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SUMMARY

A broad biological approach makes it possible to understand why ageing exists and also why different mammalian species have very different maximum longevities. The adult organism is maintained in a functional state by at least ten major mechanisms, which together comprise a substantial proportion of all biological processes. These maintenance mechanisms eventually fail, because the evolved physiological and anatomical design of higher animals is incompatible with continual survival. The lifespan of each mammalian species depends on the efficiency of maintenance of their cells, tissues and organisms, and there is much evidence that such maintenance is more effective in long-lived species, such as man, than in short-lived small mammals. It is also evident that there is an inverse relationship between reproductive potential and longevity, which would be expected if total metabolic resources are shared between investment in reproduction, and investment in the preservation of the adult body. It is proposed that the eventual failure of maintenance leads to the pathological changes seen in age-associated disease. Although we now have a biological understanding of the ageing process, much future research will be needed to uncover the cellular and molecular changes which give rise to age-associated diseases. The major aim of such research is to devise procedures to delay or prevent the onset of these diseases.

1. INTRODUCTION

Forty-five years ago, Medawar (1952) published an authoritative and influential lecture on ageing: 'An unsolved problem in biology'. Many people believe that ageing is still an unsolved problem. I disagree, because at the broad biological level a great deal of information has been gained about ageing in the last four decades or so. Moreover, much of this information comes from a wide spectrum of biological and biomedical research, rather than from the study of gerontology itself. I have argued the case in my book *Understanding ageing* (Holliday 1995). This overview will provide, in effect, a summary of my book, in non-technical language (apart from table 2) and with the omission of many pertinent references, which can be found in the book.

2. ANCIENT ORIGINS OF AGEING

Early multicellular animals evolved a germ line which was transmitted from generation to generation, and a soma or body. This probably consisted of, or contained, cells which were totipotent, that is, they had the ability to replace any cell of the body that was damaged or lost. This meant that they were potentially immortal, and a few existing animal species (flatworms and coelenterates) retain this regenerative ability, since they have a pool of totipotent cells. As evolution proceeded the soma often contained more and more post-mitotic cells, which are incapable of division, and in some successful groups (such as the insects and nematodes) the soma can consist entirely of non-replaceable post-mitotic cells. For many reasons, these cells cannot be expected to survive indefinitely, so the soma necessarily has a finite lifespan.

Given two comparable organisms, one of which is potentially immortal and the other mortal, we might expect that the former had a selective advantage over the latter, because it can reproduce indefinitely. However, Darwin realized that organisms almost always produce more offspring than can survive to adulthood and themselves reproduce. The cornerstone of the principle of natural selection is the fact that the environment is hostile, and individuals compete for survival. The high rate of attrition means that the population is age-structured, with many more young individuals than old ones, and with decreasing cohorts of animals of increasing age. Thus, the likelihood of a potentially immortal animal reproducing for a long period becomes extremely small.

The ability to repair and regenerate the soma depends on the investment of metabolic resources, which can be saved in an organism with finite survival time. It simply becomes a better strategy to use these saved resources for rapid and efficient reproduction, so that the genes are transmitted to subsequent generations, rather than use them to maintain a soma in an environment where death from predators, disease, starvation or drought are all too likely to terminate life. This disposable soma theory (Kirkwood & Holliday

Table 1. *The allocation of all available energy resources in mammals*

normal functions	reproduction	maintenance
biochemical synthesis	gonads, gametes and sex	wound healing
metabolism	development	immunity
respiration	gestation	protein turnover
cell turnover	suckling	defence against free radicals
movement	care of offspring	DNA repair
feeding and digestion	growth to adult	detoxification
excretion		epigenetic stability
		homeostasis
		fat storage

1979; Kirkwood 1997) explains why ageing evolved in all major groups of animals. Ageing can therefore be regarded as a failure to maintain the soma.

3. MAINTENANCE AND THE AGEING OF MAMMALS

In this and subsequent sections I will discuss only the ageing of mammals. All animals survive by obtaining energy from the environment to create biological order and to reproduce themselves. The available resources are allocated to three major functions. First, ongoing metabolism of the organism, second, all aspects of reproduction, and third a set of maintenance mechanisms. These three functions consume all available metabolic energy and although there may be some overlap between them, it is possible to itemize their main features as shown in table 1. With regard to understanding ageing, we are mainly concerned with maintenance mechanisms and their eventual failure.

Wound healing is one of the most obvious, and this also includes clotting of blood and the rejoining of broken bones. However, mammals have lost the ability to replace lost limbs, or even digits, whereas some cold-blooded vertebrates have this regenerative capacity. The immune response is essential to counter parasites and pathogens. Individuals do not survive very long if their immune system is severely impaired, as AIDS patients show. Proteins carry out a vast range of cellular functions, but individual molecules are subject to damage. A wide range of deleterious chemical modifications can occur, and these molecules are normally degraded by a set of protease enzymes. Such protein turnover occurs continually in all cells of the body. It is also essential to maintain the integrity of DNA, which carries all genetic information. A complex set of repair mechanisms exist that can recognize spontaneous or induced damage to DNA and restore its normal base sequence. The synthesis of DNA, and also RNA and protein, is very accurate, and this is achieved by proof-reading mechanisms, which detect and remove almost all errors in synthesis. Such proof-reading depends on the investment of metabolic energy. During respiration and some other metabolic processes, oxygen free radicals are produced. These are short-lived but also highly reactive, and they can damage DNA, proteins and membranes. Defences against free radicals *in toto* comprise a very important maintenance mechanism. Plants defend themselves against herbivorous animals by producing a variety of toxic chemicals. In turn, animals have evolved the means to detoxify such chemicals. A very large family of enzymes exist in liver, and some other tissues, to destroy these dangerous compounds (as well as many that have been synthesized artificially). The cells of the body have specialized functions, with each type of cell having a particular morphology, or phenotype. These phenotypes are stably maintained by means of epigenetic mechanisms. The breakdown of normal controls can have disastrous consequences, particularly the formation of cancer cells. The many different physiological functions of cells and tissues are also regulated by a set of homeostatic mechanisms, the most important of which (in mammals and birds) is temperature control. This ensures stability of the internal body environment, irrespective of fluctuations in the external environment. Hormones and growth factors are very important components of homeostatic mechanisms. Finally, the ability of organisms to store energy in the form of fat or glycogen, can also be regarded as a long-term maintenance mechanism.

It should be noted that the study of maintenance mechanisms comprises a very substantial proportion of all biological research, most of which is not thought to have anything to do with mainstream gerontology. It is also obvious that the efficiency of maintenance depends on many genes, which specify the components of each mechanism. Taken as a whole, maintenance consumes a large proportion of the body's available metabolic resources.

Whereas the normal functions of metabolism are essential for survival of an animal, there could be different allocations of the remaining resources to reproduction and maintenance. Thus, a mammalian species which grows and reproduces rapidly, would necessarily have fewer resources available for maintenance. Such an organism will have a short lifespan. In contrast, a species which invested heavily in maintenance and thereby acquired a long lifespan, would necessarily reproduce more slowly. This is illustrated in figure 1. In principle, it would be possible to invest sufficient resources in maintenance to survive indefinitely, but this has never happened, either in mammals or any other highly evolved species.

4. THE EVOLVED DESIGN OF MAMMALS

It is proposed that ageing is due to the failure of maintenance. It is also due to the fact that mammals evolved a body structure that is not compatible with indefinite survival. Major organs such as the brain and heart consist largely of post-mitotic cells, and they have limited capacity to replace such cells, or repair accumulated damage. The heart is a very efficient pump, but its capacity for repair and maintenance is very limited, so eventually it will cease to function. Similar considerations apply to major blood vessels, the

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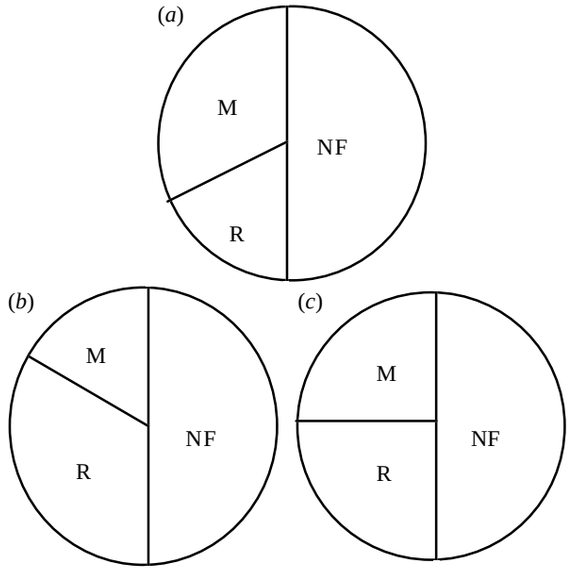

Figure 1. Strategies for survival and the allocation of resources. NF, normal functions, which are assumed to be a constant fraction of all available resources. R, all reproductive functions and M, all maintenance functions. (*a*) An organism which is potentially immortal, (*b*) an organism with a short lifespan, and (*c*) an organism with a long lifespan.

structure of which is not conducive to ongoing repair. Teeth are instructive. They are genetically programmed to be a certain size and strength, yet they wear down or suffer decay during a lifetime. Indeed, teeth neatly demonstrate that the distinction between programming and 'wear and tear', which is often made in relation to ageing, is quite artificial. Both are important in determining the lifetime of teeth. In many species, non-replaceable teeth have evolved 'to last a lifetime'. The retina of the eye consists of a single layer of cells, which cannot be replaced. There is continual turnover of photoreceptors throughout life, and the underlying epithelial cell layer is not totally efficient in removing discarded photoreceptor material. In consequence, the retina gradually loses efficiency in function. Also, the lens of the eye is laid down early in life, and the major proteins, the crystallins, are never replaced. With time, many modifications to these proteins occur, until eventually transparency can be lost and cataracts are formed. There are other long-lived proteins in the body, in particular, the families of collagens and elastins, which have particularly important functional roles in connective tissues, joints, the walls of arteries and so on. With time these molecules become progressively cross-linked and lose elasticity. The cross-linking of collagen is a well-known 'biomarker' of ageing.

It is instructive to consider the similarities and differences between machines and organisms. No matter how well a machine is designed, it requires maintenance for ongoing function, and the better the maintenance, the longer it will survive. Effective maintenance is normally carried out by stopping the machine, something that is impossible in a living organism. Machine components will eventually wear out and have to be replaced. Replacement of parts allows a machine to survive for a very long time, or indefinitely, as we see in the preservation of vintage cars. This long-term survival of a machine is, of course, extremely expensive.

In the case of organisms, maintenance has to be carried out whilst the organism is alive, and many parts cannot be replaced. (However, surgeons are continually increasing the range of components that can be replaced.) It is interesting to consider the anatomical design of a complex organism which could live indefinitely. For example, there would have to be two cardiovascular systems, so that one could be shut down and repaired, whilst the other continues to function. It is even harder to envisage duplication of brain structures and functions, and particularly the fate of memory in such a binary system.

5. THE MODULATION OF LONGEVITY

Mammalian species have about a 50-fold range in maximum lifespans. In general, species living in a high-risk environment with high mortality, would be expected to evolve short lifespans, and rapid reproduction. In contrast, species living in a low-risk environment with much less mortality, would be expected to evolve long lifespans. Examples of both trends are seen in mammalian evolution. Amongst the carnivores, the stoats and weasels have a high metabolic rate and are dependent on a continual supply of food. They also have large litters and rapidly growing offspring. The reverse has occurred in the primates, where small monkeys and marmosets breed quite rapidly and have short lifespans, whereas larger monkeys, smaller apes, the great apes and man have progressively longer lifespans.

Comparative studies with different species should reveal differences in the efficiency of maintenance mechanisms. This is confirmed for DNA repair, where four out of five studies show a clear relationship between repair of ultraviolet light-induced damage and species longevity, and the fifth is equivocal (Tice & Setlow 1985). Many other maintenance parameters have also been examined, and the correlation with longevity is convincingly demonstrated. I show here in table 2 a comparison between some human maintenance activities and the same activities in mouse or rat, with lifespans of about three years. In most of these studies, other species were also examined and these showed the expected intermediate efficiencies.

6. THEORIES OF AGEING

Many theories of ageing have been proposed in this century, and very often the proposer attempts to explain the whole complex process of ageing in terms of a single theory. These attempts are probably doomed to failure, since it has become obvious that ageing is multicausal, or multifactorial. It is in fact quite striking that individual theories, often relate rather closely to individual maintenance mechanisms. For example, the popular free radical theory of ageing relates to the failure of defences against oxygen free radicals. The somatic mutation theory relates to the

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Table 2. *A comparison of the efficiency of some maintenance functions in man and mouse, or rat*

(In most studies other mammalian species were also included (Holliday 1995, 1996*a*). + in the result column indicates that the parameter value is correlated with longevity (ratio > 1); − in the same column indicates that the parameter value is negatively correlated with longevity (ratio < 1).)

parameter measured	no. of species	result	ratio human/rodent	reference
longevity of fibroblasts *in vitro*	8	+	4–6	Rohme 1981
longevity of erythrocytes *in vivo*	11	+	2–4	Rohme 1981
cross-linking of collagen	3[a]	−	$\sim \frac{1}{30}$	Everitt *et al*. 1968; Yamauchi *et al*. 1988
DNA repair	7–34[b]	+	4–7	Tice & Setlow 1985
polyADP ribose polymerase	13	+	4.5	Grube & Burkle 1992
γ ray-induced ADP ribosyl transferase	12	+	15–22	Pero *et al*. 1985
DNA methylation decline	3[c]	−	∼ 12	Wilson & Jones 1983
carcinogen binding to DNA	6	−	$\frac{1}{20}$	Schwartz & Moore 1977
mutagenicity of activated carcinogen	6	−	$< \frac{1}{500}$	Schwartz 1975
age-related cancers	2[d]	−	$< 10^{-5}$	Holliday 1996*a*
carotenoids in serum	13	+	33	Cutler 1984
auto-oxidation of tissues	9	−	$\frac{1}{5}-\frac{1}{10}$	Cutler 1985
metabolic rate and oxidized DNA bases	4	−	$\frac{1}{15}$	Adelman *et al*. 1988
production of oxygen free radicals	7	−	N.D.[e]	Ku *et al*. 1993

[a]Human, bovine and rat.
[b]Three separate studies.
[c]Human, hamster and mouse.
[d]Human and mouse (the incidence of cancer in aged individuals is comparable. 10^{-5} is the ratio of the product of longevity and body weight in mouse and man).
[e]No human study; the ratio between bovine and mouse is about one-fifth.

failure of DNA repair. Various forms of abnormal protein theories relate in one way or another to errors or defects in protein molecules, and the failure to remove such molecules. The autoimmune theory of ageing proposes that the immune system eventually fails to distinguish self from non-self antigens. Others relate to the loss of epigenetic controls, or the deleterious effects of toxic chemicals and so on.

It is probable that there is some truth in all these theories, and that a broader more global view should be taken of all the deleterious changes that can occur in a complex organism. Failure of maintenance encompasses all mechanisms, although we might well expect that some are more important than others.

7. REPRODUCTION AND LIFESPAN

It has already been mentioned that there should be some relationship between the longevity of a species and its reproductive capacity. The parameters which have to be considered are (i) gestation period, (ii) litter size, (iii) time to develop to adulthood, (iv) litter intervals, and (v) period of reproduction during the total lifespan. These were assessed from 47 mammalian genera, for which the best data are available (Holliday 1994, 1995). The result shows a very clear inverse relationship between the log of the maximum total number of offspring that could be produced under ideal conditions, and the maximum lifespan, as measured by the survival of captive animals kept under good conditions in zoos. In approximate order of offspring/longevity ratios are rodents and rabbits, small carnivores and herbivores, larger carnivores, large herbivores, pachyderms and higher primates. An exception is the temperate bear (*Ursus*) which has greater reproductive potential than expected for its longevity, possibly because it hibernates each year. Bats provide an interesting and important exception in the various attempts that have been made over the years to relate longevity to size or metabolic rate. They have long lifespans and reproduce slowly (commonly one offspring per year). This can almost certainly be related to their specialized and safe life-style, namely, rapid flight and hanging from the roofs of caves. Clearly annual mortality is far lower than for ground-living species of comparable size and similar metabolic rate.

8. AGEING AND DISEASE

It has been said in jest that ageing is a sexually transmitted terminal disease. Nevertheless, since ageing is a totally natural phenomenon it cannot be considered to be a pathological condition. That is certainly not to say, however, that age-related diseases have nothing to do with natural ageing. Such a view is often maintained, because many elderly people do not suffer from dementia, heart disease, osteoporosis, carcinoma and so on. Since ageing is multicausal, one would expect that the failure of maintenance would affect a number of organ systems with some degree of synchrony, but one particular failure is quite likely to be in advance of others. The loss of neurones—from whatever cause—will lead to dementia. Failure to control blood pressure may lead to stroke. The development of atherosclerotic plaques in major arteries, may lead to the failure of blood supply to the heart and a heart attack. Cataracts

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and retinopathy cause blindness. The wearing out of joints leads to osteoarthritis, and failure to maintain bone structure to osteoporosis. The failure to secrete or respond to insulin causes late-onset diabetes. Loss of normal cellular regulation leads to cancer and so on.

All these age-related diseases, and many others, are the subject of intense research effort around the world, yet very few of the scientists involved consider that they are working in the field of gerontology. This is unfortunate, because if an age-related disease is to be prevented, or its onset delayed, then it is necessary to know the primary causes of the degenerative change (Holliday 1996*b*). Nowadays, disease research involves molecular and cellular studies of primary events, and that is very much in the province of gerontology. If we are to have a better understanding of the onset of the many important age-related diseases, then much more research should be supported in the field of gerontology. This was very clearly realized by the pioneer geriatrician Edward Stieglitz 55 years ago in his article 'The social urgency of research on ageing' (Steiglitz 1942). In the UK, very little action has been taken in the last half century.

9. CONCLUSIONS

I believe we now have answers to three basic questions, 'Why do we age?', 'Why do we live as long as we do?', 'Why do different mammalian species have different maximum lifespans?'. We age because we evolved from organisms which also age. We age because our evolved body structure is incompatible with indefinite survival. We age because our various maintenance mechanisms fail to preserve the normal structure and function of cells and tissues. As humans, we live as long as we do, because we have evolved a lifestyle with low annual mortality (Holliday 1996*c*). This has allowed more resources to be invested in maintenance and less in reproduction. In contrast, species which live in a high-risk environment can only survive by investing more heavily in reproduction, with correspondingly less resources allocated to maintenance. Thus, the adaptive radiation of mammals to different ecological niches has also resulted in the evolution of longevities over an approximately 50-fold range. When considered at the level of the organism, ageing is no longer an unsolved problem in biology. However, at the level of fine detail—the actual molecular and cellular changes that bring about the ageing phenotype—then there is a great deal of ignorance. I believe these changes will best be understood by detailed studies of maintenance in various species, and particularly the reasons for the failure of maintenance.

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