

The Metabolic & Molecular Bases of Inherited Disease

eighth edition

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Genetics and Aging

George M. Martin

1. The current unprecedented rate of growth of the population over age 85 years underscores the importance of investigating genetic factors modulating age-related disabilities and diseases. An equally important and neglected task, however, is to discover genetic factors leading to unusual degrees of maintenance of structure and function in late life (*successful* or *elite* aging).
2. There are six stages in the life cycle of humans: developing, maturing, reproducing, *sageing* (characterized by extensive use of physiological and behavioral compensations), senescing (characterized by increasing degrees of homeostatic failures), and dying. Gene action at all of these stages is relevant to the biology of aging.
3. Senescence can occur in the absence of overt specific disease entities but cannot easily be dissociated from disease states. Senescent changes in tissues may be direct precursors of common late-onset diseases via mechanisms that remain to be fully elucidated. One example is somatic mutation, a precursor of the many neoplasms that emerge in late life. Late-onset diseases may therefore be viewed as senescent phenotypes.
4. Senescent phenotypes are nonadaptive traits that occur because of the decline in the force of natural selection with respect to the age of gene effects. Senescence is not "programmed" in the sense that determinative, sequential gene action programs development.
5. Two broad classes of gene action are postulated to differentially modulate senescent phenotypes and life span. The first involves constitutional mutations with neutral effects on reproductive fitness but with deleterious effects late in the life course, thus escaping the force of natural selection. These modulations can be regarded as *private* in that their frequencies in various populations are largely functions of genetic drift. The second involves genes with antagonistic pleiotropic actions. These involve allelic variants selected to enhance reproductive fitness but with deleterious effects late in the life course. Because such alleles are likely to spread widely within many populations, they can be considered to lead to *public* modulations of senescence. Polymorphisms, rather than rare mutations, are more likely to be responsible for differential public modulations within populations.
6. It is probably the case that variants at thousands of genetic loci have the potential to modulate the pathobiology of senescence. These can be divided into two classes: variants that lead to *segmental progeroid syndromes*, which impact upon multiple senescent phenotypes, and variants that lead to *unimodal progeroid syndromes*, which impact upon a single tissue or phenotype. The prototypic example of a segmental progeroid syndrome is the Werner syndrome ("Progeria of The Adult"). It is caused by null mutations at a member of the RecQ class of DNA helicases and leads to accelerated replicative senescence and a mutator phenotype. Although it is best viewed as a private modulation of aging, polymorphic forms of the gene might prove to be of

more general significance. Examples of unimodal progeroid syndromes include familial forms of dementias of the Alzheimer type. These are also rare private modulations, but these may inform us as to general pathogenetic mechanisms. The apolipoprotein E locus, however, serves as an example of a public polymorphic modulation of that disorder.

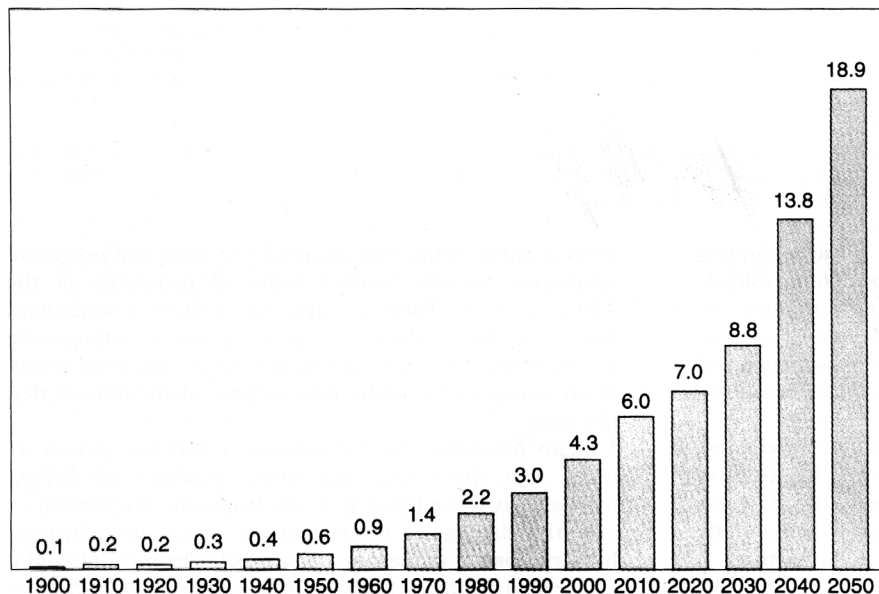
7. A highly polygenic basis for senescence does not necessarily mean that there are very large numbers of distinct mechanisms of senescence. A single generic mechanism—oxidative damage to macromolecules—can be influenced by variations at numerous genetic loci. The possibility of a single dominating pathway to senescence is supported by the results of caloric restriction experiments in rodents. These have yet to be replicated in nonhuman primates, however.
8. Single gene mutations in *Caenorhabditis elegans* and in *Drosophila melanogaster* have been shown to result in substantial increments in life span. The former, however, may simply be the result of lowered metabolic rates and the latter the result of complementation for a particular genetic abnormality of genetically inbred laboratory strains. Other experiments with hybrid nematodes and genetically heterogeneous flies provide evidence of a polygenic basis for life span.
9. Great opportunities for new directions of research on genetic aspects of the pathobiology of aging include quantitative trait analysis of longevity in experimental animals, investigations of mouse models of human senescent disorders, including searches for suppressor and enhancer genes, genetic aspects of comparative gerontology, and a variety of investigations in humans, including sib-pair analyses of unusually well-preserved structure and function in specific physiological domains (*elite* aging).

THE DEMOGRAPHIC IMPERATIVE

Physicians are faced with the care of an exponentially growing population of people over the age of 85 years¹ (Fig. 8-1), who account for an increasing proportion of medical care. For example, in 1992, 88.2 percent of individuals over the age of 65 had sought consultation from a physician within the previous year (Fig. 8-2). To what extent do inborn genetic susceptibilities contribute to the large range of morbidities exhibited by our geriatric patients? Medical geneticists are usually preoccupied with gene action in the early stages of the life history. The unprecedented growth of the elderly population, particularly of the "old old" (the subset over age 85), is changing the patterns of medical practice in virtually all specialties. It should be the same for medical geneticists. Moreover, primary care physicians and geriatricians will require a deeper understanding of biologic aspects of aging, including relevant concepts of evolutionary biology and genetics. This chapter summarizes these principles for our readership and point out the need for more research on the mechanisms of biologic aging; these surely serve as substrates for virtually all of the common disorders of late life. A major theme for such future

Population 85 Years and Over: 1900 to 2050

(In millions)



Source: U.S. Bureau of the Census, Decennial Censuses for specified years and *Population Projections of the United States by Age, Sex, Race, and Hispanic Origin: 1993 to 2050*, Current Population Reports, P25-1104, U. S. Government Printing Office, Washington, DC, 1993. Data for 1990 from *1990 Census of Population and Housing, CPH-L-74, Modified and Actual Age, Sex, Race, and Hispanic Origin Data*.

Fig. 8-1 Past and projected future numbers of individuals in U.S. population ages 85 years and over (in millions). (From Hobbs and Damon.¹ Used by permission.)

research will be the search for alleles that confer unusual protection against specific components of aging and of age-related disorders. Until very recently, this area of inquiry has been almost entirely neglected by physician scientists.

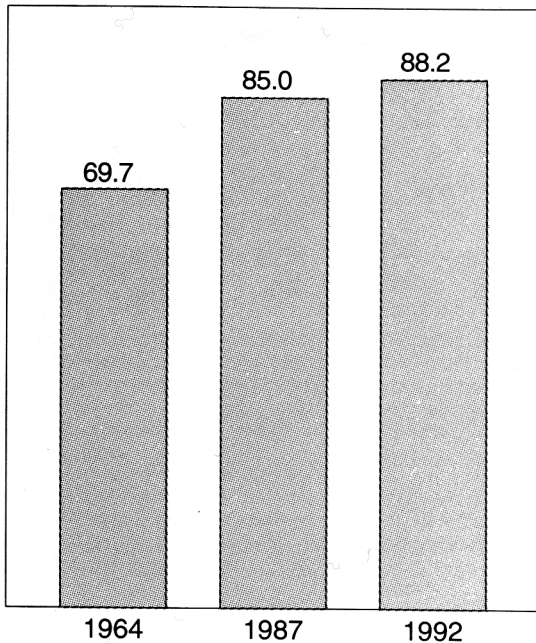
THE SIX STAGES OF THE LIFE CYCLE OF *HOMO SAPIENS*

There is considerable confusion concerning definitions of aging. Botanists use that term to refer to all changes in structure and function within an organism, from conception to death.² They have a more restricted use of the term *senescence*, using it to refer to the deleterious alterations that precede tissue or organismal death. Mammalian gerontologists, however, generally use *aging* and *senescence* interchangeably to refer to the changes in structure and function that gradually and insidiously unfold after the attainment of the fully mature adult phenotype, including sexual maturity. Thus, for mouse experiments, the “young” animals are 6 months old. Observations with “young” human subjects typically utilize subjects in their third decade. This is not to say that gene action in development is not of great significance to the biology of aging. Clearly, how one “builds” an organism makes a great deal of difference in how long it lasts and how well it functions. Conceptually, however, there is a major difference between gene action in development and gene action in senescence. The former clearly involves adaptive, determinative, sequential gene action, although with some stochastic elements. (For example, the random inactivation, early in development, of one of the two X chromosomes could lead to skewed distributions; in the case of female identical twins, this could manifest as significant differences in gene expression.) By contrast, senescence is nonadaptive and not “programmed” in the sense that development is programmed. These conclusions derive from evolutionary biologic concepts discussed below.

Not all changes in structure and function that unfold during the last half of the usual life span of humans are deleterious. Some (both behavioral and biologic) may be compensations for functional declines. The biologic mechanisms that are employed for such compensations are likely to be those that evolved as adaptations to periodic exogenous and endogenous stresses in young organisms. We might refer to them as being in “part-time” use in the young organism. There are reasons to believe that these adaptations are invoked more often when an organism is past the prime of reproductive activity, but not yet overtly senescent. These compensations may be invoked on a “full-time” basis. Let me cite two possible examples. Research by Ed Lakatta and his colleagues,³ using subjects in the Baltimore Longitudinal Study of Aging, has shown that subjects selected because of a lack of evidence of ischemic heart disease are capable of maintaining normal cardiac output. They manage to achieve this happy status by the full-time use of the Starling phenomenon, which leads to an increased diastolic filling and stroke volume. A second example comes from observations of human brains stained by the Golgi method. Paul Coleman and his colleagues have provided statistical evidence for enhanced focal neuritic sprouting of pyramidal neurons, presumably as compensations for loss of synapses previously provided by atrophic or deleted neighboring neurons.^{4,5} For human subjects, this stage would be roughly between ages 50 and 75. These various compensations ultimately fail, however, leading to a stage that might be more properly referred to as senescence. The loss of the ability to maintain homeostasis, coupled with the increased vulnerability to major geriatric disorders such as cancer, stroke, diabetes, infections, and heart failure, inevitably leads to organismal death. These concepts are summarized in Fig. 8-3.⁶

Senescence may occur in the absence of overt disease but is difficult to dissociate from late-life diseases, which are highly prevalent. An interesting line of evidence that demonstrates subtle

Percent of Elderly Visiting a Physician in the Last Year: 1964, 1987, and 1992



Source: National Center for Health Statistics, *Health, United States, 1993*, Hyattsville, MD, Public Health Service, 1994, table 88.

Fig. 8-2 Percent of elderly U.S. residents visiting a physician in the years prior to 1964, 1987, and 1992. (From Hobbs and Damon.¹ Used by permission.)

and progressive declines in function is presented in Fig. 8-4, which charts the record times for marathon races as a function of age.⁷ This “bioassay” serves nicely as a probe for essentially all body systems. We can assume that cohorts of exceptionally healthy individuals free of clinically significant disease have achieved these records, at least until the most advanced ages. How might these declines in function, which must have some structural basis,

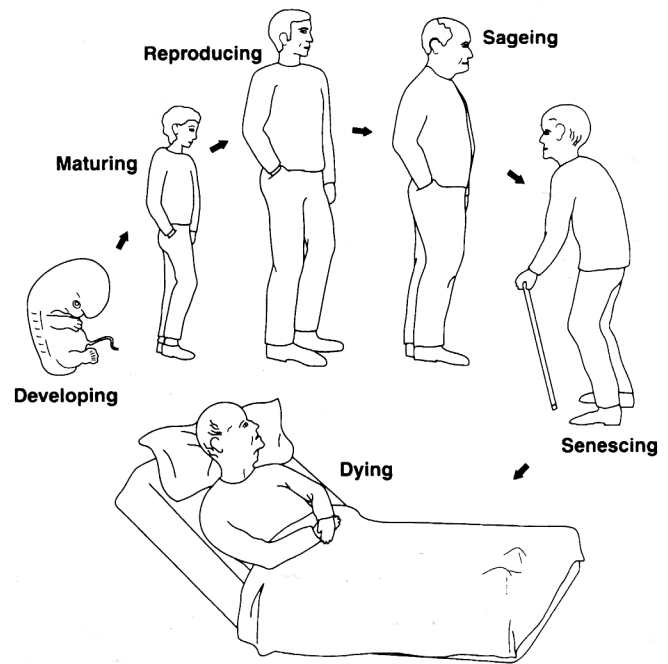


Fig. 8-3 The six stages in the life history of *Homo sapiens*. (From Martin.⁶ Used by permission.)

“set the stage” for the emergence of late-life disease? This raises the question of *how* we age, which is briefly discussed at the end of this chapter. We do not know the answers to this question, but there are likely to be many. We can cite two plausible examples, however. The first deals with the pathogenesis of neoplasms. Except for a subset of childhood neoplasms, the prevalence of malignancies, particularly of carcinomas, appears to be coupled to the biology of aging in that rates of increase appear to scale to life span for a number of mammalian species. Particularly compelling data come from comparisons of age-specific rates of malignancies in beagles compared with populations of human subjects.⁸ Somatic mutations in tumor suppressor genes and oncogenes are now exceedingly well-documented components of the pathogenesis of cancer. Somatic mutations are also known to accumulate in the tissues of aging mammals.^{9–11} Although we need a great deal more information on quantitative and qualitative aspects of these age-related mutations, it is a reasonable assumption that they do indeed set the stage for the emergence of late-life cancers. The

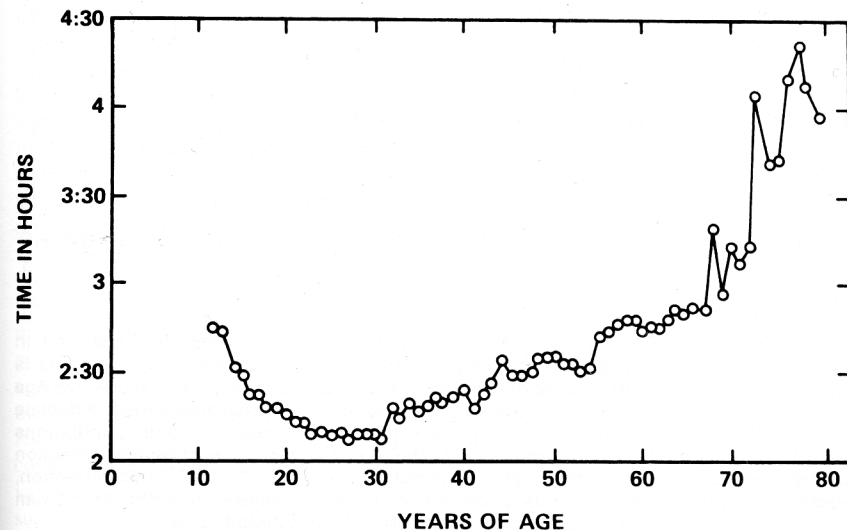


Fig. 8-4 Records for marathon runners as a function of age. (From Fries and Crapo.⁷ Used by permission.)

pathogenesis of "senile" ocular cataracts may serve as a second example. Proteins with little turnover are subject to a variety of posttranslational alterations. These steadily accumulate with age and are considered to be among the basic mechanisms of aging. Lens crystallins are in this class.¹² A common such posttranslational alteration involves the glycation and glycoxidation of proteins.¹³ Thus, there may be a line of continuum of aging processes and late-life disease.

THE EVOLUTIONARY BIOLOGIC BASIS FOR WHY WE AGE

Evolutionary biologists are confident that they have a satisfactory explanation for *why* we age, although they can tell us little about *how* we age (i.e., the proximal mechanisms of aging). Readers wishing a more thorough analysis of this most crucial aspect of the science of gerontology are referred to the excellent popular expositions by Steven N. Austad,^{14,15} the more mathematically oriented monographs by Brian Charlesworth,¹⁶ Michael R. Rose,¹⁷ and the writings by T. B. Kirkwood and his colleagues.^{18–22} The essence of the evolutionary theory of aging is that we age because of the decline in the force of natural selection with respect to the age of gene effects. The theory applies to age-structured populations with repeated rounds of reproduction. This would apply to all placental mammals and to numerous other species, including fruit flies and nematodes. For such populations in the wild, one finds very few old adults. This is because such phenomena as predation, infectious disease, accidents, malnutrition, and droughts deplete individuals as functions of time even in the absence of any natural aging processes. These ecologic considerations (operating over thousands of years) were in fact the prime determinants of the very different life history strategies found among extant species. For species that have evolved under conditions of high hazard, there was strong selective pressure for alleles that conferred rapid growth, development, and sexual maturation and large numbers of progeny over short periods. This was coupled with relatively short life spans, for reasons that are discussed below. As environmental hazards decrease, there is the opportunity to evolve different life history strategies, including those that are associated with longer life spans. These ideas have been confirmed by field studies of sibling species of Virginia opossums.²³ One species evolved under the hazardous conditions of the mainland while its sibling species evolved in an insular environment free of predators. The island species exhibited a decrease in its actuarial rate of aging²³ (Fig. 8-5).

Now let us consider the degree to which alleles that reach expressions at different ages within age-structured populations are passed on to the subsequent generation. Let us start with the lucky

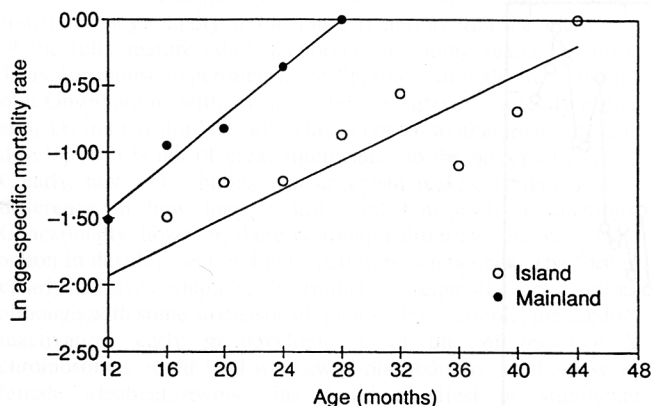


Fig. 8-5 The rate of aging of two sibling species of Virginia opossums. The species that evolved under the protected insular environment has a slower rate of aging. (From Austad.²³ Used by permission.)

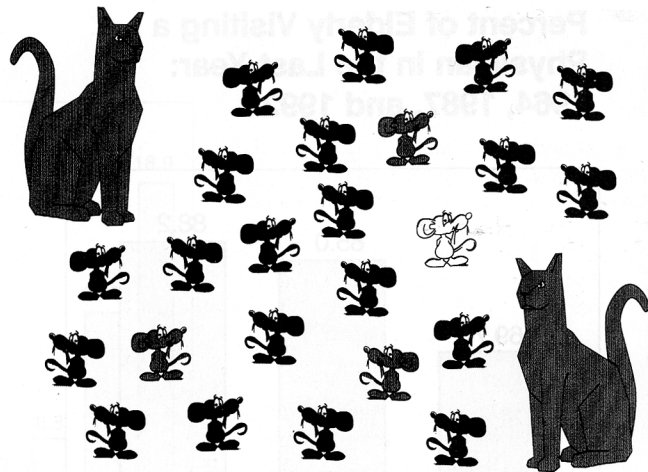


Fig. 8-6 A diagrammatic illustration of a fundamental principle of the evolutionary biologic theory of aging. We illustrate a population of rodents and its natural predator, felines. Even in the absence of any biologic aging, the predominant members of the population will be young (black). With time, very few middle-aged rodents (gray) will have survived predation and other environmental hazards and only very rare old rodents (white) will have survived. Neither beneficial nor deleterious alleles that reach phenotypic expression only in the middle-aged or old members of the population will have any significant impact upon the genetic structure of future populations and thus will have escaped the force of natural selection.

few that manage to survive numerous environmental hazards for exceptionally long periods. It should become obvious that any allele that reaches phenotypic expression only in those few surviving older members will have a substantially smaller representation in the following generation, as compared with the alleles contributed by the much more numerous younger members of the population. This concept is caricaturized in Fig. 8-6. A more quantitative analysis for the case of humans is presented in Fig. 8-7.²⁴ A striking conclusion of that analysis is that there is virtually no contribution to the next generation of alleles that do

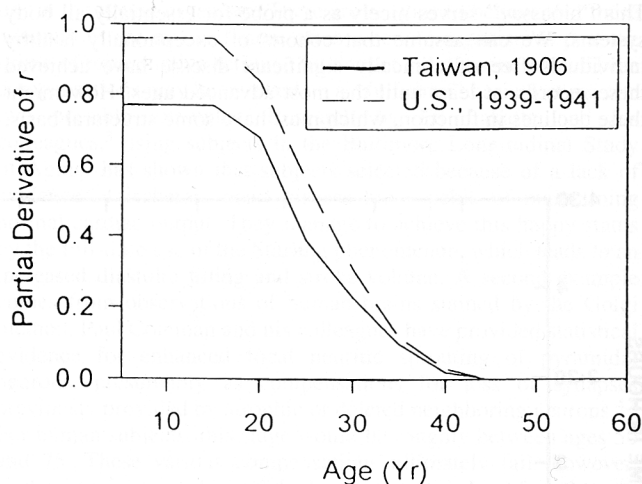


Fig. 8-7 A quantitative expression of the principle illustrated in Fig. 8-6 for the case of two human populations. On the y-axis is plotted a partial derivative of the Malthusian parameter, r . Age brackets are plotted on the x-axis. The curve represents the decline in the force of natural selection with age. For both populations (exhibiting different mortality rates), the force of natural selection approaches zero by about age 45. For details of the derivation, which is based on earlier work of William Hamilton and Brian Charlesworth, see Martin et al.²⁴ and citations therein.

not reach phenotypic expression until after the age of around 45 years. This finding has important implications for new directions of genetic research on aging discussed at the end of this chapter.

Two classes of gene action are thought to underlie senescence. The first class invokes constitutional mutations that have neutral effects during the early phases of the life history but that eventually achieve deleterious types of gene action late in the life span, when they escape the force of natural selection. This concept was best articulated by Peter B. Medawar,^{25–27} who cites J. B. S. Haldane as having given the first exposition of the idea, using the Huntington disease mutation as an example. Medawar also pointed out that even if such mutations did impact upon reproductive fitness, there would be strong selection pressure to postpone the phenotypic effects via the evolution of suppressor alleles at other loci. Eventually, however, such suppression would become ineffectual because of the waning of the force of natural selection at older ages. My colleagues and I have referred to this type of gene action as leading to *private* modulations of aging, as the individual mutations, though collectively numerous, would be individually rare, the prevalence being determined as functions of genetic drift.²⁴

The second class of gene action thought to be responsible for senescence invokes alleles selected because of beneficial effects early in the life course but with deleterious effects in late life. This phenomenon has been referred to as *antagonistic pleiotropy*.¹⁷ The idea was first clearly articulated by George C. Williams.²⁸ Such genes can be considered to lead to *public* modulations of aging as, once selected, these alleles should spread throughout the population.²⁴ Moreover, one can imagine that at least a subset of such alleles will have appeared independently during evolution within many species. Because rare mutations at such loci are more likely to be deleterious than beneficial, I suggest that polymorphisms, rather than mutations, are what lead to *public* modulations of aging for that particular class of genes. Here again we have a principle that could serve as a guide to future research on the genetics of aging, particularly in our species, which is so rich in polymorphisms and which offers such diverse opportunities for the study of gene action as functions of environment and genetic background.

IMPLICATIONS OF THE EVOLUTIONARY BIOLOGIC THEORY OF AGING

There are a number of very important implications of the evolutionary biologic theory of aging. First of all, the theory predicts that life span is plastic. There is no fixed species-specific maximum life span (although one can certainly specify some range for a given genotype in a given environment). There is strong experimental confirmation of this prediction for the case of *D. melanogaster*, using both indirect^{29–32} and direct³³ selection for increased life span. Second, given the conclusion that aging is not subject to determinative, sequential gene action (there are no “switches” that evolved for the purpose of inducing aging), the theory anticipates strong stochastic elements in the playing out of senescence. Third, the theory predicts that many genes should be involved in the determination of life span and the age-related disorders that limit life span. Although still an active area of research, the aforementioned fruit fly experiments clearly involve polygenes.^{34,35} The same is true of life span determination in *C. elegans*.³⁶ (See below, however, for a discussion of single gene mutations in *C. elegans* and *D. melanogaster* that lead to enhanced life span.) Fourth, there is the expectation that a variety of mechanisms are likely to be involved in the genesis of senescent phenotypes and life span, as the constitutional mutations and antagonistic pleiotropic gene actions could be quite varied. Fifth, these mechanisms may well vary among different species. Although, as just indicated, there could well be commonalities, consider the striking differences in mating behaviors among various species. Antagonistic pleiotropic alleles impacting upon such behavior are likely to involve very different biochemical

pathways. Thus, while the probable existence of a subset of public mechanisms of aging provides a strong rationale for research on aging in a wide range of organisms, in the last analysis, we will have to investigate specific processes in our own species. Sixth, the theory predicts substantial intraspecific variation in patterns of aging. Documentation of this prediction for the case of *Homo sapiens* is given in the following section.

There have been several challenges to the evolutionary biologic theory of aging. The first derives from the fact that single gene mutations can result in substantial increments in the life spans of animals. While a highly polygenic basis of life span is predicted by the evolutionary theory of aging, several single gene mutations leading to enhanced life spans have been found in *C. elegans*. These mutations involve loci concerned with a signal transduction pathway that functions in the implementation of an alternative life strategy, the dauer stage.^{37–39} A second set of “clock” mutants appear to impact upon a different pathway.^{40,41} Wild-type nematodes, when faced with nutritional deprivation, cease reproductive activities and exhibit extended periods of survival as dauers. There is evidence, however, that all of the mutants in each of these pathways exhibit decreased metabolic rates.⁴² Thus, their increased life spans could be analogous to the enhanced life spans resulting from maintaining such poikilothermic animals at lower temperatures. I therefore do not regard these mutants as serious challenges to evolutionary theory. Moreover, the mutants would not likely survive competition with wild-type organisms under nonlaboratory conditions. Nevertheless, long-lived mutants with low metabolic rates are of interest in that they are consistent with an important role for oxidative damage in the genesis of aging.

Simple genetic manipulations have also been claimed to increase the life spans of *D. melanogaster*. The first such report, involving introduction of additional genetic information for the synthesis of a component of the protein synthesis apparatus (elongation factor 1 α)⁴³ could not be confirmed.⁴⁴ Two other reports have indicated that relatively simple genetic manipulations can significantly increase the life spans of fruit flies. One used overexpression of both superoxide dismutase 1 and catalase⁴⁵ and another of superoxide dismutase 1 alone (expressed in motor neurons).⁴⁶ All of these experiments were performed on laboratory stocks. As such, a genetic manipulation that enhanced life span might function by complementing a particular and special deficiency of that strain. Inbred laboratory strains of flies are typically developed from a small number of breeding founders and selected for reproductive fitness in an artificial laboratory environment. It would thus not be surprising to discover that such strains might exhibit private modulations of aging. Nevertheless, it is certainly of interest that the experiments by Orr and Sohal⁴⁵ and Parkes et al.⁴⁶ provide support for the oxidative damage theory of aging. The same is true of *C. elegans* mutants.^{47,48}

Caloric restriction experiments in rodents (most of them performed on genetically defined inbred lines) result in substantial increments in life span, with concomitant delays in the expression of the major causes of death of these animals (for mice, mostly B-cell lymphomas and renal disease).^{49,51} The finding that a single environmental manipulation (moderate caloric restriction) can enhance life span argues for a single major mechanism underlying mammalian aging. By contrast, as we have already noted, an implication of the evolutionary theory is that there exist multiple mechanisms of aging. Although there are important ongoing experiments with rhesus and squirrel monkeys,⁵² it remains to be determined whether caloric restriction increases the life spans of long-lived organisms. The life history strategies of higher primates and other long-lived organisms are quite different than those of short-lived species such as rodents, which is a reason for caution in extrapolating the results of experiments in mice to humans. Some skeptics also argue that the control animals in caloric restriction experiments are overfed. By such a view, the restricted animals may represent a state more appropriate for their ancestral genes

under wild-type conditions. On the other hand, caloric restriction may have evolved as a particularly useful mechanism for many species in order to temporarily shunt energetic resources from reproduction to survival.⁵³

The best current evidence in rodents is that caloric restriction, except for a transient reduction in metabolic rate, does not have its effect via a reduction in the oxygen consumption per gram of lean body mass.⁵⁴ It is conceivable, however, that caloric restriction leads to a more efficient utilization of the electron transport system of mitochondria, resulting in a lower rate of production of univalent modes of oxygen reduction. Upregulation of mechanisms to protect against oxidative damage may also accompany caloric reduction.⁵¹ This line of experimentation thus supports the *free radical* or *oxidative stress* theory of aging.^{51,55}

VARIANTS AT NUMEROUS GENETIC LOCI HAVE THE POTENTIAL TO MODULATE THE PATHOBIOLOGY OF AGING IN *HOMO SAPIENS*

As indicated in the introductory paragraph, physicians have rarely investigated the Mendelian basis of unusually well-preserved structure and function. This should have a high priority for future research in aging. Meanwhile, we can take advantage of a large body of literature concerning mutations and allelic variations that lead to premature and severe expressions of senescent phenotypes. Many of these are severe loss or gain of function mutations that impact upon reproductive fitness and, therefore, would not fit the evolutionary definition of the types of alleles that impact upon senescence. For each such highly deleterious allele, however, there may be a number of "leaky alleles" or polymorphic variants whose phenotypic effects do indeed escape the force of natural selection. Moreover, alleles that confer unusual *resistance* to senescent phenotypes may exist in some individuals. Given this rationale, the author examined McKusick's *Mendelian Inheritance in Man* for loci that impacted upon a limited number of senescent phenotypes and concluded that almost 7 percent of entries had the potential to modulate the pathobiology of aging.⁵⁶ Assuming a total of 100,000 genes, it became apparent that variants at many thousands of loci could potentially explain, in part, clinical observations indicating considerable variations in patterns of senescence among the geriatric population. A more recent unpublished preliminary study, based on a search of a computerized version of that catalogue, addressed certain deficiencies of the 1978 study, which considered only a limited numbers of phenotypes and which included several nonphenotypic criteria (relevance to certain postulated mechanisms of aging). This more recent study suggests that an even larger proportion of the human genome could play a role in the modulation of senescent phenotypes. Nevertheless, there remains the possibility that a subset of such loci could be of major importance, either because of an impact upon multiple senescent phenotypes or because of a potential to elucidate the pathogenesis of a single, but exceptionally common, senescent phenotype. The first category leads to what have been termed *segmental progeroid syndromes*.⁵⁶ The second category leads to what have been termed *unimodal progeroid syndromes*.⁵⁷ The prototypic example of a segmental progeroid syndrome is the Werner syndrome (WS).⁵⁸ It is also known as "Progeria of the Adult" in order to distinguish it from the Hutchinson-Gilford syndrome ("Progeria of Childhood" or "Progeria," a clinically and genetically distinct entity).⁵⁹

WS is a rare autosomal recessive disorder discussed in detail in Chap. 33. For the reader of this chapter, however, it will be helpful to briefly review the phenotype in order to give some specific examples of important *senescent phenotypes*. WS patients appear normal until about the time of puberty, when they fail to undergo the usual adolescent growth spurt. They subsequently develop premature graying and thinning of scalp hair, atrophy of the skin, regional atrophy of subcutaneous fat, bilateral ocular cataracts, several varieties of arteriosclerosis (atherosclerosis, arterio-

sclerosis, medial calcinosis), severe calcifications of heart valves, type-2 diabetes mellitus, osteoporosis, benign and malignant neoplasms, and gonadal atrophy. Caucasian WS subjects typically die of a myocardial infarction, at a median age of 47 years.⁵⁸ Cancer appears to be a more common cause of death among Japanese patients.⁶⁰ It is important to point out that there are a number of clinical and cell biologic discordances with what is seen in "usual" aging, however.⁵⁶ To cite just one example of a clinical discordance, the ratio of epithelial-mesenchymal neoplasms in WS is approximately 1:1, whereas the ratio in usual aging is about 10:1.⁶¹ Moreover, WS patients are extraordinarily susceptible to certain rare neoplasms. For example, acral lentiginous melanoma is about 1000 times more common than in controls in a Japanese series.⁶¹ There are cell biologic discordances as well. For example, while WS somatic cells exhibit a striking acceleration of replicative senescence,⁶² transcription of the *cFOS* gene in senescent WS cells is quite responsive to mitogenic stimulation, unlike senescent cells from control subjects.⁶³ WS subjects have null mutations at a member (*WRN*) of the *RecQ* family of DNA helicases.⁶⁴⁻⁶⁶ The *WRN* protein may therefore play a role in such basic DNA transactions as replication, recombination, repair, transcription, and chromosomal segregation. WS somatic cells are genetically unstable.⁶⁷ These findings provide a reasonable explanation for the enhanced susceptibility to neoplasia. Perhaps more surprising, however, is this new evidence for a role of aberrant DNA metabolism and somatic mutation in the many other WS phenotypes. For example, posttranslational alterations in lens proteins have long been regarded as the cause of ocular cataracts.¹² Research with WS, however, provides support for an alternative pathogenetic pathway, perhaps operative in a minor proportion of the population, involving aberrations in DNA transactions of lens epithelial cells. The research on WS has also revived interest in the somatic mutational hypothesis of the origin of atheromas.⁶⁸

The discordances between the features of aging in WS and in "usual" aging suggest that the null mutations found in WS patients are best interpreted as leading to a private modulation of aging.⁶⁷ In keeping with our introductory remarks, however, we should now ask whether there is any evidence that "leaky" mutations or polymorphisms at *WRN* can result in more modest modulations of senescent phenotypes, either deleterious or beneficial. Certain of these, particularly polymorphisms, might lead to more public modulations of aging. There are only hints that this may be the case. There is a single case-control association study that provides evidence that a polymorphic form of *WRN* may protect Japanese patients from myocardial infarction.⁶⁹ There is also evidence that heterozygous carriers are hypersensitive to a genotoxic, carcinogenic agent, 4-nitroquinoline-1-oxide.⁷⁰ This finding is consistent with a clinical study indicating a high prevalence of malignancies in first-degree relatives of WS patients.⁷¹

The three autosomal dominant mutations leading to early onset familial Alzheimer disease are good examples of unimodal progeroid syndromes.⁷²⁻⁷⁴ There is as yet no compelling evidence that these mutations have any significant systemic peripheral effects. These mutations are individually and collectively exceedingly rare and are best regarded as leading to private modulations of the senescent phenotype. However, the associated neuropathology usually cannot be differentiated from what is observed in the vastly more prevalent late-onset, "sporadic" forms of Alzheimer disease. Thus, like so many inborn errors of metabolism, these rare "experiments of nature" may reveal a pathogenetic pathway or relevance to a senescent phenotype that may impact upon as many as 47 percent of individuals who live past the age of 85 years.⁷⁵ A variety of lines of evidence support this contention and indicate that the pathway involves the metabolism of the β -amyloid precursor protein.⁷⁶ There is one well-accepted polymorphic locus, *APOE*, that modulates the common late-onset form.⁷⁷ It can be regarded as leading to a public modulation of a senescent phenotype. Gene action at the *APOE* locus may be an example of antagonistic pleiotropy.⁷⁸ If this is the case, the allele that is

associated with increased susceptibility to Alzheimer disease (the epsilon 4 allele) may have provided enhanced reproductive fitness to ancestral carriers in some environments. It is a challenge for the future to discover the molecular basis and the environmental milieu for a putative beneficial effect early in life but a deleterious effect late in life. One highly speculative candidate area for research would be resistance to an infectious agent (e.g., *Mycobacterium tuberculosis*) on the basis of an altered lipid metabolism.

A BRIEF OVERVIEW OF GENETIC AND CELL BIOLOGIC ASPECTS OF HOW WE AGE

Given the present paucity of definitive information as to *how* we age, this section is of necessity brief. The study of genetic variants in a wide variety of organisms, however, has provided a surprising degree of evidence for a major role for oxidative damage as an underlying mechanism of aging. Interested readers should consult a recent review for details of this evidence.²⁴ Mutations and polymorphisms at a very large number of genetic loci can modulate the rates at which such oxidative damage can accumulate. These genes fall into seven classes (Table 8-1). The macromolecular targets of oxidative damage include lipids, proteins, and DNA, both mitochondrial and nuclear. Somatic mutations in mitochondrial DNA may be of particular importance to the aging of postreplicative cells such as skeletal muscle and neurons.⁷⁹ Replicating populations of normal diploid cells have finite replicative potentials. The bulk of the evidence indicates that the replicative potential of mammalian cells declines as functions of donor age. This is particularly evident when sensitive methods are used, such as primary cloning or clone size distribution assays.^{80,81} Transfection experiments have provided strong evidence that the epigenetic silencing of telomerase is the primary cause of this limited replicative life span.⁸² Depletion of telomere repeat units is thought to lead more directly to the exit from the cell cycle, but the precise mechanism is not clear. Telomerase is active in the germ line, consistent with its indefinite replicative potential. The enzyme is also active in most cancers.⁸³ Although intuitively attractive, there is as yet little evidence linking a limited replicative life span as causal in senescent phenotypes. An interesting line of investigation links focal replicative senescence to the emergence of atherosclerosis.⁸⁴

Replicatively senescent cells overexpress a variety of gene products. For the case of skin fibroblasts, these include gene products capable of altering the structure and function of connective tissue (via collagenases and elastases) and of regional epithelial cells (via cytokines).⁸⁵ Campisi has pointed out that only a few such cells would be capable of initiating a significant "field effect" in the contiguous tissues. Using a histochemical marker of replicatively senescent cells, she and her colleagues have indeed found evidence for such cells *in vivo*.⁸⁶

Table 8-1 Classification of Genetic Loci of Potential Relevance to the Oxidative Damage Theory of Aging

Class I	Structural and regulatory genes modulating genesis of free radicals
Class II	Structural and regulatory genes for scavenger enzymes
Class III	Genes regulating flux of nonenzymatic free radical scavengers
Class IV	Genes regulating target copy number
Class V	Genes specifying target structure
Class VI	Structural and regulatory genes for repair of target macromolecules
Class VII	Genes specifying the orderly replacement of effete cells

SOURCE: From Martin et al.²⁴ Used by permission.

SOME FUTURE DIRECTIONS FOR RESEARCH ON GENETIC ASPECTS OF AGING

Given the enormous progress in mapping and genotyping, we are now in a position to do quantitative trait locus analysis of life span and of various senescent phenotypes in experimental organisms. There are great opportunities for such research in *D. melanogaster*. There are also possibilities of useful results in *Mus domesticus* (although the usual laboratory strains represent only a small sample of the genetic variance of *M. musculus*). Methods for the creation of mouse models of dysfunction and disease should increasingly address issues relevant to the geriatric population. For recessive alleles, these should include studies of heterozygous carriers, as phenotypes may not emerge until late in the life course. They should also include efforts to map and positionally clone suppressors and enhancers of senescent phenotypes of major importance to man.

Comparative gerontology is also a neglected area from a genetic point of view. A promising avenue of research, for example, will be the delineation of avian loci responsible for their unusual resistance to oxidative stress.⁸⁷

There is currently great interest in genetic association studies with centenarians.^{88,89} It has been shown, for example, that the *APOE* epsilon 2 allele is enriched in such populations.⁹⁰ It is likely, however, that a very large number of such associations will be uncovered and that the subsets of such associations will vary among different populations. Perhaps a more useful approach will be to carry out sib-pair analyses for extreme discordances and concordances of the rates of change of highly specific physiological traits known to be impacted by aging. As can be inferred from the results of Fig. 8-7, such research could utilize middle-aged subjects. This will have the advantage of potential access to parental and filial generations, in order to obtain information on phase relationships of markers. It would also have the advantage of avoiding the complications of comorbidity for various diseases that commonly emerge much later in the life span. Such research would give us the potential of defining alleles and haplotypes that are contributing to unusually successful aging (*elite* aging).

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