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The biology of ageing

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INTRODUCTION

Although human ageing has many dimensions, at its heart it is a biological process that we share with a very broad range of animal species. If we are to understand ageing we must therefore comprehend at least the broad principles of its biology, since these provide the fundamental matrix upon which social and other factors are based. There is a particular importance in addressing the biology of ageing now, at a time when many preconceptions about the ageing process, such as that it is an essentially fixed, ineluctable part of our biological make-up, are being challenged. This challenge is coming from two directions. First, the continuing increases in life expectancy (Oeppen and Vaupel, 2002) show that – contrary to all predictions – life expectancy has not settled at some ceiling imposed by genetic programming. Second, new biological understanding of the basic mechanisms of ageing reveal that the process is intrinsically more malleable than most of us have yet appreciated (Kirkwood, 2005).

In this chapter we make a brief survey of some of the key features of the biology of ageing, looking at why and how we age, at the blend between genetic and non-genetic factors influencing longevity, and at the relationship between normal ageing and disease. We conclude with a brief discussion of the implications of these features for the future of human ageing.

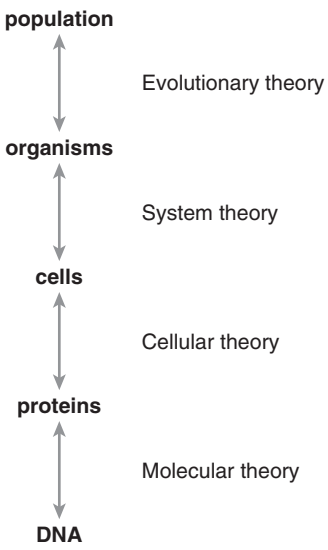


Figure 2.1 Ageing needs to be understood at a hierarchy of biological levels

From a biological perspective ageing is extremely complicated, affecting the functions of the body at all levels, from molecules to populations (see Figure 2.1). In order to understand ageing, its effects at all of these levels need to be understood.

WHY DO WE AGE?

Our species adapts to its environment. This notion not only underlies the brilliant insights of nineteenth-century Darwinian thinking, which have shaped our knowledge of why we are as we are, but it is an ongoing reality that can be observed in current populations around the world. Climates in polar and tropical regions are very different, and the people who survive there have adapted to those extreme environments. Tens of thousands of years and thousands of generations have passed since *Homo sapiens* emerged as a species in the middle of Africa and began its migration to the rest of the world. The mechanism underlying this success has been the continual drive, underpinned by natural selection, to survive even under the most adverse of conditions.

From the Darwinian point of view we have no difficulty in understanding the biology of birth, development and reproduction. However, it is much harder to understand the later end of the lifespan – why we become frail, diseased and more likely to die as we grow older (see Figure 2.2). Is such deterioration necessary, is

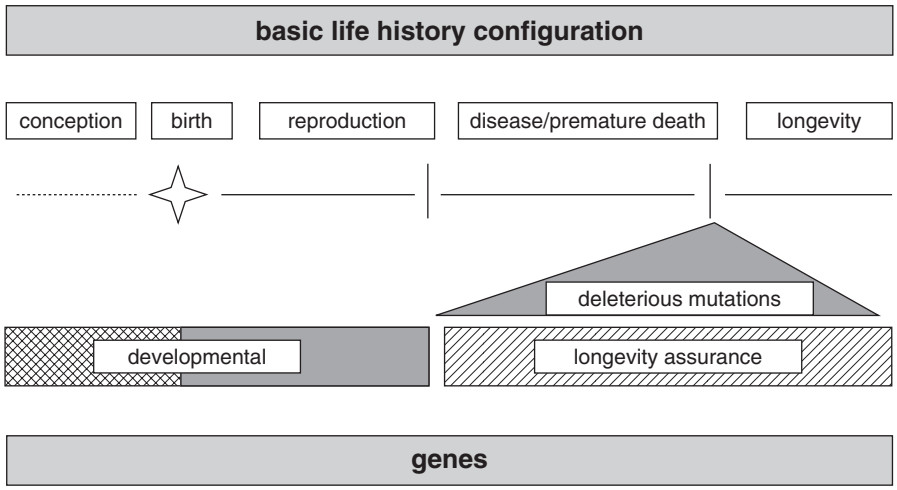


Figure 2.2 Genetic architecture of the human life history

it inevitable? For example, why do we become less able to get around, more likely to fall, and more likely to die from the post-operative complications of a hip fracture? What is it about the passage of time that renders older cells and organs more vulnerable to disease? Can the clues to these puzzles be found in the context of our adaptation to the environment?

The idea that natural selection has played its part in shaping our ageing process is reinforced by the evidence that ageing and longevity are influenced by genes (Finch and Tanzi, 1997). First, the lifespans of human monozygotic twin pairs are statistically more similar than lifespans of dizygotic twins, pointing clearly to a role for genetics. Second, there are significant differences in lifespan between different genetically inbred strains of any given laboratory animal, such as the mouse. Third, studies of simple organisms like fruit flies, nematode worms and yeast have identified gene mutations that affect duration of life. However, although genes influence longevity, it has also been shown that genes account for only about 25% of the variance in human lifespan (Finch and Tanzi, 1997; Cournil and Kirkwood, 2001). We need to look rather carefully at the evolutionary logic that might have shaped the genetic component of ageing, weak as it is.

Lack of an evolutionary programme for ageing

Many adhere to the view, often implicitly assumed, that ageing and death are simply the terminal phase of the developmental process, driven by genes like early development. If pressed to explain why it should be so, this notion is often justified on the grounds that ageing evolved as some kind of evolutionary necessity – to clear

older generations out of the way as a form of inbuilt population control. However, there is in fact scant evidence that ageing plays such a role in nature, or that such an evolutionary pressure could have worked. The reason is simple. Animals in nature die young. Only rarely do they survive long enough to reveal significant ageing. Out of a population of newborn wild mice, for example, nine out of ten of them will be dead before 10 months even though half of the same animals reared in captivity would still be alive at 2 years (Austad, 1997). Thus, ageing in mice is seen only in protected environments, and a similar statement would have applied to primitive human populations, before the advent of civilisation.

Based on the lack of an evolutionary need or opportunity to evolve genes for ageing, we are required to look elsewhere than strict genetic programming for an understanding of the genetic contribution to ageing and longevity.

Genes with late deleterious effects

The first evolutionary scenario that is not founded on the idea of a programme explained ageing through the accumulation of late-acting deleterious germ-line mutations. Medawar (1952) reasoned that mutations with late age-specific effects are subject to weaker selection than mutations with early age-specific effects, since the proportion of individuals alive must decline with increasing age *even if there is no intrinsic increase in the tendency to die*. Phrased otherwise, mortality due to extrinsic causes is a sufficient explanation why only a small proportion of the original birth cohort survives until older age. Thus, in the course of evolution there has been the opportunity for random accumulation of late-acting deleterious mutations in the genome. In humans, the theory suggests, these deleterious genes have become apparent in developed countries at a time when mortality at young age has largely disappeared, and large proportions of the population do survive up to ages far beyond those that would have been common among our ancestors. This is the so-called 'demographic transition'. As an example of a gene with a late-acting deleterious effect, Medawar cited the case of the gene for Huntington's chorea, a genetically induced fatal neurodegenerative condition which does not usually become apparent until a person is past reproductive age, putting the gene effectively beyond the reach of natural selection. Medawar's concept is now known as the 'mutation accumulation' theory.

A second scenario, suggested by Williams (1957), is also founded on the idea of late deleterious gene effects but introduces the idea of trade-offs. A gene with a beneficial effect on fitness early in life would be selected for, even if the same gene produced detrimental effects on fitness late in life. As an example, Williams cited a hypothetical gene regulating calcium deposition which might favour bone growth during development but lead to calcification of the arteries in later life. Williams' concept is now known as 'antagonistic pleiotropy' (pleiotropy referring to the property of a gene that has different effects in different contexts). Another example is that heterozygote carriers of the cystic fibrosis gene have a selective

advantage of resistance to cholera but render the carriers at risk of disabling pulmonary and gastrointestinal disease later in life (Gabriel *et al*. 1994)

Although the mutation accumulation and antagonistic pleiotropy concepts have played an important role in shaping evolutionary thinking about ageing, tests of the actions of mutation accumulation have largely proved negative (Kirkwood and Austad, 2000), while verified instances of individual genes with antagonistically pleiotropic effects remain few in number (Leroi *et al*., 2005).

The disposable soma theory

Another approach to explaining evolution of ageing comes from considering the logic of how much organisms should be expected to invest in maintenance and repair systems that underpin bodily survival. In spite of a formidable array of survival mechanisms, most species appear not to be programmed well enough to last indefinitely. The key to understanding why this should be so, and what governs how long a survival period should be catered for, comes from looking once more at the data from survival patterns in wild populations. If 90% of wild mice are dead by 10 months, any investment in programming for survival much beyond this point can benefit at most 10% of the population. This immediately suggests that there will be little evolutionary advantage in programming long-term survival capacity into a mouse. The argument is further strengthened when we observe that nearly all of the survival mechanisms required by the mouse to combat intrinsic deterioration (DNA damage, protein oxidation, etc.) require metabolic resources. Metabolic resources are scarce, as evidenced by the fact that the major cause of mortality for wild mice is cold due to insufficient energy to maintain body temperature. From a Darwinian point of view, the mouse will benefit more from investing any spare resource into thermogenesis or reproduction than into better DNA repair capacity than it needs.

This concept, with its explicit focus on evolution of optimal levels of cell maintenance, is termed the ‘disposable soma theory’ (Kirkwood, 1977, 1997). In essence, the investments in durability and maintenance of somatic (non-reproductive) tissues are predicted to be sufficient to keep the body in good repair through the normal expectation of life in the wild environment, with some measure of reserve capacity. Thus, it makes sense that mice (with 90% mortality by 10 months) have intrinsic lifespans of around three years, while humans (who probably experienced something like 90% mortality by age 50 in our ancestral environment) have intrinsic lifespans limited to about 100 years. The distinction between somatic and reproductive tissues is important because the reproductive cell lineage, or germ line, must be maintained at a level that preserves viability across the generations, whereas the soma needs only to support the survival of a single generation. As far as is known, all species that have a clear distinction between soma and germ line undergo somatic senescence while animals that do not show senescence, such as the freshwater Hydra, have germ cells distributed throughout their structure (Martinez, 1998).

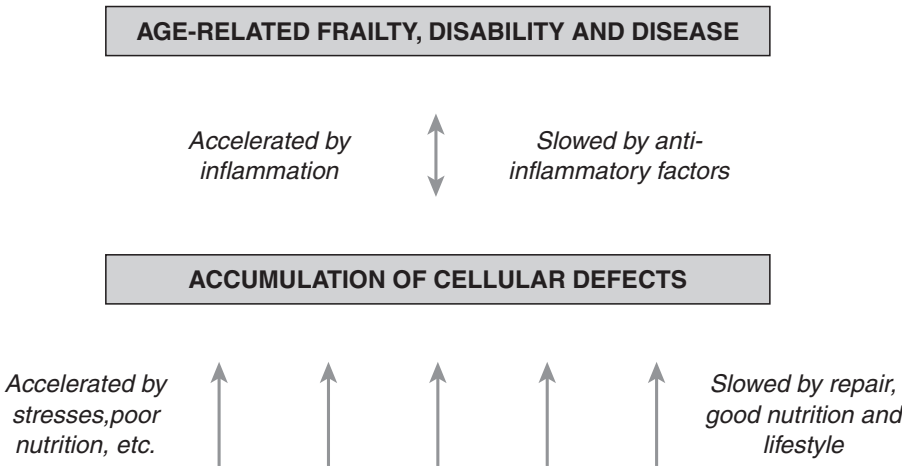


Figure 2.3 Molecular damage and ageing

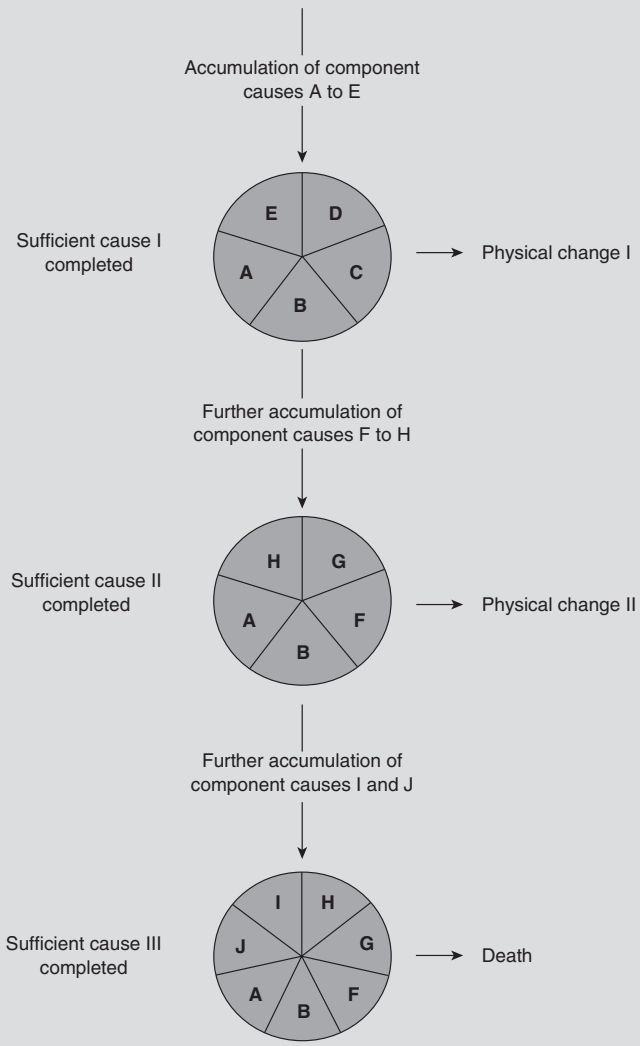
HOW AGEING IS CAUSED

The evolutionary explanation of ageing, particularly in the form of the disposable soma theory, provides a bridge between understanding not only why ageing occurs but also how ageing is caused in molecular and cellular terms. In essence, it predicts that ageing is nothing more nor less than the gradual, lifelong accumulation of subtle faults in the cells and organs of the body. These faults, as we shall see in a later section, arise from many causes and affect many targets. Faults arise on a continual basis and most are put right. However, since there has been insufficient selection to evolve higher efficiency of repair, some slip through the net. Thus, although the driving force in ageing is the accumulation of damage, genetic regulation plays its part through evolving how hard the brakes are put on this accumulation by investing effort in maintenance and repair.

The defects that cause ageing start to arise very early in life, probably even *in utero*, but in the early years both the fraction of affected cells and the average burden of damage per affected cell are low. However, over time the faults increase, resulting eventually in age-related functional impairment of tissues and organs (see Figure 2.3). This view of the ageing process makes clear the life-course nature of the underlying mechanisms. Ageing is a continuous process, starting early and developing gradually, instead of being a distinct phase that begins in middle to late life. The view also helps us to re-examine the sometimes controversial relationship between 'normal ageing' and age-related disease (see Box 2.1).

Box 2.1 Understanding the complex causes of normal ageing and its intrinsic variability

A key question in the life science perspective on ageing is whether it is meaningful to think of a 'normal' ageing process, as distinct from the collection of age-related disorders and diseases with which the conventional medical model has been primarily concerned. We examine this question in the light of the distinction between 'component causes' and 'sufficient causes' as originally developed by Rothman (1976). Here, we apply the distinction between component and sufficient causes to describe the ageing process (Izaaks and Westendorp, 2003).



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A cause is defined by Rothman as an event or a state of nature that initiates or permits a sequence of events, which results in an effect. A cause is considered 'sufficient' if it inevitably produces the effect. However, most causes of relevance in medicine are not sufficient but are merely 'components' of a sufficient cause. A component cause thus reflects what is commonly called a risk factor. The principle is that a specific combination of component causes must be present before a sufficient cause is assembled, resulting in an 'effect' or physical change (see figure first circle).

A particular effect can be caused by different combinations of component causes. Each combination of component causes then constitutes a different sufficient cause. For example, the combination of hypertension, smoking, hypercholesterolaemia, sedentary lifestyle and family predisposition is a sufficient cause of atherosclerosis. Another sufficient cause, however, might be the combination of hypertension, hypercholesterolaemia, stress, inflammation and family predisposition. These different sufficient causes of atherosclerosis have some components in common – hypertension and family predisposition – but have other components that are different. On the other hand, sometimes the same component cause may contribute to different sufficient causes, resulting in different effects. When this happens, it is found that different diseases share the same risk factors. For example, smoking is a component cause not only of atherosclerosis but also of lung cancer. It is the specific combination with other component causes that determines which effect becomes manifest.

When a component cause is present, some of the other component causes that are necessary to complete a sufficient cause may be lacking. However, over time the missing component causes can develop, and the completion of a sufficient cause will then result in a physical change. It is this gradual accumulation of component causes over a lifetime that provides a model to understand the physical changes that occur with ageing. The more component causes that have accumulated during life, the more sufficient causes will be completed, and the more effects (physical changes) seen (see figure). Since there may often be an element of chance in the occurrence of specific component causes, this model helps us to understand the diversity of the physical manifestations of ageing, even though the body may be susceptible to the same set of component causes being triggered.

Death from old age can be explained by similar reasoning. Death is an effect that has several sufficient causes. Since their pathophysiology is complex, each of the sufficient causes of death consists of a large number of component causes. At puberty, when mortality risk is lowest, only a few component causes are present. With increasing age, more component causes will have accumulated. The sufficient causes that together constitute the different potential causes of death are built up step by step throughout life. Every new component cause increases the chance that one of the sufficient causes is completed. This model, which has some formal similarity with the ideas of reliability engineering in the mechanical sciences, explains the increased mortality risk in advanced age that is the hallmark of ageing.

Some older people are characterised by frailty, with a high risk of becoming dependent or of dying. People who are frail have a reduced reserve capacity because many physiological functions decline with increasing age. In this situation, one single factor can trigger a cascade of events leading to a deterioration of physical functions and eventually death. For example, if an older person becomes bedridden due to a femoral fracture, the disease course may

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subsequently be complicated by a urinary tract infection and a delirium, followed by, pressure ulcers, septicaemia and finally by death. The cascade of adverse events occurs easily because a frail older person may have numerous almost-complete sufficient causes, with several of these almost-complete sufficient causes having missing components in common. In these circumstances, the development of a new component cause may complete a number of sufficient causes, so that several events occur together. Furthermore, the first sufficient cause to be completed may initiate an event that is itself a component cause of another almost-complete sufficient cause. Thus a run of events may follow each other in a kind of 'domino-effect' process.

In a clinical context, it often makes sense to try to draw a distinction between normal ageing and disease, since this may have implications for treatment. However, if our aim is to understand the mechanisms responsible for age-related conditions, such a distinction can obscure what is really going on. The majority of chronic, degenerative conditions, such as dementia, osteoporosis and osteoarthritis, involve the progressive accumulation of specific types of cellular and molecular lesions. Since the ageing process, as we have seen, is caused by the general accumulation of such lesions, there may be much greater overlap between the causative pathways leading to normal ageing and age-related diseases than has hitherto been recognised. In the case of osteoporosis, for example, progressive bone loss from the late twenties onwards is the norm. Whether an individual reaches a critically low bone density, making him or her highly susceptible to fracture, is governed by how much bone mass there was to start with and by the individual's rate of bone loss. The process that leads eventually to osteoporosis is thus entirely 'normal', but what distinguishes whether or not this process results in an overtly pathological outcome is a range of moderating factors. In the case of Alzheimer's disease, most people above age 70 have extensive cortical amyloid plaques and neurofibrillary tangles (the so-called 'hallmarks' of classic Alzheimer's disease) even though they may show no evidence of major cognitive decline (Esiri *et al*., 2001). In this instance, what determines whether or not the diagnosis of Alzheimer's disease is called for may be not so much the presence of lesions as which specific targets are affected.

Mechanisms of cellular damage

Ageing is highly complex, involving multiple mechanisms at different levels. Much recent evidence suggests that an important theme linking several different kinds of damage is the action of reactive oxygen species (ROS; also known as 'free radicals') which are produced as by-products of the body's essential use of oxygen to produce cellular energy (Martin *et al*., 1996; von Zglinicki *et al*., 2001). Of particular significance are the contributions of ROS-induced damage to cellular

DNA through (i) damage to the chromosomal DNA of the cell nucleus resulting in impaired gene function, (ii) damage to telomeres – the protective DNA structures that appear to 'cap' the ends of chromosomes (analogous to the plastic tips of shoelaces), and (iii) damage to the DNA that exists within the cell's energy-generating organelles, the mitochondria, resulting in impaired energy production.

Damage to DNA is particularly likely to play a role in the lifelong accumulation of molecular damage within cells, since damage to DNA can readily result in permanent alteration of the cell's DNA sequence. Cells are subject to mutation all the time, both through errors that may become fixed when cells divide and as a result of ROS-induced damage which can occur at any time. Numerous studies have reported age-related increases in somatic mutation and other forms of DNA damage, and suggested that an important determinant DNA of the rate of ageing at the cell and molecular level is the capacity for DNA repair (Promislow, 1994; Burkle *et al*., 2002).

Although DNA damage may take many forms, it is estimated that oxidative damage is among the most important, accounting for large numbers of oxidative hits per cell per day. A key player in the immediate cellular response to ROS-induced DNA damage is the enzyme poly(ADP-ribose) polymerase (PARP). Grube and Bürkle (1992) discovered a strong, positive correlation of PARP activity with the species lifespan, cells from long-lived species having higher levels of PARP activity than cells from short-lived species. In a similar vein, it was found that human centenarians, who have often maintained remarkably good general health, have a significantly greater poly(ADP-ribosyl)ation capacity than the general population (Muiras *et al*., 1998).

Short telomeres

In many human somatic tissues a decline in cellular division capacity with age appears to be linked to the fact that the telomeres, which protect the ends of chromosomes, get progressively shorter as cells divide (Kim *et al*., 2002). This is due to the absence of the enzyme telomerase, which is normally expressed only in germ cells (in testis and ovary) and in certain adult stem cells. Some have suggested that in dividing somatic cells telomeres act as an intrinsic 'division counter', perhaps to protect us against runaway cell division as happens in cancer. The price of this counting is 'collateral' damage as cells that are critical for the maintenance of the body are also discarded and thus contribute to ageing (Campisi, 1997). While the loss of telomeric DNA is often attributed mainly to the so-called 'end-replication' problem – the inability of the normal DNA copying machinery to copy right to the very end of the strand in the absence of telomerase – it has been found that stress, especially oxidative stress, has an even bigger effect on the rate of telomere loss (von Zglinicki, 2002). Telomere shortening is greatly accelerated (or slowed) in cells with increased (or reduced) levels of stress. The clinical relevance of understanding telomere maintenance and its interaction with

stress is considerable. A growing body of evidence suggests that telomere length is linked with ageing and mortality (Cawthon *et al*., 2003). Not only do telomeres shorten with normal ageing in several tissues (e.g. lymphocytes, vascular endothelial cells, kidney, liver), but also their reduction is more marked in certain disease states. For example, there appears to be a higher incidence of vascular dementia in people with prematurely short telomeres (von Zglinicki *et al*., 2000). Viewed together with the observation that oxidative stress accelerates telomere loss, the intriguing possibility arises that prematurely short telomeres *in vivo* are an indicator of previous exposure to stress and may therefore serve as a prognostic indicator for disease conditions in which oxidative stress plays a causative role (von Zglinicki, 2002). More than intriguing is the preliminary evidence that other forms of stress may chip away the ends of chromosomes also. Women with the highest levels of perceived psychological stress have shorter telomeres on average (Epel *et al*., 2004).

An important connection between oxidative stress and ageing is suggested by the accumulation of mitochondrial DNA (mtDNA) deletions and point mutations with age (Wallace, 1992). Mitochondria are intracellular organelles, each carrying its own small DNA genome, which are responsible for generating cellular energy. As a by-product of energy generation, mitochondria are also the major source of ROS within the cell, and they are therefore both responsible for, and a major target of, oxidative stress. Any age-related increase in mutation of mtDNA is likely to contribute to a progressive decline in the cell and tissue capacity for energy production. Age-related increases in frequency of cytochrome c oxidase (COX)-deficient cells have been reported in human muscle (Müller-Hõcker, 1989; Müller-Hõcker *et al*., 1993; Brierley *et al*., 1998), brain (Cottrell *et al*., 2000) and gut (Taylor *et al*., 2003) associated with increased frequency of mutated mtDNA.

Protein damage

So far, we have concentrated on damage to DNA. However, damage can also affect any of the macromolecules that make up the cell, as well as those that form extracellular structures such as cartilage and bone. In particular, damage to protein molecules occurs to a considerable extent, and accumulation of faulty proteins contributes to important age-related disorders such as cataract, Parkinson's disease and Alzheimer's disease. In some ways, the accumulation of defective proteins is harder to explain than the accumulation of DNA damage, since individual protein molecules are subject to a continual cycle of synthesis and breakdown. Thus, damage to any individual protein molecule should be cleared, as soon as that molecule is degraded. The exceptions occur when the defective protein molecules become resistant to breakdown, for example, because they form aggregates large enough to withstand the normal removal systems. It is the build-up of such aggregates that is commonly linked with cell and tissue pathology.

Metabolism

Of particular significance in terms of metabolic factors influencing ageing rates has been the discovery that insulin signalling pathways appear to have effects on ageing that may be strongly conserved across the species range (Gems and Partridge, 2001). Insulin signalling regulates responses to varying nutrient levels and so the discovery of the major role for these pathways in ageing fits well with the central concept of the disposable soma theory, namely that ageing results from and is controlled by the metabolic allocation of the organism's metabolic resources to maintenance and repair.

One of the clearest examples of how metabolic signalling affects ageing and longevity comes from a study on genes of the insulin signaling pathway in *C. elegans* (Murphy *et al*., 2003). When threatened with overcrowding, which the larval worm detects by the increasing concentration of a pheromone, it diverts its development from the normal succession of larval moults into a long-lived, dispersal form called the dauer larva (Larsen *et al*., 1995). Dauers show increased resistance to stress and can survive very much longer than the normal form, reverting to complete their development into adults should more favourable conditions be detected. An insulin/IGF-1-like gene, *daf-2* , heads the gene regulatory pathway that controls the switch into the dauer form, and mutations in *daf-2* produce animals that develop into adults with substantially increased lifespans (Kenyon *et al*., 1993). The *daf-2* gene product exerts its effects by influencing 'downstream' gene expression, in particular via the actions of another gene belonging to the dauer-formation gene family, *daf-16*, which it inhibits (Kimura *et al*. 1997). It was shown by Murphy *et al*. (2003) that more than 300 genes appeared to have their expression levels altered by *daf-16* regulation. These genes included many that were concerned with regulating key maintenance processes such are resistance to oxidative stress, capacity to clear damaged proteins and capacity to fight off bacterial infections. Thus, it is turning out that on the one hand the essential simplicity of Figure 2.3 is confirmed by the data, while on the other hand there remains a lot of complicated research to be done to unravel the multiple mechanisms of cellular damage and repair.

Hierarchy

By this point, it will be seen that, from a range of studies at the genetic, cellular and molecular levels, both in humans and a variety of other organisms, a picture is clearly emerging of the main elements of the biological science of human ageing (see Figure 2.1). These elements are the relentless role of biochemical *stresses*, such as exposure to ROS, driving a gradual but progressive accumulation of *damage* to cells, tissues and organs. The process is not entirely passive, since the rate of accumulation is strongly resisted by maintenance and repair processes, which are controlled by *genes*. Furthermore, the regulation of these genes may, at least in some organisms, be influenced by metabolic factors, such as responding to levels of nutrition.

This picture is one that readily accommodates the role of at least five major elements contributing to the individuality of the human ageing process: genes, nutrition, lifestyle (e.g. exercise), environment and chance. The recognition of this interplay of factors is likely to be crucial for integrating biological, clinical and social gerontology. For example, environment is often defined by social factors such as housing, transport and income. Poor environments may adversely affect an individual's opportunities to do the optimal things for healthy ageing in terms of nutrition, lifestyle, etc. In particular, a poor environment can reinforce a tendency for the older person to suffer social isolation, which in turn can exacerbate psychological and physical deterioration. On the positive side, the understanding that we now have of the biological science of human ageing supports the idea that the ageing process is much more malleable than has hitherto been recognised. This opens the way to a range of interventions that may improve health in old age and extend quality life.

THE RECENT DEVELOPMENT OF HUMAN LIFE SPAN

In the years to come, addressing the cumulative damage associated with ageing will be one of the biggest challenges faced by industrialised countries (Westendorp, 2006). We are now armed with the biological knowledge about ageing that can help us to make sense of the factors that have driven the recent dramatic increases in human longevity. Since the industrial revolution in the middle of the nineteenth century, average female life expectancy has increased in western societies from about 45 years to currently more than 80 years, corresponding to an increase of 2.3 years per decade (Oeppen and Vaupel, 2002). Life expectancy has also risen for men, although more slowly; over the years the gap between females and males has extended from 2 to 6 years (Oeppen and Vaupel, 2002). The increase in life expectancy since 1850 is a straight line and, despite the estimates of the United Nations, who predicted the rate of increase to plateau (United Nations Secretariat, 2003), there are no data supporting such an expectation. (see Figure 2.4).

It might have been expected, and was indeed forecast by all of the major national and international agencies, that the increase in lifespan would slow down and eventually reach a plateau as the gains from further reductions in early and middle life mortality became negligible in terms of their potential impact on life expectancy (since mortality in these age ranges was already so low), and as the fixed, ineluctable ageing process made its presence ever more clearly felt. Thus it has taken demographers and policy planners by surprise that, during the final decades of the twentieth century, life expectancy not only did not reach a plateau but to date has shown no sign of slowing its rate of increase at all. This new phase of human ageing is sometimes referred to the 'demographic transition', following upon the heels of the preceding epidemiological transition.

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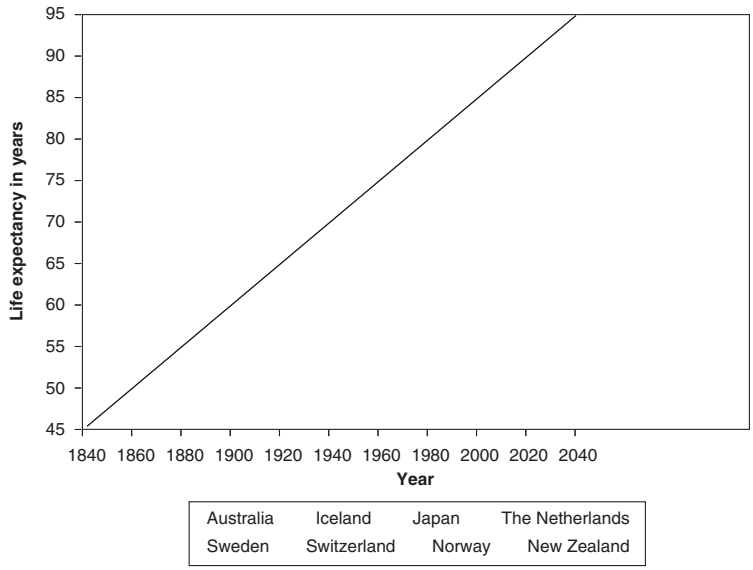

Figure 2.4 Recorded female life expectancy from 1840 to the present

The increase in life expectancy that has occurred during the last two centuries has occurred much faster than can reasonably be explained by any change in genetics, so the answer must be sought in the range of non-genetic factors. Of course the first phase of the increase in life expectancy was driven by the reduction in infectious disease mortality, through sanitation, then antisepsis followed by vaccination and antibiotics. This had a particularly important impact on child mortality, which has the biggest quantitative effect on life expectancy, but its effects on adult mortality should not be ignored. The taming of infectious disease mortality ushered in the epidemiological transition, from a pattern of disease dominated by infection to one dominated by intrinsic, age-related deterioration (Omran, 2001).

Box 2.2 Environmental effects on lifespan: the example of Japan

A unique example showing the impact of improved environmental conditions on lifespan is provided by data from Japan, which experienced an exceptionally rapid increase in life expectancy during the last 50 years. Japanese life expectancy from

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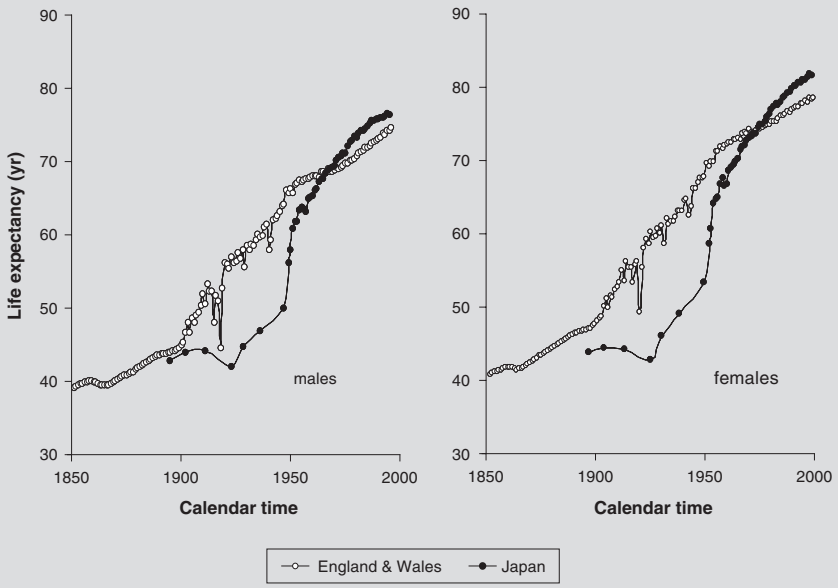


birth did not increase significantly until 1950 but since then has grown to become the longest in the world.

According to the first life tables (1891–98), life expectancy in Japan was 42.8 years for males and 44.3 years for females at the end of the nineteenth century. Life expectancy in Japan remained less than 50 years until after the Second World War. From 1950 to 1952, life expectancy increased by more than two years annually. In 1995, life expectancy at birth was 76.4 years for males and 82.9 years for females. The graphs illustrate the increase in life expectancy in Japan over calendar time for males and females. For comparison, life expectancy for males in England and Wales is also presented. In 1850, life expectancy in England and Wales was 39.2 years for males and 41.2 years for females. Life expectancy for males has been above 50 years since 1909 and for females since 1902. In 1995, life expectancy in the UK at birth was 74.2 years for males and 79.5 years for females.

The rapid increases in life expectancy in Japan and the UK reveal the epidemiologic transition that has taken place in all developed countries, with high child mortality and deaths from extrinsic causes at any age being largely replaced by mortality caused by age-associated degenerative disorders. This notion is reinforced by the observation that the mean age at death for British aristocratic women remained around 45 years until the first decades of the eighteenth century. Thereafter life span steadily increased to a mean of 68 years for women born in 1850. The epidemiologic transition among the British aristocracy thus began some 150 years earlier than in the general population.

The curve for Japan provides a key to what drives life expectancy (see Box 2.2). There is no other country that has seen such a dramatic increase in lifespan. From 1900 until the Second World War, life expectancy in Japan lagged behind other countries by as much as 30 years. At that time, Japan was an economically poor, agricultural society. Since the war, Japan has experienced unprecedented economic and social development and now has the highest life expectancy of all countries in the world. Although there is debate as to the specific elements involved, wealth and an affluent environment correlate closely with life expectancy. Improvements in sanitation, education, nutrition and medicine afforded by increased wealth are positive indicators for long-term health and decreased early mortality for entire populations.

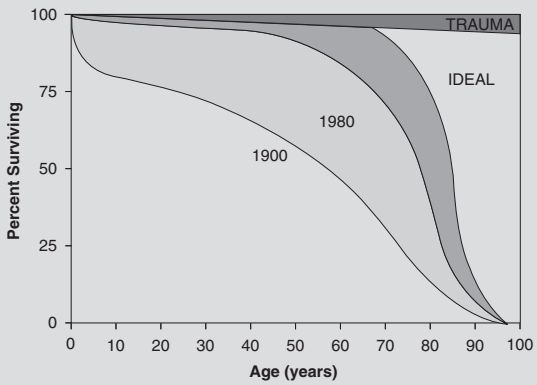
LONGER WELL OR POORLY LONGER?

The continuing increases in human life expectancy, although surprising, are entirely compatible with the understanding of the biology of ageing that has emerged from evolutionary thinking. Since there is no programme for ageing, and since ageing is driven by the gradual accumulation of faults, anything that slows the accumulation of faults will potentially extend not only lifespan but also health span. We are as yet uncertain about which of the non-genetic factors have been the more important in driving the recent increase in life expectancy, but such increase is entirely compatible with the general idea that the kinder conditions of modern life may be allowing the current cohorts of older people to have reached old age with less accumulated damage.

The increase in average lifespan observed in all developed countries is accompanied by an incremental burden of age-associated diseases. The expectation is that scientific advances will prevent disease from occurring or, if disease does strike, will protect us from permanent damage. Over the last 20 years, the United Kingdom has gained about four years in both female and male life expectancy, but only two years in female healthy life expectancy (House of Lords Science and Technology Committee, 2005). The overall increase is far greater than that for healthy living, and this contradicts recent thinking. In 1980, Fries published the concept of compression of mortality and morbidity, based on survival curves (Fries, 1980). Juxtaposing curves from 1900 and 1980, it appeared that the curve became rectangular with increasing survival to higher age (see Box 2.3). Projecting the same curve forward in time, it was expected to become ever more rectangular, to a point where individuals all survive to a similar age. Mortality would be compressed into a shorter period; individuals born around the same time would die over the same 5- to 15-year period instead of being threatened over the lifetime. And, as Fries concluded, since there is no mortality without disease, compression of mortality also implied compression of morbidity; individual suffering prior to death would also be limited to those 5–15 years.

Box 2.3 On compression of morbidity and mortality

The continuing increase in life expectancy has prompted many to make predictions about the future length of the period during which we suffer from disease and disability towards the end of life. Underlying much of the thinking to date has been an expectation that progress in medical knowledge will lead to prevention of postponement of disease, independently of the underlying process of intrinsic biological ageing. This optimism led Fries (1980) to introduce the concept of 'compression of morbidity', often linked to the progressive tendency towards rectangularisation of the survival curve (see the figure).



The concept has wide appeal on the grounds that it captures what many see as the objective of research on biomedical aspects of ageing, namely, 'to add life to years, not years to life'. The reverse possibility – that lifespan will continue to increase but that healthspan will not – is seen by most as a highly unlikely and undesirable outcome.

The idea of compression of morbidity does not, however, stand up well to scrutiny in the light of our understanding of the biology of ageing. The difficulty with this concept is that it assumed a fixed maximum human lifespan. It became clear in the 1980s that this was not the case. The concept also failed to consider the effects on survival during the extreme environmental change that occurred during the 80 years between datasets, therefore assuming that survival was independent of environmental factors.

It should also be noted that compression of morbidity and rectangularisation of the survival curve are not the same thing at all. If individuals continue to die at variable ages, due to a variety of innate and acquired characteristics, the survival curve will not become any more rectangular, even if for each individual morbidity is compressed into ever shorter periods. As for compression of morbidity, the idea that diseases can be further postponed within a fixed biological lifespan is increasingly less plausible, now that we know that ageing itself is almost certainly not programmed and at a time when we are seeing continuing increase in life expectancy driven primarily by the increased health, vitality and longevity of older people. New biological understanding of ageing tells us that the length of life is intrinsically much more malleable than was thought previously. Of course, this malleability also extends to the underlying component causes of ageing process (see Box 2.1), so whether in future our healthspan will increase faster or slower than lifespan is largely unknown.

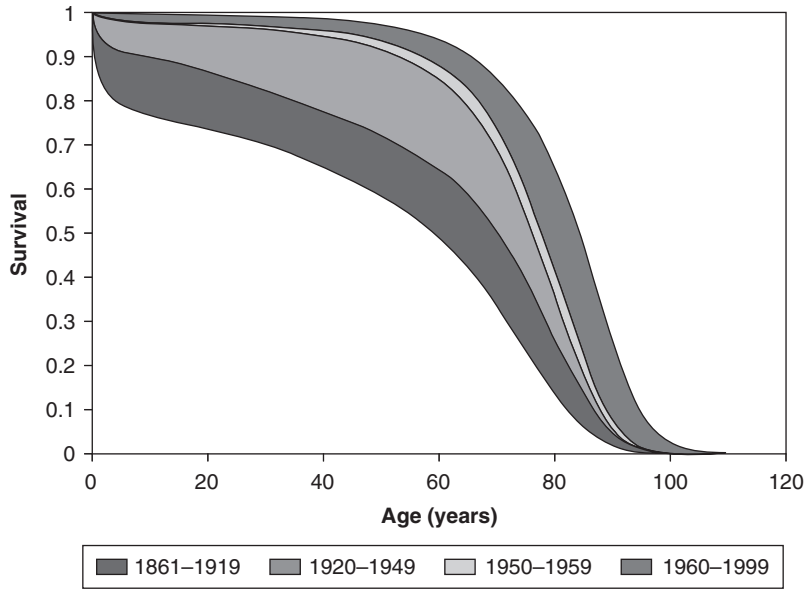


Figure 2.5 Survival curves in Sweden over the last 140 years

When we examine age at death in Sweden over the last 140 years, we notice a steep increase over the last 40–50 years (Wilmoth *et al*., 2000). Examination of trends in the improvement of survival show that the tendency of the survival curve to become rectangular existed only for the period between 1860 and 1950. From then on, there was a parallel shift of the curve to the right (Yashin *et al*., 2002) (see Figure 2.5).

Using the same data sets, Wilmoth *et al*. (2000) were able to further calculate that the rise of the maximum age at death in Sweden from the 1860s to the 1990s was due primarily to reductions in mortality at older ages. Of the total increase, 72.5% is attributable to decreased mortality above the age of 70. The increasing size of successive birth cohorts and decreased mortality below age 70 account for the balance. It is known that a reduction in old-age mortality has been a primary factor behind population ageing and the proliferation of centenarians during recent decades. It was also shown that mortality decline above age 70 has also been the main cause of a gradual increase in maximum achieved lifespan over more than a century. Only a minor part of this increase is due to the larger size of recent cohorts, defined either as numbers of children born each year or numbers of survivors to old age. It appears that, although the maximum age has increased more slowly than the average, the entire distribution of age at death has been shifting upward for more than a century in industrialised countries.

The right shift of the survival curves and analyses of changes in mortality patterns from the last half century line up with the basic idea that there is no biological limit to life. Therefore, compression of mortality and morbidity are not valid either. It may even be, since we still suffer from disease in middle age, that there is actually a decompression of morbidity, as the trend in the UK suggests. Analysis of death registries in the Netherlands corroborated the UK findings. A right shift in survival curves occurred from the 1950s onwards (Statistics Netherlands, 2004). Over the last decade in the Netherlands, comparing 1989 to 2000, there was an increase of two years in average life expectancy accompanied by an increase in the number of years with disease, hence decompression of morbidity. Under current conditions, we are going to live longer with more years spent in poor health (Perenboom *et al*., 2002). Despite this depressing forcast we are increasingly able to overcome the complications of disease, explaining that the years without functional limitations or disability is still on the increase.

ORIGINAL GENES IN A NEW ENVIRONMENT

Currently, we have a fairly solid understanding of the evolutionary mechanisms that make us age and also allow us to survive in such disparate environments as Greenland and the Sahara. Darwinian fitness constantly shapes the genome to better adapt the organism to its habitat. Our mounting lifespan is determined by genes that were originally selected for survival in an adverse environment and are now expressed under completely new affluent environmental conditions. This may result in different, sometimes opposing, biological effects. Given the surprising patterns revealed by human longevity over the last 200 years, it is perhaps unwise to speculate too much about what might yet occur in the future. Nevertheless, it is important, not least for policy planning purposes, to look at what the biology tells us might occur.

The first point to make is that populations continue to adapt. Although we might suppose that natural selection is no longer operative in human societies, where many inherited problems such as short-sightedness have no discernible effect on reproductive success, we should not lose sight of the enormous changes that have taken place in our life history and the messages that might be contained therein. We indicated earlier how the current evolutionary understanding of ageing is founded on the idea of trade-offs, particularly between fertility and survival. Recently, we sought evidence in human populations that the kind of trade-offs that have been so clearly revealed in animal populations might apply in our species too (see Box 2.4). We found strong evidence that this is so and that a genetic predisposition towards above-average longevity may be associated with a genetic predisposition towards below-average fertility, and vice versa.

Box 2.4 Life history trade-offs among British aristocratic women

When human life history data are analysed to identify trade-offs between investments in reproductive success and in body maintenance, one should take into account not only genetic factors but also the socio-economic conditions that affect both the preferred family size and the probability of attaining long life. The detailed records of births, marriages and deaths of British aristocratic families, which have been kept over the centuries, provide an unique resource which we have used to study life history trade-offs in a population that is reasonably homogeneous with respect to its socio-economic characteristics and in which social deprivation has not unduly interfered with the prospects for reaching old age and thereby revealing an individual's intrinsic capacity for longevity (Westendorp and Kirkwood, 1998).

Table 2.1 Number of progeny and age at first childbirth dependent on the age at death of married aristocratic women.

			Number of progeny		*Age at first childbirth (yr)*	
Age at death (yr)	*Number*	*Proportion childless*	*Mean*	*(95% CI)*	*Mean*	*(95% CI)*
<20	42	0.66	0.45	(0.29–0.69)	19.1	(15.9–22.5)
21–30	176	0.39	1.35	(0.86–2.11)	20.5	(19.4–21.6)
31–40	218	0.26	2.05	(1.33–3.18)	23.2	(22.3–24.2)
41–50	210	0.31	2.01	(1.30–3.11)	23.9	(22.9–24.9)
51–60	299	0.28	2.40	(1.56–3.71)	24.6	(23.8–25.4)
61–70	337	0.33	2.36	(1.53–3.63)	23.8	(23.0–24.6)
71–80	322	0.31	2.64	(1.71–4.07)	24.6	(23.8–25.3)
81–90	247	0.45	2.08	(1.35–3.24)	25.1	(24.1–26.1)
>90	57	0.49	1.80	(1.12–2.90)	27.0	(24.8–29.2)

Point estimates and 95% confidence intervals (95% CI) are adjusted for the trends over calendar time using Poisson regression (number of progeny) and linear regression (age at first childbirth) respectively.

We have also found evidence of a possible mechanistic basis for such a trade-off, in that women with an innate, pro-inflammatory immune system are likely to have greater difficulty conceiving a child but may be better protected against fatal infectious disease (Westendorp *et al*., 2001). This concept may explain why British aristocrats who lived longer were less likely to reproduce (Table 2.1). Their innate pro-inflammatory immune system favoured resistance to infection. At the same time, it prevented pregnancy from proceeding, a 'trade-off' that is more pronounced under poor environmental conditions. It also explains why a genotype associated with impaired fertility persisted in spite of its obvious disadvantage with respect to evolutionary fitness. Selection for resistance to infection was traded against selection for fertility, resulting in a compromise that was optimal for the fitness of the species in the particular environment.

From an ageing perspective, old age is associated with systemic chronic inflammation and has been found to be related to mortality risk from all causes in older persons (Bruunsgaard *et al*., 2001). Age-related diseases such as Alzheimer's disease, atherosclerosis, diabetes mellitus, sarcopenia and osteoporosis are initiated or worsened by systemic inflammation, suggesting the critical importance of unregulated systemic inflammation in old age (Bruunsgaard *et al*., 2001; Brod, 2000; Pawelec *et al*., 2002). Accordingly, pro-inflammatory cytokines are believed to play a predominant role in age-related diseases especially now in affluent societies where the majority of the population survives up to old age. In line, genetic variations located within the promoter regions of these pro- and anti-inflammatory cytokines have been shown to influence the susceptibility to age-related diseases by increasing gene transcription and therefore cytokine production (Pawelec *et al*., 2002; Bidwell *et al*., 1999; van den Biggelaar *et al*., 2004).

It is easy enough to see that during an era when infectious disease was the dominant cause of mortality, such a pro-inflammatory host immune system might have made evolutionary sense. The set point of the response, balancing resistance to infection on the one hand and successful pregnancy on the other, is genetically controlled and is likely a result of Darwinian selection in the environment we live (Westendorp, 2004). It is also clear that the effective removal in developed countries of the threat of fatal infectious disease within just a few generations may have tipped the evolutionary balance. Nowadays individuals with an anti-inflammatory host response are likely to escape death from infection, and genetic variations determining increased production of the anti-inflammatory cytokine IL-10 or decreased production of the pro-inflammatory cytokine TNF-α have been shown to be associated with healthy ageing, suggesting a role for the control of the pro-inflammatory mode in older age (Lio *et al*., 2003). Whether and how fast such a change might result in altered frequency within the population of genes affecting human longevity are interesting questions to ask.

FUTURE PERSPECTIVE

Of course, an immediate practical challenge that many developed countries must confront is the threat to health and future longevity that comes from a lifestyle of affluence, characterised by excessive food and sedentary lifestyle. This threat is not distinct from the challenge of understanding the biology of ageing. Poor nutrition and lack of physical exercise exacerbate the accumulation of cellular and molecular damage through biochemical and physiological pathways that we already understand reasonably well. A child raised on a diet with excessive saturated fat and sugar, who takes insufficient exercise, is not only more likely to suffer diseases such as diabetes and atherosclerosis; he or she is also likely to age faster as well.

An open issue in ageing research is the extent to which responses to the environment during development can influence variability in lifespan in animals,

and the health profile of older humans. Both affluence and adversity in human societies have profound impacts on survivorship curves, and some of this effect may be traceable to effects *in utero* or in infancy. Data from human observational studies suggest that a pregnant woman's diet affects not only the health of her children but also that of her grandchildren (Barker, 2002). The idea, known as the 'Barker hypothesis', links caloric restriction in very early life to disruptions of glucose–insulin metabolism in later life and has attracted much attention, as well as some controversy, in medical circles.

One crucial mechanism by which animals can respond in an adaptive manner to adverse conditions – for example in nutrition or infection – during development is *phenotypic plasticity*, which describes the ability of a genotype to express different phenotypes in response to different environments. However, it is only rarely considered by evolutionary biologists working on phenotypic plasticity, or by biogerontologists studying model organisms such as *C. elegans* or *Drosophila*. Recently, we started a discussion of adaptive plasticity in animals, asking what such a phenomenon may reveal that is relevant to the rate of ageing in animals and in man, and gathering the evidence that environmentally mediated events taking place very early in life may determine the biological status of an individual at the end of life (Brakefield *et al*., 2005).

The biological mechanisms underlying this heritable, epigenetic information have yet to be understood. The findings, however, corroborate with findings concerning the regulation of lifespan in ants and honey bees. Secretion of larvae juvenile hormone (corresponding to thyroid hormones in humans) is food-dependent. Should it be stimulated at a critical time in development, the larvae develop into diploid queens with a prolonged lifespan. In the absence of this food-triggered hormonal signal, the same larvae will develop into haploid workers with a short lifespan (Keller and Genoud, 1997). This signalling by the environment to invest particular attributes in the new organism is a clear example of early environmental programming. Applied in humans, and given our much longer average lifespan relative to ants and honey bees, depending on early environmental programming of food, a life history of 100 years could only be an average. There is enormous potential plasticity in our life history, but we have not yet identified the signals controlling it.

THE KNOWLEDGE SHADOW

Upon further improvement of our environmental conditions, with continuous increase of average life expectancy and no biologically determined limit, the question becomes one of disease-related morbidity. How do we optimise an increasingly ageing population's health such that we don't simply spend more years in misery before we die? The answer lies in a thorough understanding of the ageing process and how available interventions may be applied to protect and preserve health.

Of immediate concern for health of the ever-increasing numbers of older people is our constrained knowledge domain. The bulk of medical research has been invested in early development, adulthood and middle age. Scientific and medical advances in the last century targeted prevention and control of diseases that threatened survival through the 'prime' years, and these represented enormous contributions to the quality of life we now enjoy in youth and middle age. While this was happening, however, we were not investing in our understanding of the natural consequence of this – i.e. a growing elderly and ageing population. Using population data from 'developed' countries, approximately 80–90% of deaths now occur after the age of 75. The problem is that disease, morbidity and deaths at this age are actually occurring in a 'knowledge shadow'.

CONCLUSIONS

Ageing is under environmental and genetic control but it is not programmed nor is it inevitable. As evolutionary pressures for early survival and reproduction decrease, more metabolic resources can be invested in soma maintenance and repair, increasing both average life expectancy and maximum lifespan. Ageing is best explained as the balance between investments in fitness and investments in body maintenance: if investment in body maintenance is not optimal, ageing occurs. Increasing our understanding of the ageing process and applying available interventions will greatly enhance a healthy ageing.

FURTHER READING

Kirkwood, T. B. L. (2005) Understanding the odd science of ageing. *Cell* **120**, 437–447.

Oeppen, J. and Vaupel, J. W. (2002) Demography: broken limits to life expectancy. *Science* **296**, 1029–1031.

Westendorp, R. G. (2006) What is healthy aging in the 21st century? *American Journal of Clinical Nutrition* **83** (suppl.), S404–409.