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# Genetics and the pathobiology of ageing

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# Genetics and the pathobiology of ageing

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**SUMMARY**

Genetics offers a powerful approach to the elucidation of mechanisms underlying specific components of the senescent phenotype of our species. Perhaps thousands of gene variations have escaped the force of natural selection and thus play roles in the genesis of different patterns of ageing in man. It is possible that a subset of these genes may be of particular importance in how most people age. While variations at the Werner helicase locus could be one such example, several lines of evidence suggest that mutation at that locus leads to a 'private' mechanism of ageing. It will be important, however, to investigate polymorphisms underlying the regulation of expression of this gene in the general population. Polymorphisms (normally occurring variants of a gene, or sequence of DNA), rather than mutations, may also prove to be more relevant to our understanding of the differing susceptibilities of people to common disorders such as late onset Alzheimer's disease. Polymorphic forms of the Apolipoprotein E gene is a good example. It remains to be seen if the pathogenetic framework (beta amyloidosis) derived from studies of the several rare mutations responsible for early onset familial forms of the disease proves relevant to the pathogenesis of the vastly more prevalent sporadic forms of the disorder. In contrast to the satisfying progress on the genetics of the diseases of ageing, research on the genetic basis for unusually robust retention of structure and function in old age has been neglected and requires a higher priority for the future. Such research should include studies of environmental agents and should address mechanisms of 'sageing', a stage in the life course characterized by an extensive utilization of behavioural and physiological adaptations to compensate for functional declines. For the genetics of longevity, we have to turn to genetically tractable organisms such as nematodes and fruit flies. Such studies have provided significant support for the oxidative stress theory of ageing. It will be important to learn more about the age-related pathologies and pathophysiologies of these organisms.

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## 1. THE SIX STAGES OF THE LIFE COURSE OF *HOMO SAPIENS*

For organisms that undergo repeated episodes of reproduction, it is convenient to divide the life course into six stages, as illustrated in figure 1. Let us use the term 'ageing' in the sense that it is used by our botanical colleagues (Leopold 1978)—to encompass all changes in structure and function, from conception to death. This immediately highlights the importance of genetic and environmental influences on development and maturation for the two classes of phenotypes of interest at this conference: (i) longevity and (ii) various specific components of what we shall refer to as the senescent phenotype, such as Alzheimer's disease, atherosclerosis, cataracts, osteoporosis, diabetes, cancer, tissue atrophies, etc. If we think of the organism as a protein-synthesizing factory designed to manufacture copies of itself, every lay person will appreciate that how well one builds a factory is as important as how well one maintains the factory, if one wishes it to function efficiently for a very long period of time.

I use the term 'sageing' to refer to a stage of the lifespan approximately intermediate between that of the mature, reproducing adult and the senescing adult. It refers to the fact that, as we age, we make increasing use of both behavioural and physiological adaptations to compensate for deleterious alterations in structure and function. Examples of behavioural adaptations would include exercise to enhance cardiovascular and skeletal-muscular functions, the use of footware with high frictional coefficients to avoid falls, and the development of written lists and mnemonics to help one remember the names of guests whom your spouse has invited to dinner. Physiological adaptations would include mechanisms that evolved for the maintenance of homeostasis in response to transient endogenous or exogenous stresses, but which become invoked more regularly. The turning on of the biochemical machinery for 'neuritic sprouting' is one example. This is a mechanism of compensating for the loss of neurones via the growth of neuritic processes of neighbouring neurones. The end result is the re-establishment of many of the lost synaptic connections in the neuronal field and, thus, maintenance of function. Unfortunately, this neuronal plasticity eventually fails, leading to cognitive decline during senescence (figure 2) (Flood *et al.* 1985). This failure is seen at earlier ages in Alzheimer's disease subjects (reviewed

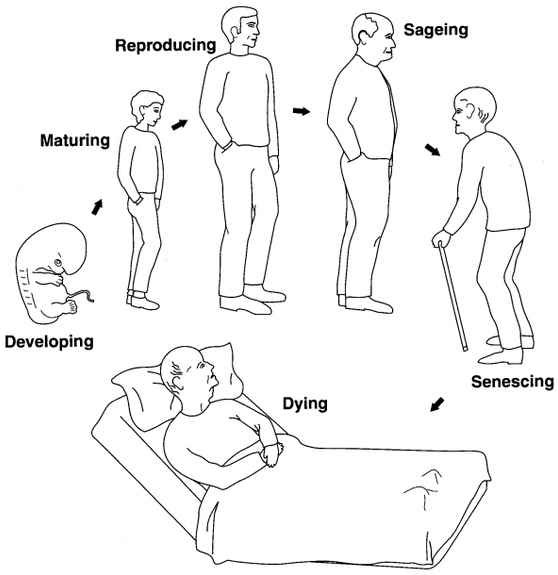


Figure 1. The six stages of the life course of *Homo sapiens*.

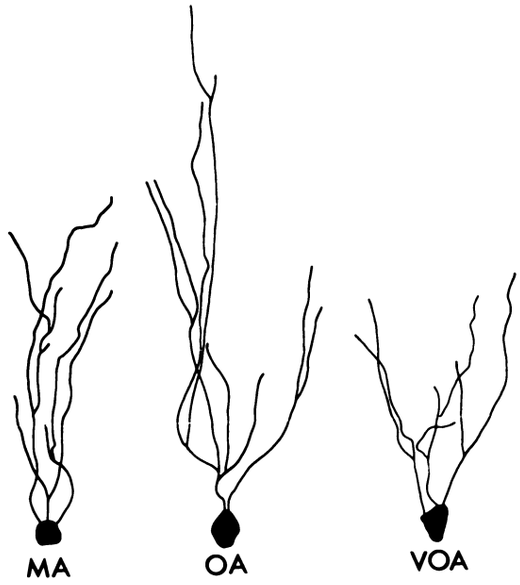


Figure 2. Drawings of Golgi-stained granule cells of the dentate gyrus of normal ageing brains. MA: middle-aged (fifties); OA: old age (seventies); VOA: very old age (nineties). The authors provide statistical confirmations of these patterns, which show evidence of compensatory neuronal sprouting for the OA group, but a failure of such sprouting in the VOA group. From Flood *et al.* (1985) with permission.

by Coleman *et al.* 1990). A second example is the use of the Frank–Starling mechanism (increase in stroke volume) to maintain cardiac output by increasing the diastolic filling of the heart (Lakatta 1985).

It seems to me that detailed knowledge of both behavioural and physiological aspects of the 'sageing' process may provide important opportunities to develop useful preventive and therapeutic interventions such that the stage of senescing is further delayed.

## 2. THE ROLE OF ENVIRONMENT IN MODULATING AGEING

All phenotypes of course result from nature–nature interactions. While the major purpose of this paper is to highlight the power of genetic analysis for the elucidation of problems of ageing, it will be instructive to consider briefly the role of environmental agents. Such agents may be of two types: 'gerontogens' or 'antigerontogens'. I have defined gerontogens as those putative environmental agents that modulate the times of onset and/or the rates of development of specific aspects of the senescent phenotype (Martin 1987). One can imagine that any agent that impeded the synaptic connectivity of the developing nervous system or diminished the population of dopaminergic neurones of the developing *substantia nigra* would lower the threshold for the development, respectively, of dementia of the Alzheimer's type or Parkinson's disease, since the former is associated with an age-related deficiency of cortical synapses (Masliah *et al.* 1991) and the latter with an age-related deficiency of subcortical dopaminergic function (Morgan *et al.* 1987). Gerontogens may of course also act during the adult stages of the life course. An example is the virtual overnight emergence of Parkinson's disease in young adults who consumed an illicitly synthesized drug contaminated with a compound (1-methyl-4-1,2,3,6-tetrahydropyridine) (MPTP) that could be metabolized into a powerful nigral neurotoxin (1-methyl-4-phenylpyridinium) (MPP+) (reviewed by Marsden & Jenner 1987). The consumption of diets relatively high in calories may also be viewed as a potential gerontogen. Although yet to be documented in human subjects, caloric restriction can have near-global effects in experimental rodents, who exhibit enhanced lifespans, maintenance of youthful physiological parameters, and retardations of late-life chronic renal disease and late-life neoplasms (reviewed by Masoro 1995).

## 3. EVOLUTIONARY THEORY PREDICTS TWO CLASSES OF GENE ACTION THAT UNDERLIE THE SENESCENT PHENOTYPE

Kirkwood (this volume) has clearly articulated the evolutionary basis of ageing. Here we shall briefly review the two classes of relevant gene action that may differentially modulate how we age. The first class, attributed to the ideas of Medawar (1946, 1952, 1957) (note also Medawar's recognition of J. B. S. Haldane's original research on this subject), invokes mutations with neutral effects upon reproductive fitness, but with deleterious effects late in the life course, when these effects have escaped the force of natural selection. Medawar imagined that we all have such mutations and that, while perhaps initially interfering with reproductive fitness, there evolved changes at other genetic loci that increasingly retarded the time of expression of the deleterious effects such that they did indeed become established in a segment of the population. My colleagues and I (Martin *et al.* 1996) have suggested that these mutations are likely to lead to 'private' mechanisms of




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ageing, in that they are likely to be individually distinct, their prevalence being largely determined by the genetic drift of the population. My favourite molecular example of a mutation leading to such a private mechanism of ageing is a rare type of amyloidosis found predominately in the Finnish population (figure 3). It is due to an autosomal dominant mutation involving the gene coding for gelsolin, a protein that interacts with actin and thus plays a role in cytoskeletal structure and function (Hiltunen *et al.* 1991). The facial nerve is particularly affected late in the lifespan of some patients, leading to partial facial paralysis (Meretoja 1973). The chief complaint in some patients with relatively late onsets may be that there is difficulty drinking soup. There is also involvement of the corneas and of the kidneys.

The second class of gene action predicted by evolutionary theory was best described by Williams (1957) and has become known as 'antagonistic pleiotropy' (Kirkwood & Rose 1991). This theory refers to alleles that have beneficial effects early in the lifespan but which have detrimental effects late in the life course, when they will have escaped the force of natural selection. My favourite molecular example of this type of gene action is the polymorphism for variable numbers of a triplet nucleotide repeat (repeats of CAG) at the genetic locus coding for the androgen receptor. Individuals with fewer repeats, whose cells appear to be more responsive to testosterone, are more likely to develop carcinoma of the prostate (Ingles *et al.* 1997; Stanford *et al.* 1997) and, moreover, are more likely to develop such cancers at earlier ages (Hardy *et al.* 1996).

Once antagonistic pleiotropic gene action has evolved, it is likely to be fixed within the population because of the selective advantage of its early life-course effects. Moreover, such alleles are more likely to be present in a variety of populations and, perhaps (at least for some subsets), in a variety of species. We have therefore suggested that such gene action is more likely to lead to 'public' mechanisms of ageing (Martin *et al.* 1996). These arguments logically lead to a public policy issue. Should not society be funding relatively more research on the evaluation of polymorphisms that might underlie 'public' mechanisms of ageing rather than on rare mutations leading to 'private' mechanisms of ageing? However, rare experiments of nature have almost always led us to new understanding of fundamental life processes. The biology and pathobiology of ageing should be no exception. Once a gerontologically relevant private mutation is discovered, one can immediately ask about the potential roles of polymorphic forms of the gene upon patterns of ageing in the general populations. We shall give a concrete example of this approach below, when we review research on a rare progeroid syndrome, the Werner syndrome.

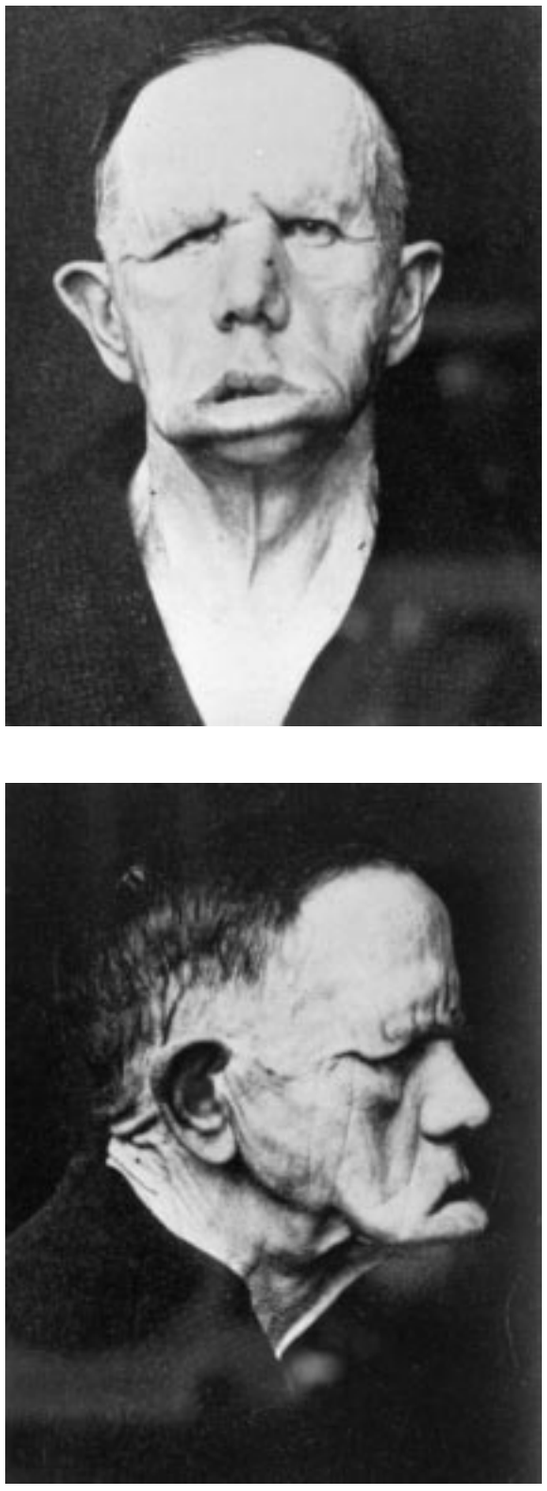

Figure 3. A 72-year-old Finnish male with a facial nerve paralysis resulting from amyloid deposits derived from a mutant form of gelsolin. From Meretoja (1973) with permission.

## 4. HOW MANY GENES DETERMINE LIFESPAN AND MODULATE THE PATHOBIOLOGY OF AGEING IN MAN?

The important question of the genetic control of longevity cannot be easily addressed in our species. First of all, we know from evolutionary theory that there are no genes that specifically evolved to induce senescence. The senescent phenotype consists of a diverse collection of epiphenomena or by-products of gene action selected to enhance reproductive fitness. The control of lifespan is therefore likely to be subject




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to variations at a very large number of genes. Some years ago (Martin 1978), I made a crude estimate, based upon an analysis of the phenotypes of all of the loci in three editions of McKusick's catalogue of Mendelian Inheritance of Man, that allelic variation or mutation at up to about 7% of the genome might modulate patterns of ageing in man. Assuming that we have around 100 000 genes, that would give some 7000 relevant genes. A smaller subset of these, however, may have rather widespread effects, as epitomized by the Werner syndrome mutation.

## 5. A STRATEGY FOR THE GENETIC ANALYSIS OF LONGEVITY AND THE PATHOBIOLOGY OF AGEING

While conducting the study mentioned above, I was disappointed (and remain disappointed) to discover how little is known about the genetic basis of unusually well-preserved structure and function during ageing in man. McKusick's catalogue largely deals with deleterious effects of mutations and polymorphisms. This is a consequence of the bias of ascertainment of the material that forms the basis for most Mendelian investigations of man. A public policy recommendation therefore emerges. We now have at our disposal large numbers of genetic markers (Polymeropoulos & Schaffer 1996) and powerful statistical tools (Kruglyak *et al*. 1996; Risch & Zhang 1996; Zhang & Risch 1996) for genetic analysis in man, as well as increasingly sophisticated methodologies for phenotypic analysis (e.g. functional magnetic resonance imaging) (Engel 1996). One is therefore in a position to discover genetic contributions to specific domains of high level functioning in human subjects.

Much has been learned and much more can be learned, however, via a genetic analysis of important senescent phenotypes of man. I shall give two examples from my own research experience, one dealing with a gene mutation responsible for multiple segments of the senescent phenotype (I have referred to these as 'segmental progeroid syndromes') (Martin 1978) and one involving several genes affecting a single disease entity or entities, dementia of the Alzheimer type. We shall use these as models for what could be done with the numerous genetic disorders that have the potential to inform us as to mechanisms of particular aspects of the senescent phenotype (Martin 1978, 1982).

## 6. THE WERNER SYNDROME

First described in 1904 by Otto Werner, a University of Kiel medical student (Hoehn 1985), the Werner syndrome is characterized by the premature onsets of a striking array of signs and symptoms suggestive of premature ageing. These include premature greying and thinning of hair, atrophy of skin, regional atrophy of subcutaneous fat, bilateral ocular cataracts, several forms of arteriosclerosis (atherosclerosis, arteriolosclerosis and medial calcinosis), calcification of heart valves, non-insulin-dependent diabetes mellitus, osteoporosis, gonadal atrophy, and benign and malignant neoplasms; the median age of death is 47 years, either from a myocardial infarction or from cancer (Epstein *et al*. 1966). The mode of inheritance is autosomal recessive, and the frequency of homozygotes has been estimated to range from 1–22 per million (Epstein *et al*. 1966). The disorder is sometimes known as 'Progeria of the adult' to distinguish it from 'Progeria of childhood'. The latter is also known as Progeria or the Hutchinson–Gilford syndrome (Brown 1992). These patients can be diagnosed within the first few months after birth, whereas patients with the Werner syndrome do not show obvious abnormalities until the peripubertal phase, when they fail to enjoy the usual adolescent growth spurt. Progeria is likely to be caused by an autosomal dominant gene mutation because of the absence of parental consanguinity and the relatively advanced ages of fathers.

A more careful analysis of the Werner syndrome phenotype reveals several discordances with what one observes in usual ageing. There is severe soft tissue calcification, often associated with deep ulcerations around the ankles (figure 4) and 'punched out' ulcerations around the elbows. These may occur in the presence of only mild diabetes and with the presence of good pedal pulses. I suspect that the pathogenesis could be related to a deficiency of some trophic factors contributed by subcutaneous adipose tissues, which are extremely atrophic. The distribution of the osteoporosis is peculiar in that it is more severe in the long bones of the limbs than in the vertebral column. The patterns of neoplasms vary considerably from what is usually observed in old age (Goto *et al*. 1996). There are proportionately large numbers of benign and malignant mesenchymal neoplasms as well as very rare tumours. The prevalence of certain tumours is extraordinarily high. For the case of acral lentiginous melanoma, a rare form of melanoma involving the soles of the feet or the mucosal membranes, its prevalence is perhaps one thousand times that of the general population. The ocular cataracts are posterior subcapsular rather than nuclear. There are peculiar osteosclerotic lesions of the distal phalanges associated with endosteal thickening (Goto *et al*. 1989). The short stature is not acquired, as in usual ageing, but is a result of a deficiency of growth during adolescence. Finally, other common phenotypes that might be expected with a mutation alleged to cause a global acceleration of ageing, such as the neuritic plaques and tangles of Alzheimer's disease, hypertension and osteoarthritis, do not occur. Thus, from a strictly clinical point of view, the Werner syndrome is best considered to be merely a 'caricature' of ageing (Epstein *et al*. 1966).

There are also some significant discordances from the phenotype one sees in ordinary ageing at the cellular and molecular levels. While somatic cells from Werner syndrome subjects exhibit a striking deficiency of replicative capacity (Martin *et al*. 1970), the mechanism of exit from the cell cycle may differ from that of cultures from controls. There are three lines of evidence to support this assertion. First, an early marker of cell cycle exit found in cultures from normal individuals, loss of the response of the c-*fos* gene to mitogenic stimulation, is not observed in senescent Werner cultures (Oshima *et al*. 1995). Second, the




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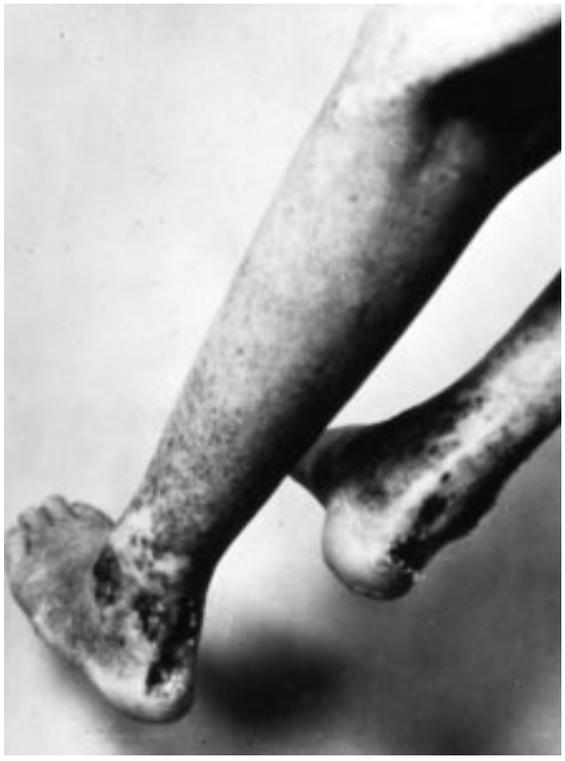

Figure 4. Severe ulcerations around the ankles of a 48-year-old female patient with the Werner syndrome. Such lesions heal with great difficulty and may require partial leg amputations. After Epstein *et al*. (1966), with permission.

phase of the mitotic cell cycle that is involved in the synthesis of DNA (the S phase) is abnormally elongated in Werner cells (Takeuchi *et al*. 1982; Poot *et al*. 1992). Third, the length of the telomeric repeat units at the ends of chromosomes, which become markedly shortened in normal cells as they approach replicative senescence, are not markedly shortened in senescent Werner cultures (Schulz *et al*. 1996). Thus, there are molecular as well as clinical lines of evidence to lead one to tentatively conclude that the Werner syndrome may represent a 'private' mechanism of ageing.

Finally, given the substantially diminished fertility of Werner syndrome patients, the mutation could not possibly escape the force of natural selection and therefore does not fulfil the evolutionary biological definition of a gene of relevance to ageing. It is possible, of course, that various alleles at this locus could result in phenotypes that could escape the force of natural selection. It was therefore of importance to define the responsible gene and to look for a variety of alleles in the population.

A team of investigators in Seattle, with the assistance of an international network of physicians, has recently discovered the gene (*WRN*), mutation at which is responsible for the Werner syndrome. It is a member of the *RecQ* family of helicases (Yu *et al*. 1996). It had previously been mapped to the short arm of chromosome 8 (Goto *et al*. 1992; Schellenberg *et al*. 1992). (A recent study has shown that this locus is not involved in Progeria; Oshima *et al*. 1996.) Helicase genes code for proteins that function to 'unwind' double-stranded DNA or RNA. In order to 'do business' with DNA, such as replication, repair, transcription or recombination of the genetic material, it is necessary for teams of proteins to gain access to the individual strands. This is done by helicases in conjunction with other enzymes. Since the original report of four distinct mutations, many other new mutations have been discovered (Oshima *et al*. 1996; Yu *et al*. 1997). Current evidence suggests that all function as 'null' mutations, such that there is little or no protein product made by cells from affected patients. While not yet measured, one can presume that parents and siblings of patients who carry one abnormal copy of the gene have only 50% of the normal activity. Yet they seem to be perfectly well except, perhaps, for an increased susceptibility to cancers (Goto *et al*. 1981).

From the point of view of the phenotype of neoplasia, the discovery that the cause of the Werner syndrome may involve an abnormality in the metabolism of DNA (the nature of which remains to be established) was not surprising, as it had been previously established that somatic cells from such patients were hypermutable (Hoehn *et al*. 1975; Salk *et al*. 1981; Fukuchi *et al*. 1989; Fukuchi *et al*. 1990; Runger *et al*. 1994). What is surprising, however, is the possibility that an abnormality in DNA metabolism may underlie the pathogenesis of other features of the disorder, such as the ocular cataracts (which are usually thought to be due to post-translational alterations of the crystallin proteins of the lens) and atherosclerosis (which is often associated with alterations in lipid metabolism). The relevance of these findings for atherosclerosis is of major potential clinical significance, given that it is the most common cause of morbidity and mortality in the developed societies. Essentially the only other clue in the literature pointing to a role of DNA metabolism in the pathogenesis of atheromas was the work of Benditt & Benditt (1973). These investigators developed evidence consistent with an interpretation that the individual atheromas had been derived from single cells and, as such, could have resulted from somatic mutations.

## 7. DO POLYMORPHIC FORMS OF THE WERNER GENE MODULATE SUSCEPTIBILITY OF THE GENERAL POPULATION TO MYOCARDIAL INFARCTION?

Motivated by the findings discussed above, we set out to determine if normal variations of the Werner syndrome gene could be associated with variable sensitivity or resistance to the development of ischaemic heart disease. Having discovered some five different polymorphic forms of the gene, we enlisted the assistance of our Japanese collaborators to carry out an initial case–control association study with one such polymorphism, involving a substitution of an arginine for a cysteine in the coding sequence. The results did indeed suggest that individuals with the less prevalent arginine allele were more resistant to myocardial infarction (and, presumably, to an underlying atherogenic

process within the coronary arteries) (Ye *et al.* 1997). It is now essential that such studies be repeated with independent populations of Japanese and with other populations. A working hypothesis of the mechanisms underlying the apparent protection afforded by the minor allele is that it is a surrogate for closely linked structural differences in regulatory domains of the gene that provide for more rapid and efficient responses to cellular injury, either via the participation of the helicase in DNA replication, repair or transcription. It is highly unlikely that such polymorphisms result in functionally significant alterations in the catalytic efficiency of the enzyme, for, as noted above, heterozygotic carriers, who are likely to have only 50% of the normal activity, appear to be phenotypically normal. These speculations must await more information on the normal functions of the wild type gene, however. It may well be the case that the arginine allele is in linkage disequilibrium (the term 'linkage disequilibrium' refers to the tendency for some linked genes to remain physically associated, rather than distributed at random in a population (Kimura 1956)) with a closely linked locus that is entirely unrelated to helicase function.

## 8. OTHER NEW RESEARCH DIRECTIONS MADE POSSIBLE BY THE CLONING OF THE *WRN* GENE

The positional cloning of *WRN* makes possible a number of powerful new research directions. To name two such new directions that presently occupy our laboratory, there is first of all the task of making a mouse model of the disorder via gene targeting of the mouse gene in embryonic stem cells. This has required that we determine the genomic structure of the murine counterpart (which has proven to be highly homologous to the human *WRN*). Among the many questions that can be efficiently addressed with a mouse model is the degree to which a single dose of the *WRN* mutation predisposes to neoplasia. This is an important public health issue, as we have estimated that the prevalence of heterozygotic carriers (in the Japanese population) is in the range of 1/150 to 1/200 (Yu *et al.* 1996).

A second exciting new research direction is the use of the yeast protein interaction trap (Warbrick 1997) for the capture of cDNAs coding for proteins that interact with the WRN protein. Such research should contribute to our understanding of the structure of the molecular machinery of which the WRN helicase is a member. They will also uncover new candidate genes of importance to aspects of the pathobiology of ageing.

## 9. THE SEARCH FOR GENES OF IMPORTANCE TO DEMENTIAS OF THE ALZHEIMER TYPE

When I did my 1978 survey of genetic syndromes of potential relevance to the pathobiology of ageing in man, there was a single entry in McKusick's catalogue for an autosomal dominant gene associated with Alzheimer's pathology. By 1996, four different genes had been identified that play major roles in susceptibility to the development of the characteristic pathology. It is highly likely that additional such loci will be defined in the near future, given the extensive efforts at several centres to discover such genes using linkage and association methodologies.

Given the knowledge that patients with the Down syndrome develop Alzheimer's pathology with regularity by the time of middle age and earlier, attention was initially drawn to genes on chromosome 21, which, when trisomic, causes the Down's syndrome. This led to the discovery that a small number of families (the total number currently known is probably no greater than 30 worldwide) in whom a mutation in the gene on chromosome 21 coding for the beta amyloid precursor protein was responsible for an autosomal dominant form of the disease (Goate *et al.* 1991). This was the first of three so called 'early-onset' familial Alzheimer's diseases, as the ages of onset typically range from ages *ca.* 45–65 years. But as we have seen earlier, disorders with phenotypic thresholds later than around age 45 years escape the force of natural selection and are thus fit within the evolutionary biological conception of the genetic basis of senescence. An even rarer form of the familial disease has been seen mainly in a small group of families whose ancestors derive from ethnic Volga Germans (Bird *et al.* 1989). This is therefore a good example of a genetic founder effect. The responsible gene (Levy-Lahad *et al.* 1995) is now known as presenilin 2 (*PS2*). The commonest form of 'early onset' familial Alzheimer's disease is due to a mutation on a gene on chromosome 14 (Sherrington *et al.* 1995) that is now know as the presenilin 1 gene (*PS1*), but even here we are dealing with an extremely rare event. Perhaps no more than 130 families have so far been discovered worldwide. Contrast this to the estimate that there are perhaps four million people with Alzheimer's disease in the United States, the vast majority of whom have 'sporadic' (i.e. non-familial) disease and who develop the disease well beyond the age of 65. The only genetic locus so far implicated as playing a role in susceptibility of the sporadic, late onset disease is the Apolipoprotein E gene (*APOE*) (Corder *et al.* 1993). A relatively uncommon allele (the epsilon 4 allele) appears to act as an age-of-onset modifier, resulting in earlier manifestations.

The currently favoured null hypothesis of pathogenesis is largely based upon the above genetic findings, especially those responsible for the early onset familial diseases. All three of those genes appear to alter the metabolism of the beta amyloid precursor protein such that a slightly longer form of the beta amyloid peptide is likely to act to seed amyloidosis in plaques and cerebral blood vessels (reviewed by Hardy 1997). Beta amyloid is thus seen as the universal culprit in the disease. Evidence implicating a role for polymorphic forms of the *APOE* gene is less compelling. One therefore needs to remain sceptical that the amyloid hypothesis will prove to be the pathogenetic key to the more common forms of the disease. It could well be that beta amyloid is sometimes a cause of neuronal injury, sometimes a result of neuronal injury, and sometimes both a cause and a result of neuronal injury.

## 10. INSIGHTS INTO THE PATHOBIOLOGY OF AGEING FROM GENETIC STUDIES OF NON-MAMMALIAN ORGANISMS

Organisms such as *Caenorhabditis elegans* (a roundworm) and *Drosophila melanogaster* (a fruit fly) have been used for studies of the genetic basis of longevity because of their comparatively short lifespans and their amenability to genetic analysis. Research on these and other organisms have recently been reviewed (Martin *et al*. 1996). An interesting tentative generalization can be made from an overview of these studies. Long-lived genetic variants appear to exhibit enhanced resistance to various modalities of endogenous and exogenous stressors, notably oxidative stress. This fits with what is currently the most popular theory of senescence, the free radical theory (reviewed by Yu & Yang 1996). Unfortunately, we know virtually nothing about the senescent phenotypes of such experimental organisms. What types of age-related pathologies do they have? What types of pathophysiologies? What are the causes of death? Such research is essential if we are to make maximum utilization of these valuable experimental models.

## 11. CONCLUSIONS

A responsible public policy of research on ageing should give a relatively high priority to genetic approaches to this problem. First of all, genetic analysis has the potential to address primary mechanisms. Second, it has proven productive in this field, both for the case of the genetic basis for susceptibility to important age-related diseases such as Alzheimer's disease, and for studies of gene action in long-lived strains of model experimental organisms. For the human situation, the author suggests that the research agenda should emphasize research on polymorphisms likely to play roles in antagonistic pleiotropic types of gene action (i.e. gene action exhibiting trade-offs, with good effects early, but deleterious effects late). These are more likely to be responsible for common or 'public' mechanisms of ageing, whereas the study of rare mutations may often lead to the elucidation of relatively uncommon 'private' mechanisms of ageing. Much more research is also needed on the genetic basis for unusually robust preservations of structure and function in old age. Advances in molecular and statistical methodologies set the stage for significant new knowledge in this area, provided that specific phenotypes of interest are clearly defined.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES