Genetics and the future of human longevity

Thomas B L Kirkwood
MA, MSc, PhD

The first half of the 20th century saw a rapid increase in expectation of life in industrialised nations due to improved sanitation, public health, housing, nutrition and medical skills. The second half of the 20th century has seen a growing concern with the biomedical challenge generated by the increasing prevalence of old people in society. Much of this work has focused on genetics. It is perhaps noteworthy that the discovery by Watson and Crick[1] of the double helical structure of DNA occurred in the same decade as the first genetic theories on the evolution of ageing were proposed by Medawar[2] and Williams[3], and when two mechanistic theories of ageing, the free radical and somatic mutation theories, were suggested by Harman[4] and Szilard[5], respectively. A union of evolutionary and mechanistic theories occurred in 1977, in the form of the disposable soma theory of ageing[6,7]. In recent years the evidence for genetic factors being involved in ageing has expanded at a great rate[8–10].

The major lines of empirical evidence for the role of genetic factors in ageing are as follows: first, life span in human populations shows significant, though low, heritability[11,12] (in the order of 20–35%); second, different species have different intrinsic life spans which can reasonably be attributed to differences in their genomes; third, in human populations there exist inherited progeroid disorders such as Werner's syndrome[13] in which affected individuals have a complex phenotype characterised by premature development of a variety of age-related diseases, including arteriosclerosis, type II diabetes, cataracts, osteoporosis and cancers; fourth, in invertebrate model systems such as the fruitfly, *Drosophila melanogaster*, and nematode worm, *Caenorhabditis elegans*, clear evidence of genetic effects on life span has been discovered[14,15].

As the 20th century draws to its close, the amount of genetic information concerning human health and disease is expanding at an enormous rate, due to the efforts of the various human genome projects. What will be the impact of research on human longevity in the 21st century and beyond? It is already clear that the science of human ageing will be perhaps the pre-eminent biomedical research challenge in this period.

This article is based on the FE Williams Lecture given at the Royal College of Physicians on 4 December 1996 by **THOMAS KIRKWOOD**, Professor of Biological Gerontology, University of Manchester

Terminology

In human gerontology the words 'ageing' and 'senescence' are used more or less interchangeably, and this will be the practice here. This is not to deny the importance of development and maturation, which some also count as 'ageing', but my primary concern is with the declines in structure and function that unfold gradually and progressively during adulthood. The measure of senescence most commonly used is one based on the increase in age-specific death rates[16,17].

In 1825, Gompertz[18] observed that adult human mortality rates show an approximately exponential rise with increasing chronological age, and similar patterns have been noted in other species[17]. The Gompertz model has been generalised by adding a constant to represent age-independent mortality due to extrinsic causes[19], and the resulting model for mortality rate can be written as

$$\mu(x) = \alpha e^{\beta x} + \gamma$$

where α, β, and γ are constants and x denotes age. The parameter β denotes the 'actuarial ageing rate' and determines how fast the age-dependent component of adult mortality increases with time. The parameter α denotes 'initial vulnerability' and acts as a scale parameter for the age-dependent component of adult mortality (note that the Gompertz model does not make any attempt to describe juvenile mortality). The parameter γ denotes the age-independent component of adult mortality.

There is some evidence that human mortality increases more slowly than the Gompertz model predicts among centenarians[20] but it is not yet clear whether this slowing at extreme old age reflects: (i) genetic heterogeneity within the population, (ii) particularly assiduous care of the oldest old, or (iii) intrinsic biological processes. Genetic heterogeneity is likely to be at least part of the explanation as centenarians probably comprise a genetically robust subset of the population whose below-average ageing rate becomes apparent only when the frailer genotypes have already died[11].

An exponential increase in mortality rates within human populations does not require that the underlying physiological processes follow exponential kinetics. Cross-sectional studies reveal great variability

in both the slopes and patterns of the changes observed with age. However, many important diseases of late life do show exponential increases in age-specific incidence; examples include Alzheimer's disease, carcinoma of the prostate, and carcinoma of the colon.

Theories on evolution of ageing

Theories on evolution of ageing seek to explain why ageing occurs and to identify what kinds of genes are responsible. The puzzle, of course, is to explain why ageing occurs in spite of its clearly deleterious impact on Darwinian fitness.

Because ageing is so obviously deleterious for the individual, attempts have been made to explain its evolution in terms of an advantage to the population as a whole[21]. Is it a form of population control to prevent overcrowding? This theory is given little credence today – first, because there is no evidence that animal numbers in the wild are regulated to any significant extent by senescence, most deaths occurring at younger ages from extrinsic causes such as predation, and second, because it invokes the controversial concept of group selection, which is unlikely to be effective in this context. Nevertheless, these ideas periodically reappear, presumably because they appeal to the notion that ageing is programmed like development and will yield to the same kinds of genetic analysis that have proved so successful in developmental biology.

Greatest weight is now attached to evolutionary theories which are 'non-adaptive', in the sense that they do not suggest ageing confers any fitness benefit *of itself*, and they recognise that it may indeed be harmful. The non-adaptive theories explain evolution of ageing through the *indirect* action of natural selection.

One such theory is the 'mutation accumulation' theory[2]. This is based on the observation that natural selection is relatively powerless to act on genes which express their effects late in the lifespan at ages when, because of *extrinsic* mortality, survivorship has fallen to a low level. The assumption is that in the starting population there would be no age-related increase in intrinsic mortality, otherwise the theory would be circular. In such a context, late-acting deleterious mutations are predicted to accumulate over a large number of generations within the genome. The practical consequences of such an accumulation would be minimal in the wild environment but will have a serious effect upon the organism if it is moved to a protected environment. In the protected environment, the reduction in extrinsic mortality permits survival to ages when the intrinsic effects of the accumulated mutations are felt. In other words, ageing has evolved where beforehand it did not exist.

A second concept invokes the idea that there may be pleiotropic genes whose expression involves trade-offs between early-life fitness benefits and late-life fitness disadvantages[3]. Like the mutation accumulation theory, this 'antagonistic pleiotropy' theory rests on the observation that the declining force of natural selection provides a differential weighting across the life span which will ensure that quite modest early-life fitness benefits outweigh major fitness disadvantages in later life.

The trade-off principle is also at the heart of the 'disposable soma' theory[6,7,22]. This theory provides a direct connection between evolutionary and physiological aspects of ageing by recognising the importance of the allocation of metabolic resources between activities of growth, somatic maintenance, and reproduction. Increasing maintenance promotes the survival and longevity of the organism but only at the expense of significant metabolic investments that could otherwise be used to accelerate growth and reproduction. It has been demonstrated with formal models that the optimum allocation strategy results in a smaller investment in maintenance of the soma than would be required for indefinite lifespan[23,24]. In effect, the organism sacrifices the potential for indefinite survival in favour of earlier and more prolific fecundity.

Three categories of genes are thus predicted by the evolutionary theories to affect ageing and longevity:

1 Genes that regulate levels of somatic maintenance and repair;
2 Pleiotropic genes involved in trade-offs that do not include somatic maintenance;
3 Purely deleterious late-acting mutations that have escaped elimination due to the decline in the force of natural selection at old ages.

Martin *et al*[10] have suggested the terminology 'public' and 'private' to distinguish genes associated with ageing that are likely to be shared or individual. Genes involved in trade-offs, especially genes regulating fundamental aspects of somatic maintenance such as antioxidant systems, are expected to be public. Conversely, late-acting deleterious mutations are expected to be private, since the fate of these alleles will be strongly influenced by random genetic drift.

Implications of the evolutionary theories

A number of implications follow from the evolutionary theories. First, it is predicted that multiple kinds of genes contribute to senescence and that the total number of such genes may be large (Fig 1). This suggests that uncovering the genetic basis of senescence will be a complex task requiring a combination of approaches and methodologies.

Second, the theories readily explain differences in the rate of ageing between different species, which are likely to be the result of different levels of extrinsic mortality. This is because extrinsic mortality determines the rate of decline in the force of natural selection. Extrinsic mortality also has a major effect on the

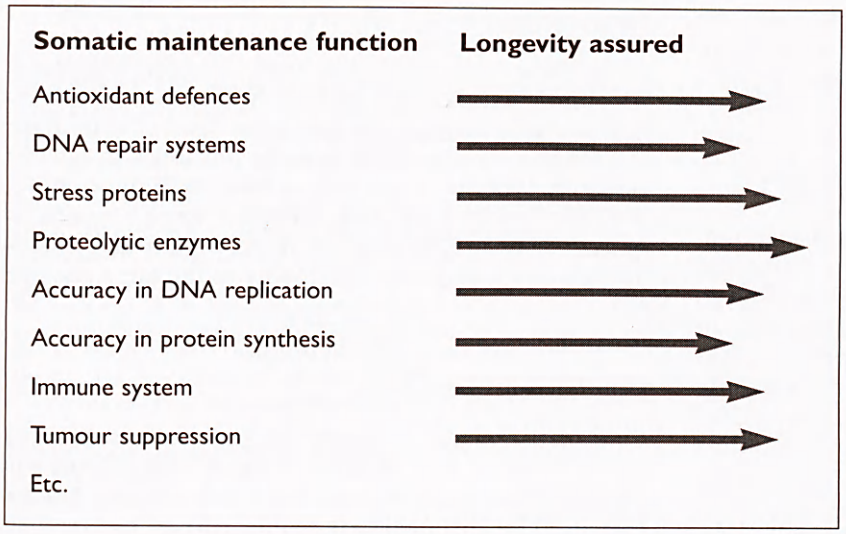

Fig 1. Diagram illustrating how polygenic control of longevity is effected, as predicted by the disposable soma theory of ageing. Natural selection acts in a similar way on the different genes regulating individual somatic maintenance functions. The precise setting of each function in an individual determines the period of 'longevity assured', as indicated by the lengths of the arrows. At the level of the population, the average period of longevity assured by each maintenance function is expected to be similar. However, some variance within the population is expected, so that within and between individuals the relative lengths of the arrows may vary. (Reproduced from reference 7 by permission of the *Annals of the New York Academy of Science*).

optimal allocation of energy between maintenance, growth and reproduction, species at higher risk from extrinsic mortality being expected to invest relatively less in maintenance and more in reproduction. The disposable soma theory thus predicts higher levels of maintenance in somatic cells of long-lived species, for which there is growing evidence.

Third, in the case of the disposable soma theory, there is a clear prediction that the actual mechanisms of senescence will be stochastic, involving processes like the random accumulation of somatic mutations or oxidative damage to macromolecules. Biological gerontology has long been divided between the 'programme' and 'stochastic' views. The idea that ageing might be due to the accumulation of random damage, but that the *rates* of damage are programmed in a statistical sense through the evolved settings of the maintenance systems, offers some accommodation of these apparently opposite views.

A fourth implication of the evolutionary theories is that senescence may be malleable. From the human perspective, the trade-off principle is one that needs to be borne in mind when considering possible interventions in the ageing process. Interventions that would increase longevity or postpone a late-age disease may turn out to have side effects due to the existence of trade-offs.

Genetics of human longevity

Two strategies have been delineated to identify genes associated with human longevity[11]. The major interest is in genes that may confer above-average or extreme longevity, since there is potentially a large number of alleles that shorten life span through mechanisms that are unconnected or only indirectly connected with ageing.

One strategy is the 'candidate gene' approach using case-control methodology. The aim is to identify extremely long-lived individuals and compare their allele frequencies at the candidate gene locus to the allele frequencies of a control population, who will be less long-lived individuals from the same genetic background. This assumes that the controls are unlikely themselves to reach the extreme old age of the 'cases', which is not unreasonable if the age criteria are appropriately defined. Candidate gene studies have identified significant differences in allele frequencies between centenarians and controls at the HLA[25,26], apolipoprotein E[27], and angiotensin converting enzyme loci[27], but have not so far been applied to their full potential.

The second approach is the sib-pair method designed to detect loci that segregate within kin groups with traits of interest, such as inherited diseases. In the case of ageing, the trait of interest is extreme longevity. This method requires the recruitment of a sufficiently large sample of extremely long-lived sib pairs and its application has not yet been reported.

In the case of progeroid diseases, 1996 saw the identification by positional cloning of the gene responsible for Werner's syndrome which appears to code for a DNA helicase[28]. This finding is highly significant in that it supports the idea that accumulation of DNA damage may be a contributing factor to ageing, especially in dividing cells. In patients with Werner's syndrome post-mitotic tissue is relatively spared, which is consistent with the discovery that the gene defect is one that will principally affect DNA replication.

The future of human longevity

Our present understanding of the genetics of human ageing permits some consideration of how human life spans might conceivably change in the future, although a great deal more research will be needed. Human longevity may be altered as a result of (i)

natural selection, (ii) artificial selection, (iii) genetic engineering, (iv) drug interventions, (v) genetic risk assessment coupled with prophylactic measures, (vi) behavioural and lifestyle modifications.

Natural selection

Even though human populations now live in circumstances that many regard as 'unnatural', the process of Darwinian natural selection continues. The fact that so many humans now live to experience old age will, in principle, expose the genetic factors involved in ageing to new selection forces tending to increase life span. On the other hand, selection against inherited weaknesses has been diminished through medical interventions and the generally more comfortable circumstances of life, and this may lead to the accumulation of minor gene defects that will eventually have deleterious effects on long-term survival. Patterns of reproduction have also altered profoundly through the development of reliable contraception, resulting in extensive family planning governed mostly by social and economic circumstances. The net effect of these changes on the genetics of the future human life history are hard to predict but merit consideration.

Artificial selection

Artificial selection has produced significant effects on the life histories of fruitflies[29,30], but such procedures are neither ethical nor feasible in human populations. The fruitfly experiments are interesting for the information that they provide on genetic variance in populations and on the rate and extent of the response to selection. However, the genetic variance within a population reflects the evolutionary history of that population, and there are likely to be major differences between fruitflies and humans with regard to the genetic variance in factors affecting life span.

Genetic engineering

In the popular mind, advances in genetic research are often linked to the idea of genetic engineering. Genetic engineering is a conceivable route to modification of human longevity although this presupposes major advances in the technology of gene therapy and in the detailed dissection of the genetic factors influencing life span. At present, effective gene therapy is still unavailable even for monogenic inherited diseases like cystic fibrosis which are, rightly, the primary targets of research. Whether genetic modification of a 'normal' process like ageing will ever be ethically acceptable or practically feasible is far from clear, and meaningful discussion must await the further identification of possible genetic targets. Nevertheless, the broad issues can and should be addressed as part of the wider debate on application of the 'new genetics'.

Drug interventions

Drug interventions based on understanding of genetic mechanisms involved in late life diseases such as Alzheimer's disease are the most likely immediate benefits to emerge from genetic advances in ageing research. Whether these will, in time, have the cumulative effect of altering underlying life spans remains to be seen, but in any case the more urgent and attainable goal is to improve the quality of the later years of life.

Genetic risk assessment

One of the major successes of genome research to date has been the identification of risk alleles for conditions such as Alzheimer's disease and breast cancer. The discovery of alleles linked to late life diseases is likely to continue at an accelerating pace. If such discoveries are coupled with the development of effective drug treatments or prophylaxis, they are likely to result in further extension of average life expectancy through reducing the negative impact of risk alleles on survivorship. It is less likely, however, that this approach will alter maximum life span, since the longest lived at present are probably those who are at lowest genetic risk.

Behavioural and lifestyle modifications

Advances in genetic understanding of ageing will not necessarily require genetic or drug-based interventions to produce enhancement in the quality of later life, or even life extension. Knowledge of genetic mechanisms is also likely to help to identify non-genetic factors (nutrition, exercise, etc) which may be beneficial. It is already clear that genes are only a part of what influences duration of life. The identification and exploitation of gene-environment and gene-lifestyle interactions will be of great importance too.

References

1 Watson JD, Crick FHC. Genetical implications of the structure of deoxyribonucleic acid. *Nature* 1953;**171**:964–7.
2 Medawar PB. *An unsolved problem of biology*. London: HK Lewis, 1952.
3 Williams GC. (1957) Pleiotropy, natural selection and the evolution of senescence. *Evolution* 1957;**11**:398–411.
4 Harman D. A theory based on free radical and radiation chemistry. *J Gerontol* 1956;**11**:298–300.
5 Szilard L. On the nature of the aging process. *Proc Natl Acad Sci USA* 1959;**45**:35–45.
6 Kirkwood TBL. Evolution of ageing. *Nature* 1977;**270**:301–4.
7 Kirkwood TBL, Franceschi C. Is ageing as complex as it would appear? New perspectives in ageing research. *Ann NY Acad Sci* 1992; **663**:412–7.
8 Jazwinski SM. Longevity, genes, and aging. *Science* 1996; **273**:54–9.
9 Kirkwood TBL. Human senescence. *BioEssays* 1996;**18**:1009–16.

10 Martin GM, Austad SN, Johnson TE. Genetic analysis of ageing: role of oxidative damage and environmental stresses. *Nat Genet* 1996;**13**:25–34.
11 Schächter F, Cohen D, Kirkwood TBL. Prospects for the genetics of human longevity. *Hum Genet* 1993;**91**:519–526.
12 McGue M, Vaupel JW, Holm N, Harvald B. Longevity is moderately heritable in a sample of Danish twins born 1870-1880. *J Gerontol* 1993;**48**:B237–44.
13 Martin GM. Genetic syndromes in man with potential relevance to the pathobiology of aging. *Birth Defects* 1978;**14**:5–39.
14 Tower J. Aging mechanisms in fruit flies. *BioEssays* 1996; **18**:799–807.
15 Lithgow GJ. Invertebrate gerontology: the age mutations of *Caenorhabditis elegans*. *BioEssays* 1996;**18**:809–15.
16 Kirkwood TBL. Comparative and evolutionary aspects of longevity. In: CE Finch and EL Schneider (eds) *Handbook of the biology of aging*, 2nd edn. New York: Van Nostrand Reinhold, 1985: 27–44.
17 Finch CE. *Longevity, senescence and the genome*. Chicago: Chicago University Press, 1990.
18 Gompertz B. On the nature and function expressive of the law of human mortality and on a new mode of determining life contingencies. *Phil Trans R Soc Lond* 1825;**115**:513–85.
19 Makeham WM. On the law of mortality and the construction of annuity tables. *J Inst Actuaries* 1860;**6**:301–10.
20 Smith DWE. The tails of survival curves. *BioEssays* 1994; **16**:907–11.
21 Kirkwood TBL, Cremer T. Cytogerontology since 1881: a reappraisal of August Weismann and a review of modern progress. *Hum Genet* 1982;**60**:101–21.
22 Kirkwood TBL, Holliday R. Evolution of ageing and longevity. *Proc R Soc Lond B* 1979;**205**:531–46.
23 Kirkwood TBL, Rose MR. Evolution of senescence: late survival sacrificed for reproduction. *Phil Trans R Soc Lond B* 1991; **332**:15–24.
24 Abrams PA, Ludwig D. Optimality theory, Gompertz' law and the disposable soma theory of senescence. *Evolution* 1995; **49**:1055–66.
25 Proust J, Moulias R, Fumeron F, Bekkhoucha F, *et al.* HLA antigens and longevity. *Tissue Antigens* 1982;**19**:168–73.
26 Takata H, Ishii T, Suzuki M, Sekiguchi S, Iri H. Influence of major histocompatibility complex region genes on human longevity among Okinawan-Japanese centenarians and nonagenarians. *Lancet* 1987;**ii**:824–6.
27 Schächter F, Faure-Delanef L, Guénot F, Rouger H, *et al.* Genetic associations with human longevity at the *APOE* and *ACE* loci. *Nat Genet* 1994;**6**:29–32.
28 Yu C-E, Oshima J, Fu Y-H, Wijsman EM, *et al.* Positional cloning of the Werner's syndrome gene. *Science* 1996;**272**:258–62.
29 Partridge L, Barton NH. Optimality, mutation and the evolution of ageing. *Nature* 1993;**362**:305–11.
30 Zwaan BJ, Biljsma R, Hoekstra RF. Direct selection on life span in *Drosophila melanogaster*. *Evolution* 1995;**49**:649–59.

Address for correspondence: Professor Thomas Kirkwood, Biological Gerontology Group, Department of Geriatric Medicine and School of Biologiocal Sciences, University of Manchester 3.239 Stopford Building, Oxford Road, Manchester M13 9PT.