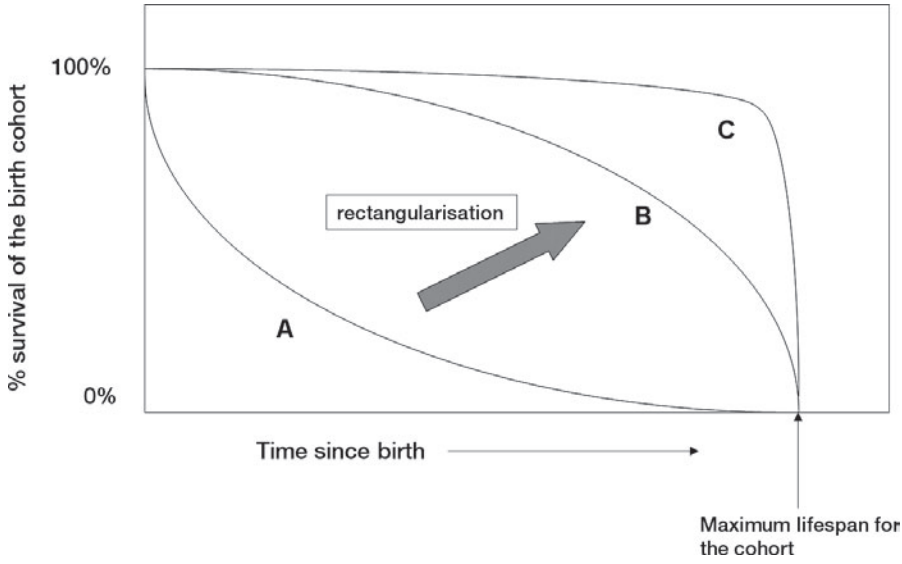

Figure 1.3 Different patterns of cohort ageing: **A** represents the survival curve for most animals in the wild, with time since birth having little or no influence on death rate; **B** is the survival curve pattern for domesticated animals and human populations that is typical of developed countries in recent centuries, with time since birth influencing death rate but still with many 'premature' deaths; **C** is the idealised survival curve to represent ageing societies, with most individuals reaching old age before death; this is typical of current developed countries

the maximum lifespan. Longevity is species specific and closely related species with substantial genetic similarity can have markedly different longevity if their natural habitat or habitus differ. Fast-ageing 'progeria' syndromes such as Werner syndrome, which is due to genetic mutation, produces a dramatic and visible acceleration of ageing, with life expectancy of about 40 years, but the genetic change is sufficiently specific not to prevent normal intrauterine development and infancy. We know from these genetically based fast-ageing syndromes and from animal studies that there are multiple genes that can adversely affect ageing. However, while genes may be powerful agents of maximum potential, it is important to note that twin studies suggest that only about 25% of the explanation for long-lived families is genetic.[7] The rest is due to shared environmental exposures.

Has ageing evolved?

Most animals in the wild, like humans until a few hundred years ago, live no more than 50% of their potential lifespan. This maximum potential survival was thus achieved by inheritance through the reproduction of relatively young animals and not as a result of selective survival and successful reproduction of long-lived animals. In this sense, the maximum potential lifespan has exerted little or no direct evolutionary pressure. On the contrary, it must have developed as an indirect result of evolutionary pressures on other characteristics. To put it another way, natural selection has favoured genotypes that produce (i) fitness to successfully reproduce during young adulthood and (ii) a phenotype that ages and has a maximum lifespan built in. Ageing has thus not evolved

'for itself' but as a consequence of other characteristics being preferentially selected under evolutionary pressures.

Central to understanding this dichotomy is the fact that tissues in multicellular animals show specialisation, with separation of the tissues concerned with maintaining life now (the soma) from the tissues concerned with propagation of the species through inheritance (the germ line). The biological activity resulting in the molecular, cellular and tissue 'ageing' changes described below may sooner or later impair cellular or organ function and survival. There is thus evolutionary pressure to develop ways of preventing or overcoming these deleterious changes but only in so far as they impede the fitness of the animal. In evolutionary terms, the fitness of an animal is its ability to produce offspring. When the risk of 'premature' death is high, this means producing viable offspring soon after reaching maturity. In conditions of finite environmental resources such as food, the evolution of form and function capable of reaching this fitness involves a number of compromises in the best use of biological energy. In Kirkwood's 'disposable soma' theory, the separation of the germ line from other cells in the body has allowed the selection of mechanisms for specific accurate preservation of the germ line but at the expense of the biological adaptability needed to preserve the soma.[8] Since the soma and the genetic material in the cells of the soma are not available for inheritance, preserving them for immortality in the face of inevitable death through predation, accident or deprivation would be energy wasted.

Development, ageing and disease

The stages of the lifespan of mammals can be distinguished as (i) fertilisation and birth, (ii) infancy to sexual maturity and (iii) adult reproductive life through to death, which may include a distinct post-reproductive phase. The molecular changes that are commonly regarded as ageing, and which will be described below in more detail, do not begin at a defined stage but seem to develop gradually. There is no evidence of an overall switch or controlling clock governing the pace of changes observed over time in various cells, tissues and physiological systems. The leading biogerontologist Strehler[9] proposed that the term 'ageing' should be reserved for those changes that occur gradually and universally, that are intrinsic in origin and that are detrimental to life. Universality must allow for some variability between members of a species. To show that biological changes are gradual is challenging. Most natural phenomena exhibit episodic changes, even if underlying processes are gradual. Life consists of an organism's biological interaction with the environment, so 'intrinsic' can only sensibly imply that the changes do not depend upon particular non-essential environmental factors. Below, we discuss some of these changes that could credibly contribute to death or disease but the relationship for others is not established. If we therefore limit the term 'ageing' to those changes for which such causality has been established, we would have a severely restricting definition. The current consensus in biological gerontology is to view ageing as those changes that deviate from the state presumed to be advantageous at the stage of optimal reproductive capacity. This makes sense from an evolutionary viewpoint.

Employing this broader approach to ageing, Rowe and Khan[10] drew attention to the difference between those older people without apparent disease and who remain independent until sudden death at advanced age and those people who clearly suffer one or a series of potentially avoidable degenerative or involutional diseases resulting in frailty and dependency. Both groups must surely be subject to degrees of ageing change: the difference is the result of the complex and cumulative interaction

between genes, ageing-related molecular damage and environmental factors. The simple view that we can strictly distinguish degenerative diseases from ageing is no longer tenable.

Ageing of the soma – cellular and molecular processes

At the molecular level, it is clear that damage to all cellular components accumulates with increasing age. Some of these changes occur whether in the test tube or in the living cell; for example, the progressive increase in cross-links between the strands in a collagen molecule. Others occur as a product of biological activity, such as cell division. Recent findings have supported integration of the long-standing and apparently conflicting theories that favoured either programmed ageing or wear and tear as the underlying explanations.

Of central importance in current thinking is the integrity of DNA. This macromolecule is inherently unstable. Spontaneous changes include base alteration and single-strand or double-strand breaks and are seen at increasing rates with ageing.[11] Added to this is damage caused by deleterious agents, such as reactive oxygen species (ROS). The most common ROS in mammals are the superoxide anion, hydrogen peroxide, the hydroxyl radical and the nitric oxide radical. They arise from a variety of sources, primarily the mitochondria that form superoxide free radical anions alongside ATP in the vital process of oxidative phosphorylation. Other sources of ROS include the macrophages, particularly during chronic infections, the peroxisomes involved in lipid degradation and cytochrome P450 involved in drug detoxification.

Interaction of ROS with DNA, both mitochondrial and nuclear, can result in breaks in the sugar–phosphate backbone, resulting in mutations or deletions. A variety of effects may result, including transformation into an immortal cell line – a step on the route to a neoplastic tumour. The outcome of ROS-induced damage in the vascular system endothelial cells is production of adhesion molecules by dying cells that attract neutrophils and macrophages in a local inflammatory reaction releasing hydrogen peroxide. This additional ROS load further damages the compromised cell as well as the extracellular matrix and surrounding cells, resulting in a cascade of oxidative stress.[12,]

The free radical theory of ageing based on ROS-induced damage has received more attention than any other aspect of biogerontology. Although an attractive rationale for somatic ageing, not to mention the basis for a large industry promoting antioxidants, its prominence as the cause of ageing is now being questioned. Although ROS are estimated to 'hit' genomic DNA around 10 000 times each day, it seems that these random events are usually balanced by effective DNA repair enzymes, which are largely able to negate the negative consequences of damage.[13] Furthermore, interventions to modify antioxidant activity, such as studies using transgenic mice adapted to enhance the exogenous antioxidants superoxide dismutase and catalase, have not shown improvements in life expectancy.[14] Although epidemiological studies on humans have suggested a protective effect of a high dietary intake of antioxidants against visual cataract, memory loss and vascular damage, prospective clinical trials have been largely negative. Nevertheless, oxidative stress is still an important avenue for research into specific age-related disease states such as neurodegeneration and cardiovascular disease.

However, the importance of effective DNA maintenance remains and is illustrated by the fast-ageing progeria syndromes. People with Werner syndrome display damaged DNA due to lack of helicase required for DNA repair and mRNA formation. In

Hutchinson–Gilford progeria syndrome, DNA replication does not take place, owing to alterations in the nuclear envelope. In both cases, rapid progression to an aged phenotype results in extremely premature death from ostensibly 'old-age' related disorders.

The effectiveness of DNA repair correlates reasonably well with species lifespan. Short-lived mammals such as the mouse and shrew have around one-fifth the rate of DNA repair compared with humans. According to the disposable soma theory, evolution has favoured strategies that devote energy and resources to enable the soma to attain reproductive fitness with the germ line safe from damage. There are indeed several features evident in the germ cell line, for example the ovary, that may result in enhanced protection for the genetic material compared with those present in the cells of other tissues. It would be expected from this theory that the cellular mechanisms to protect the soma from damage would be better developed in species likely to live longer. Thus, those adapted to their environment in such a way as to experience a lower rate of predatory or accidental deaths, for example primates, would differ in their anti-ageing mechanisms from species demonstrating an almost exponential survival curve such as the mouse. In neither case then would the effects of ageing be prominent. Available evidence confirms this prediction.[15]

Cell senescence and loss of telomeres

Two particular aspects of DNA damage have received much attention over the past decade: loss of telomeric ends of nuclear DNA and mutations to mitochondrial DNA. In the early 1960s, Hayflick and Moorhead[16] made the observation that cells in culture could undergo only a limited number of cell divisions (subsequently termed the 'Hayflick limit'). Further research showed that cultured fibroblasts from old donors could undergo fewer cell divisions than those from young donors, that cells frozen for extended periods could 'remember' how many divisions they had left and, more recently, that senescent cells that had stopped dividing could be identified *in vivo*. These studies, and others, pointed to a biological clock capable of counting the number of cell divisions and whose possible function was to prevent cancer, allowing the animal to reach healthy reproductive maturity, with the trade-off being limited cellular replication. The site of this clock is now largely held to be the telomere end regions of DNA, the repeat sequences of nuclear DNA that cap both ends of chromosomes and that shorten with each cell division. Telomeres are particularly vulnerable to free radical attack because they contain a short region of single-strand DNA and have few specific repair enzymes in the majority of somatic cells. People with Werner syndrome demonstrate shortened telomeres.[17]

In addition to free radical damage, portions of telomeres are lost during normal DNA replication and after several cell divisions (around 100 in humans) the telomere is eroded to such an extent that the cell enters replicative senescence and is no longer able to divide. This process is speeded up either by high exposure to oxidative stress or in rapidly dividing cells such as lymphocytes in response to infection or vascular endothelium in response to damage. Detection of senescent cells *in vivo* poses technical difficulties but studies have implicated them in the cornea, blood vessels and skin. It is suggested that senescent cells have a role in tissue ageing because of the limited regenerative potential of tissues containing large numbers of senescent cells. This would be important for cells with a naturally high turnover, such as the immune system, and in response to damage, such as in turbulent or branched regions of the vascular system and skin or eye wounding; evidence is accumulating that this holds true.[18.]