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SUMMARY

The origins of human ageing are to be found in the origins and evolution of senescence as a general feature in the life histories of higher animals. Ageing is an intriguing problem in evolutionary biology because a trait that limits the duration of life, including the fertile period, has a negative impact on Darwinian fitness. Current theory suggests that senescence occurs because the force of natural selection declines with age and because longevity is only acquired at some metabolic cost. In effect, organisms may trade late survival for enhanced reproductive investments in earlier life. The comparative study of ageing supports the general evolutionary theory and reveals that human senescence, while broadly similar to senescence in other mammalian species, has distinct features, such as menopause, that may derive from the interplay of biological and social evolution.

1. INTRODUCTION

A near doubling in human life expectancy at birth has taken place in developed countries since the mid-19th century, with the well-known consequence that the age structure of populations has altered dramatically (United Nations 1989). The fraction of older (65+) individuals has climbed to nearly 20%, due to increased survival through the early and middle stages of life, while the fraction of younger individuals has declined, due to reduction in the birth rate. These changes are now also occurring, later but faster, in many developing countries. Research into the biological basis of ageing has therefore received new impetus from the urgency of addressing the underlying causes of the many age-associated diseases and disabilities, whose prevalence has increased in parallel with the chance of remaining alive into the age range where these infirmities most commonly arise (Holliday 1996*a*).

The impact of ageing on the human life history is most often described in terms of its effect on mortality. Mortality rates in humans show an approximately exponential rise with increasing chronological age, noted first by Gompertz (1825), and a similar pattern has been observed in other mammalian species (see Sacher 1978; Finch 1990). For this reason ageing is commonly defined as a 'progressive, generalized impairment of function resulting in a loss of adaptive response to stress and an increasing probability of death' (Maynard Smith 1962). There is evidence that the exponential rate of increase in human mortality slows down among centenarians (Smith 1994), but it is not known whether this reflects: (i) genetic heterogeneity within the population; (ii) particularly assiduous medical and social care of the very old; or (iii) intrinsic biological processes. Heterogeneity is likely to be at least part of the explanation if, as seems probable, centenarians represent an exceptionally robust subset of the population (Vaupel *et al.* 1979; Schächter *et al.* 1993). When a cohort ages, the frailer individuals die sooner and, as a consequence, the mortality rate of the survivors comes to be based on a shrinking fraction of the population who may have started their adult lives with intrinsically greater capacity for survival.

While humans are unique among other animal species in the extent to which ageing impacts on our lives, there are many outward similarities between the senescent changes that occur in us and in other higher animals. Senescence is a general characteristic of mammals, birds, reptiles and many invertebrates (see Comfort 1979; Finch 1990). It is therefore instructive to consider the comparative and evolutionary background of ageing as a means of gaining insight into the nature and causes of our own ageing process (Kirkwood 1985; Finch 1990; Rose 1991; Holliday 1995).

2. THE EVOLUTIONARY ORIGINS OF HUMAN AGEING

The wide phylogenetic distribution of ageing strongly suggests that senescence long predates the emergence of *Homo sapiens*, so that to explain the origins of human ageing requires at least two components: first, an explanation of why ageing occurs at all, and second, an explanation of the special features of human ageing. This section examines the first of these points. It is important to understand why ageing occurs because there are in principle many ways that ageing might be caused. A bewildering array of mechanistic theories exists, based on the fact that during ageing almost every character of the body undergoes some form of change. However, many of these changes are secondary

rather than primary events, and a major problem is to devise ways of disentangling causes from effects. The way that we answer the 'Why?' question will influence the types of mechanisms we might look for experimentally. That ageing requires an evolutionary explanation at all is evident from the fact that there exist some species, such as sea anemones and hydra, that do not show increasing age-specific death rates (Comfort 1979). Furthermore, in all species the germ line—that is, the lineage of reproductive cells that form the male and female gametes—must be immortal (Weismann 1891; see Kirkwood & Cremer 1982). Indeed, the central puzzle of gerontology is to explain why the soma—i.e. those parts of the organism that are not germ line—is mortal, given that somatic and germ cells consist of the same basic materials (Williams 1957; Kirkwood 1987).

One explanation for the evolution of ageing is that senescence provides a mechanism to guard against overcrowding (Wynne-Edwards 1962; Beutler 1986). This suggests that ageing is a programmed process under active genetic control and that genes have evolved specifically to cause it (Kenyon 1996). Despite the popularity of this view, there are compelling reasons why it is unsound. First, mortality in wild populations is usually so great that individuals rarely live long enough to show clear signs of senescence (Medawar 1952). Second, for ageing to have arisen in this way would have required that selection for advantage to the species or group was stronger than selection at the level of the individual for the advantages of a longer life. The conditions under which selection at the group level can outweigh selection at the level of the individual are stringent (Maynard Smith 1976), and it is unlikely that they apply to the evolution of ageing (Kirkwood 1985).

If ageing is not beneficial then its evolution needs to be understood in terms of the indirect action of natural selection. Two broad approaches to this problem can be distinguished (see Kirkwood & Rose 1991). Firstly, we may note that the force of natural selection—that is, its ability to discriminate between alternative genotypes—progressively weakens with advancing age (Haldane 1941; Medawar 1952; Williams 1957; Hamilton 1966; Charlesworth 1980, 1994). This happens simply because at older ages fewer individuals remain alive, regardless of whether or not the species exhibits senescence. The upshot is that there is only loose genetic control over the later stages of the lifespan. If germ-line mutations occur which give rise to deleterious effects late in life, there is little or no selection to eliminate the mutations from the population. Similarly, if genes have pleiotropic effects such that they produce favourable effects early in life, but have deleterious consequences later, they will be selected for on the basis of their early benefits with scant regard to their delayed side effects. Either or both of these types of genes can accumulate within the genome. In individuals who escape earlier death from accidental causes or in protected populations, ageing and death may result from the combined expression of the late-acting deleterious gene effects (Medawar 1952; Williams 1957).

The second evolutionary approach is more specific about the nature of ageing processes. It examines the optimum investment in the maintenance of somatic parts of the organism and demonstrates that this optimum is less than is required for indefinite survival. Given the hazard of accidental death, to which no species is entirely immune, each individual has only a finite expectation of life, even in the absence of senescence. When the individual dies, the resources invested in the maintenance of its soma are lost. Too low an investment in the prevention or repair of somatic damage is obviously a mistake because then the individual may disintegrate too soon. However, too high an investment in maintenance is also wasteful because there is no advantage in maintaining the soma better than is necessary to survive the expected lifetime in the wild environment in reasonably sound condition, and excess investment in maintenance will reduce the resources available for growth and reproduction. Fitness is therefore maximized at a level of investment in somatic maintenance which is less than would be required for indefinite survival.

This conclusion is the basis for the disposable soma theory of ageing (Kirkwood 1977, 1981; Kirkwood & Holliday 1979), named for its analogy with disposable goods that are manufactured with limited investment in durability on the principle that they have a short expected duration of use. The disposable soma theory has important implications concerning the mechanisms of ageing. It strongly supports the view that ageing results from the accumulation of random somatic damage.

3. IMPLICATIONS OF THE EVOLUTIONARY THEORIES

(*a*) *Genetic control of lifespan*

The evolutionary theories give broad insights into the genetic factors that control lifespan. In the disposable soma theory, selection acts on the genes that regulate the key mechanisms of somatic maintenance and repair in order to secure the optimum balance between surviving long enough and spending too much on maintenance. A simple model illustrates how this may result in control of the rate of ageing.

Consider a specific type of maintenance, e.g. antioxidant defences. By increasing or decreasing the level of protection provided by the antioxidant defences, the rate at which oxidative damage accumulates is altered. This, in turn, influences the time taken for oxidative damage to build up to a level that causes cellular dysfunction, contributing eventually to senescence and death.

We can understand how this kind of genetic factor can be acted upon by natural selection to determine species-specific lifespans if we recall that in the disposable soma theory it is the presence of environmental mortality that makes it not worthwhile to invest in better antioxidant defences than are needed to preserve somatic functions through the normal expectation of life in the wild. A species subject to high environmental mortality will do better not to invest heavily in somatic maintenance, and should concentrate instead on more

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rapid and prolific reproduction. A species subject to low environmental mortality may profit by doing the reverse.

An important feature of this argument is its generality. It applies to any somatic maintenance function that involves any kind of metabolic cost for its operation, and nearly all of them do. This conclusion is important for it tells us that we should not expect to find a single mechanism at the basis of ageing but a network of interacting, possibly synergistic processes at work (Kirkwood & Franceschi 1992; Holliday 1995; Kowald & Kirkwood 1996; Kirkwood 1996).

(*b*) *Mechanisms of ageing*

A wide variety of specific mechanisms of ageing has been proposed involving various kinds of damage in cells and tissues. The major theories address the roles of oxidative damage, aberrant proteins, defective mitochondria and somatic mutations.

Oxidative damage is caused by reactive oxygen species, or 'free radicals', which are highly reactive molecules that are produced as by-products of oxidative metabolism within cells. Free radicals can damage almost any component in the cell, including proteins, nucleic acids and membranes. Protection against the damaging actions of free radicals is provided by vitamins A, C and E and by enzymes such as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase. The fact that all aerobic organisms have evolved defences against free radicals is evidence of the threat they pose. There is extensive evidence that oxidative damage accumulates with ageing and that long-lived species have better antioxidant defences than short-lived species (Sohal 1993; Martin *et al.* 1996).

Accumulation of aberrant proteins within cells and tissues is observed during normal ageing (Adelman & Roth 1983; Rosenberger 1991) and is specifically linked to the pathogenesis of age-associated conditions such as cataract and Alzheimer's disease (see Anderton 1997). Aberrant proteins can arise as the results of errors in synthesis and/or abnormalities of post-translational modification such as misfolding of the peptide chain or abnormal phosphorylation. Protection against accumulation of aberrant proteins is mainly by means of selective proteolytic degradation of damaged, erroneous or misfolded molecules. The proteins that accumulate during ageing tend to be variant forms that are resistant to proteolysis.

Eukaryotic cells rely for energy on oxidative phosphorylation occurring in their mitochondria, which are subcellular organelles containing their own DNA. Because free radicals are by-products of this process, the mitochondrial genome is particularly prone to mutational damage caused by free radicals. Damage to mitochondria is of great importance to the cell because it impairs energy production, but damaged mitochondria can still replicate because the proteins required for mitochondrial replication are encoded in the DNA of the cell nucleus. This arrangement means that defective mitochondria can accumulate in cells and may be an important cause of cellular ageing. There is growing evidence that defective mitochondria accumulate during ageing, especially in post-mitotic tissues, and that this is responsible for age-related declines in cell energy production (Linnane *et al.* 1989; Kadenbach *et al.* 1995).

The DNA in cells can be damaged in a great variety of ways and the importance of this threat is evident in the array of DNA repair mechanisms. Damage to DNA is a natural candidate for a molecular mechanism of ageing because once an alteration to the DNA sequence has occurred the altered sequence is preserved as faithfully as the original (Hanawalt 1987; Vijg 1990). Thus, mutations can accumulate progressively during the lifetime and interrupt normal cell functions. Somatic mutations can also be a source of autoimmune reactions if they give rise to modified proteins that trigger an immune response (Burnet 1974). Somatic mutations are known to be an important contributor to the age-associated development of many kinds of cancers, but it is not yet known if they contribute significantly to the overall process of ageing.

A longstanding debate in ageing research has concerned the relative importance in ageing of programmed events versus the kinds of stochastic damage just considered. The absence of evolutionary support for the idea that ageing is programmed as an overall process to terminate the life of an organism weakens the case for programme theories at the mechanistic level. Nevertheless, it is known that programmed cell death (apoptosis) is essential in development and may serve as an important mechanism for tissue maintenance (Potten 1992). It also appears that active genetic controls on DNA synthesis and cell division play a part in the limited cell proliferation of fibroblast cultures that are commonly used as a model of cell ageing (Smith 1990; Ning & Pereira-Smith 1991; Smith & Pereira-Smith 1996). It is difficult to sustain the argument that apoptosis or programmed cell ageing are primary causes for the ageing of the organism, but it is quite possible that they contribute, perhaps extensively, to senescence as secondary consequences of stochastic damage to cells. For instance, a cell that is normally prevented from apoptosis by a signal from outside, will die if the ability to receive and transduce the signal appropriately is compromised by damage. Such a process could even be adaptive if it serves to bring about the suicide and replacement of a defective cell. Taken to an extreme, one could imagine a scenario where active cell death is the major, outward sign of senescence, while stochastic damage is the pervasive, underlying cause (see Kirkwood 1991).

(*c*) *Diversity in causes of death*

There is no single cause of death in old age. Humans who live a long time may die of a diversity of causes, and old age is commonly associated with pathological changes in many tissues and organs of the body. The development of senescent changes in the various organs of the body over similar time scales is often seen as evidence for the existence of a central pacemaker or clock that regulates the overall process of ageing (for discussion, see, Warner *et al.* 1987). The case

for a central clock is weakened, however, by the evolutionary arguments that point to the gradual loosening, and eventual disappearance, of genetic control over the late stages of the lifespan.

The synchronicity of ageing changes in different organs is more satisfactorily explained by the fact that, in so far as selection works against the occurrence of senescence in the wild, any organ that consistently failed before the others would be subject to selection to improve its durability. On the other hand, any organ that failed long after the others would be 'over-engineered' and the resources invested in the maintenance and durability of this organ would be trimmed by natural selection, bringing its rate of senescence into line with that of other organs.

For all organs it is to be expected that selection will have favoured the evolution of a measure of 'reserve capacity', such that most organs remain in reasonably good condition at the time when the organism dies a natural death. As noted earlier, natural death usually results from some kind of accident rather than ageing. Humans are unusual in that our rapid social and cultural evolution has led to greatly increased life expectancy, resulting in the situation where we erode the reserve capacities of our organs to an unprecedented extent.

(*d*) *Ageing and disease*

We now briefly consider the relationship between human ageing and disease. Several general observations can be made. First, the view suggested by theory is that ageing is due primarily to the accumulation of defects. This results in progressive deviation from the more ordered condition of young cells and tissues. This process is 'normal', and yet by its very nature involves the production of abnormality.

The process of ageing is driven primarily by stochastic events and it is therefore not surprising that even in genetically homogeneous populations of inbred laboratory animals there is variation both in lifespan and in age-related pathology. Some age changes occur universally, such as those that affect elasticity of skin. These presumably result from stochastic events that are so numerous that by the law of large numbers, their aggregate effect is highly reproducible. Other changes, such as those that give rise to cell proliferative disorders like cancer, vary greatly between individuals. The triggering events for the latter changes are presumably rare, so that the element of chance is revealed much more clearly.

In outbred populations individuals are likely also to be genetically variable in the levels at which specific cell maintenance functions are set from conception. Some individuals may be genetically less well protected against certain types of somatic damage than others, thus predisposing them to show particular kinds of disorders during ageing. Finally, lifestyle factors (diet, stress, occupation, etc.) may contribute differentially to the rates at which defects may accumulate.

The upshot is that theories of ageing lead to a picture in which there is a progressive, roughly synchronous decline in function of many different organs, but where the rate of decline may be influenced by chance and/or heredity and/or lifestyle. Longitudinal studies of human ageing reveal increasing heterogeneity in many physiological functions, coupled with an overall average decline, consistent with this picture. If it is indeed true, as appears increasingly likely, that the ageing process is neither more nor less than the progressive accumulation of somatic damage resulting in abnormal or impaired function, there is no reason conceptually to separate many of the conditions commonly labelled as age-related 'diseases' from the spectrum of states that define 'normal' ageing, although in practice, the labelling of a condition as a 'disease' may properly reflect the fact that some clinical action is appropriate.

4. EVOLUTION OF HUMAN LONGEVITY

Humans have the longest lifespan of any mammal, being significantly longer-lived than non-human primates (Comfort 1979; Finch 1990). There is, of course, a major difficulty in comparing maximum lifespans of different species when the sample sizes from which the data are obtained vary enormously. Maximum lifespan is an extreme value statistic and therefore particularly affected by sample size, so that a more robust comparator would be, say, the 95th percentile of the lifespan distribution within a population (Kirkwood 1985). Such data are not always available, however, and in any case tend to be based on captive individuals rather than natural populations. Nevertheless, it appears likely that humans outlive chimpanzees and gorillas by 50% or more.

The chief factor likely to have been responsible for the increase in longevity during the human ancestral lineage is increasing brain size, and the consequent reduction in the level of environmental risk that presumably arose from increasing intelligence and a growing tendency to social living. Martin (1983) suggests that there was more than a doubling of mean endocranial capacity between *Australopithecus africanus* and *Homo erectus*, and Sacher (1975, 1976) has emphasized the significance of a general correlation between 'index of cephalization' and longevity in relationship to the evolution of human lifespan. We can readily see from the evolutionary theories of ageing, reviewed above, how a progressive reduction in the level of environmental risk is expected to result in selection for increased lifespan, particularly through the upregulation of the cell and molecular mechanisms for maintenance and repair of somatic tissues (see Kirkwood & Rose 1991). Thus, it is significant that a number of comparative studies of cell maintenance systems has repeatedly demonstrated that human cells have greater capacity than cells from other mammalian species for DNA repair (Hart & Setlow 1974; Francis *et al.* 1981; Treton & Courtois 1982; Hall *et al.* 1984; Grube & Bürkle 1992) and for resistance to oxidative and other stresses (Tolmasoff *et al.* 1980; Sohal *et al.* 1990; Sohal 1993; P. Kapahi, L. C. Gibbons, M. E. Boulton & T.B.L.K., unpublished data).

Increased investment in human somatic maintenance is predicted by the disposable soma theory to have

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imposed some cost in terms of the resources available for reproduction, and there is likely to have been additional selection pressure affecting fecundity and maturation rate arising from the increase in brain size and growing dependency of hominid infants on postnatal parental care. As revealed from skeletal remains, the transition from australopithecines to *Homo* was accompanied both by an increasing tendency towards bipedal locomotion (Susman & Sterns 1982) and by increasing cranial capacity (Martin 1983). The former process required changes in pelvic dimensions which resulted in a narrowing birth canal, while the latter lead to an increasing neonatal brain size. This conflict is believed to be responsible for the fact that human infants came to be born significantly more altricial than other mammals, requiring a significant phase of postnatal brain growth, during which the human infant was heavily dependent on its parents, particularly its mother, for nutrition and for protection. These adaptations presumably imposed additional constraints on female fecundity and maturation rate within the human life history.

It is relevant to note that the evolutionary theories of ageing suggest that natural selection will normally operate so that senescence has little or no impact on populations in the wild. Evidence suggests that this is generally so, although there is some detectable senescent mortality among certain longer-lived species, such as birds (Promislow & Harvey 1990). Humans are an interesting exception. Life expectancy *at birth* prior to the demographic revolution of the last century was only about 45 years, but there is evidence that life expectancy once adulthood was attained was considerably longer (Young 1971). Studies of contemporary hunter–gatherer societies such as the !Kung (Howell 1979) and Ache (Hill & Hurtado 1996) suggest that despite high infant mortality rates, those who survive to adulthood have reasonably long lifespans. In the case of the Ache, by the age of first reproduction women had a life expectancy of 60 years.

There are, in principle, two explanations for why senescent individuals might be found at relatively high frequency in human populations, even under conditions that might approximate to our evolutionary origins. One is simply that social and cultural evolution has proceeded so fast that the biological determinants of longevity have not yet caught up. The other is that the trade-off principle on which the disposable soma and more general pleiotropy arguments are based, does not guarantee that senescence will be rare 'in the wild', even though its impact is normally expected to be small. If, during the evolution of the hominid life history, the costs to Darwinian fitness of further delaying growth and maturation, or of reducing fecundity, were high enough, then an optimum might have been reached in spite of the fact that senescence affected a significant number of individuals (Kirkwood & Holliday 1986). The factors identified above as characterizing the process through which human longevity presumably evolved, in particular the increasing dependency of human offspring on an extended period of learning and development, make this second possibility rather plausible, and this is also supported by some of the arguments that have been advanced to explain the evolution of menopause.

5. EVOLUTION OF MENOPAUSE

The menopause in women occurs around the age of 45–50 in all regions of the world (Gosden 1985). The proximate cause appears to be oocyte depletion, which triggers endocrine changes. Menopause is generally thought to be unique to humans, although there is some suggestion that a similar process occurs in female toothed whales (Marsh & Kasuya 1986). All mammals, and many other species, show a decline in fertility with age in females but this tends to be a more gradual process involving increasing irregularity of cycling, rather than a complete shutdown of reproductive function. Fertility in males also declines with age, but does not come to an abrupt halt.

The Darwinian puzzle about menopause is why a woman should cease reproducing at an age when she is only about half-way through her biological lifespan, and when the impact of senescence on most somatic functions is still small. Assisted fertilization techniques have recently demonstrated that post-menopausal women can successfully bear children without serious complications. Oocyte depletion triggers menopause, but this begs the question of why natural selection has not produced a larger store of oocytes. The idea that oocytes, being formed early in development, have only a finite period of viability, seems unlikely, even though the increased frequency of chromosomal abnormalities among children born to older mothers suggests some deterioration with time. Female elephants and baleen whales remain fertile at ages past that of the human menopause (Crooze *et al.* 1981; Mizrooh 1981)

The explanation for the evolution of menopause appears most likely to be found in a combination of the factors discussed in the previous section in connection with evolution of human longevity (Medawar 1952; Williams 1957; Hamilton 1966; Kirkwood & Holliday 1986; Hill & Hurtado 1991 1996; Rogers 1993; Austad 1994; Peccei 1995; Holliday 1996*b*). Increased neonatal brain size coupled with the constraint on the birth canal linked to bipedal gait has made giving birth unusually difficult for human females, and the risks of child-bearing would presumably increase steeply if reproduction were to be continued during the senescent stages of the lifespan. Infants are highly dependent on parental, particularly maternal, care for extended periods and their survival in a harsh environment will be unlikely if the mother dies while they are still young. Both of these factors suggest that there may be an advantage in terms of Darwinian fitness in limiting reproduction to ages when it is comparatively safe, and thus increasing the likelihood of the mother surviving herself to raise any existing young to a state of successful independence. An alternative, and perhaps complementary advantage of menopause, is that post-menopausal women may contribute to the successful rearing of their grandchildren, by providing assistance to their own adult offspring, and thereby increasing their inclusive fitness, i.e. their overall genetic contribution to future generations (this hypothesis is sometimes

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known as the 'grandmother effect'). The relative importance of these factors has been studied in a number of recent theoretical models, but as yet no clear consensus has been formed (Hill & Hurtado 1991, 1996; Rogers 1993; Peccei 1995).

6. WHEN DOES HUMAN AGEING BEGIN?

This section briefly addresses the other meaning of 'the origins of human ageing', namely, the point in the human lifespan at which the ageing process can be said to begin. Some have suggested that senescence begins at the time when age-specific mortality rates are a minimum, which is around the age of puberty (Medawar 1955). Partridge & Barton (1996) suggest that the best measure of ageing is based on 'residual reproductive value' which is calculated taking account of effects of ageing on both survivorship and fertility. The advantage of this definition is that it acknowledges that in Darwinian terms, the impact of senescence on fertility may be just as important as its impact on survivorship. Residual reproductive value begins to decline following the start of reproduction and therefore also suggests that ageing begins around the time of reproductive maturation. However, both of these measures concern the *impact* of ageing on the organism. If it is true that ageing is caused by the gradual accumulation of somatic damage through life, resulting from limited investments in somatic maintenance and repair (the 'disposable soma' concept), then the *process* of ageing begins earlier, even *in utero*. The ontogenetic origin of human ageing may be the point at which the first, committed somatic cells differentiate from the germ cell lineage, early in embryonic development.

7. CONCLUSIONS

The biological origins of human ageing can be understood in evolutionary terms as a consequence of (i) the declining force of natural selection with age, and (ii) the fact that long-term survival requires investments in somatic maintenance which divert resources from growth and reproduction, and which therefore have costs as well as benefits. The two evolutionary processes responsible for ageing therefore involve trade-offs, as in the disposable soma and pleiotropy concepts, and the accumulation of late-acting deleterious mutations through the mutation–selection balance. Given that ageing occurs in all higher animals, the phylogenetic origins of human ageing are likely to be in our distant evolutionary past, perhaps dating from the primordial origin of a 'division of labour' between germ and somatic cells (Weismann 1891; Kirkwood & Cremer 1982).

The evolution of human longevity can most plausibly be explained in terms of the selection pressure for increased lifespan arising from the progressive increase in the size of the brain. This will have had ecological consequences in terms of reduced levels of mortality, due to heightened intelligence and social cooperation in food gathering and defence, and physiological consequences in terms of the resources required to grow and programme a larger brain. Together, these factors will have favoured increased longevity. The paradox of menopause can be resolved by noting the increasing altriciality of human babies, making it possible that the fitness loss which is incurred by shutting down reproductive functions at age 45–50 is at least partially compensated for by the enhanced survival of existing offspring. This effect will be strengthened if post-menopausal women contribute to the successful rearing of their grandchildren, thereby increasing their own inclusive fitness.

The evolutionary explanation for human ageing suggests that the mechanisms of ageing involve progressive accumulation through life of unrepaired somatic damage. Such damage is likely to be of various kinds, which implies that lifespan is influenced by a diverse repertoire of genes which regulate somatic maintenance functions, and which may be involved in other kinds of trade-offs as well. It is also possible that there exist purely deleterious late-acting mutations that have escaped the force of natural selection. In this view, many of the age-related diseases in humans may share common causative mechanisms with each other and with 'normal' ageing itself. The process of ageing probably begins early in life, even before birth, although the outward signs do not become apparent until later.

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