

Cambridge Studies in Biological and Evolutionary Anthropology

Human Senescence

Evolutionary and Biocultural Perspectives

DOUGLAS E. CREWS

*Department of Anthropology and School of Public Health,
Ohio State University, Columbus, Ohio, U.S.A.*



CAMBRIDGE
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE
The Pitt Building, Trumpington Street, Cambridge, United Kingdom

CAMBRIDGE UNIVERSITY PRESS

The Edinburgh Building, Cambridge CB2 2RU, UK

40 West 20th Street, New York, NY 10011-4211, USA

477 Williamstown Road, Port Melbourne, VIC 3207, Australia

Ruiz de Alarcón 13, 28014 Madrid, Spain

Dock House, The Waterfront, Cape Town 8001, South Africa

<http://www.cambridge.org>

© Douglas E. Crews 2003

This book is in copyright. Subject to statutory exception
and to the provisions of relevant collective licensing agreements,
no reproduction of any part may take place without
the written permission of Cambridge University Press.

First published 2003

Printed in the United Kingdom at the University Press, Cambridge

Typeface Times 10/12.5 pt *System* L^AT_EX 2_ε [TB]

A catalog record for this book is available from the British Library

Library of Congress Cataloging in Publication data

Crews, Douglas E.

Human senescence: evolutionary and biocultural perspectives /

Douglas E. Crews.

p. cm.

Includes bibliographical references and index.

ISBN 0 521 57173 1

1. Aging. 2. Human evolution. I. Title.

QP86 .C74 2003

612.6'7-dc21

2002034951

ISBN 0 521 57173 1 hardback

Contents

Preface

page vii

1	Introduction and background	1
	Basic terminology and related concepts	3
	Senescence and aging	3
	Longevity and life span	6
	Evolutionary biology	9
	History of research on senescence and longevity	12
	Demographic perspectives on human longevity and life span	24
	Chapter synopsis	33
2	Evolutionary and biological theories of senescence	34
	Background	34
	Evolutionary (ultimate) theories: the basis of senescence	37
	Biological (proximate) theories: mechanisms/models of senescence	47
	Chapter synopsis	69
3	Human variation: growth, development, life history, and senescence	71
	Homeostasis	74
	Growth and development	83
	Life history	95
	Chapter synopsis	127
4	Human variation: chronic diseases, risk factors, and senescence	131
	Chronic degenerative conditions	132
	Risk factors	136
	Systems/integration	166
	Variation in human life span	184
	Chapter synopsis	196
5	Human life span and life extension	197
	Life span	197
	Non-human animal models	201
	Applications to humans	208
	Limits to human longevity?	218
	Chapter synopsis	221

6 Discussion and perspectives	226
Human senescence	226
Sex differences in life span	234
Human senescence, health, and disease	236
Aging and senescence	237
Old age: uniquely human?	240
Theory in gerontology	243
Current research directions	246
Conclusion	247
<i>References</i>	251
<i>Index</i>	283

1 *Introduction and background*

Interests in aging and senescence have characterized human thought since the earliest of recorded histories. Ancient Egyptian papyri and Chinese medical treatises, along with the writings of Aristotle and Socrates, describe various aspects of senescence and chronic degenerative conditions. They also detail methods for halting the insidious loss of function that accompanies longevity. Thoughts of mortality and immortality likely characterized the minds of our earliest *Homo* ancestors as well. The search for ways to halt the functional losses associated with growing old continues today. Humans are a long-lived species by any available standard. We are also unusual in that we remember our past and worry about the future: characteristics that we may share with a few other long-lived species or that may set us apart from all other species on earth. Long life provides ample time and opportunity to observe and remark on differences in longevity and vitality among relatives, friends, and acquaintances.

Prior to recent times, it is unlikely that many individuals ever actually survived sufficiently long enough to be considered very old by today's standards. Until recent times, anyone who survived 40 years was likely a grandparent and an elder; those still walking about at ages past 50 years were quite exceptional. Although some small proportion may have survived into their seventh decade of life, few would survive much beyond. Until recent decades, speculation and discourse on why and how particular persons outlived others and why one or another survived all others has outpaced scientific understanding. A major reason for the recency of studies of human senescence is the rapidity with which the aged population has grown. Increasing numbers of elders worldwide and their health care costs have fostered expanded research on the determinants of chronic degenerative conditions (CDCs), senescence, and life span (Smith and Tompkins 1995). These data are generating a greater understanding of both the physiological complexity and evolutionary simplicity of senescence. No simple mechanism(s) of senescence has been found, or ever will be. Instead, a range of phenotypic variability, systemic and local age-related alterations and dysfunctions, and variable genetic influences appear to structure senescence.

Humans represent about 6 million years of hominid and over 65 million years of primate/mammalian evolution. During this period, human life history – including fetal growth and development, neonatal maturation, infant and child

growth, ages at menarche and reproductive maturity – life expectancy, and life span have responded to a variety of evolutionary (biological) and sociocultural (biocultural) processes. This biocultural interplay, which does not influence senescence or life spans in cells, worms, insects, or rodents, has structured all aspects of human life history. This biocultural complexity is often slighted or not fully conveyed in both sociocultural and biological studies of human senescence and life span. As gerontologists have turned their attention to individual and population variation in human senescence and to the soma as a complex senescing system, their interests have merged more with biological and biomedical anthropology, human adaptability studies, and biocultural studies on senescence and life history. Anthropologists have helped to document the range of variation in multiple aspects of life history, including reproduction, growth, development, maturation, and adulthood survival. Unlike growth, development, and reproductive adulthood, until recently few humans ever before experienced late-life survival (70+ years). Late life represents a new phase in human and mammalian life history and an emerging area for biocultural, biomedical, and bioanthropological research.

This book explores the biological, cultural, and biocultural processes and environmental stressors through which human senescence, life span, and life history have evolved. The emphasis is on evolutionary, biocultural, and ecological aspects of human aging and senescence, rather than animal and cellular senescence, which are examined extensively elsewhere (Finch 1990; Rose 1991). Human life history evolved as part of the adaptive repertoire of a unique, bipedal, large-brained, large-bodied, gregarious, and polygamous hominid. These specific aspects of hominid evolutionary history necessarily determine to some degree current variation in our species' life history and our individual life spans – minimal/maximum metabolic rates, patterns of reproduction, maximum rates of growth, development and maturation, encephalization, and the DNA content of our cells. Although many such variables show high correlations with observed average and maximum life spans across species, they may provide little information on the determinants of senescence and mortality within species. Many such phenotypic traits simply scale to or are allometric outcomes of antecedent evolutionarily balanced tradeoffs between reproductive investment, environmental stress, and minimum necessary survival times.

In six chapters, this book explores some of the complex interplay of biological, cultural, and environmental forces through which human senescence and life span have evolved. This introductory chapter briefly examines terminological and definitional issues and the genesis and history of studies of human life span, before reviewing demographic trends in human longevity and life span. Chapter 2 examines evolutionary and biological theories of senescence. This is followed by an examination of human variation and the changes

in physiological function that appear to be age associated, along with an exploration of how evolutionary biology and biocultural adaptations may help to explain some processes of human senescence. Chapter 4 explores humankind's unique biocultural adaptations to variable environments and biocultural influences on patterns of senescence and life history. This is followed by an examination of the applicability of life extension methods, proven successful in animal models, to humans in Chapter 5. The final chapter discusses current perspectives and future possibilities for advances in our understanding of human senescence from an anthropological and biocultural perspective.

Basic terminology and related concepts

As with any area of scientific pursuit, the study of senescence has its unique vocabulary. A basic division is geriatrics (a branch of medicine that deals with the problems and diseases of old age and aging individuals) and gerontology (a branch of knowledge dealing with aging and problems of the aged) (Webster's Unabridged, 1983, p. 482). Biological or biomedical gerontology is the study of the processes by which individuals within species show post-maturational decline, senesce, and ultimately die. Conversely, geriatrics is a medical specialty concerned with halting and/or retarding the insidious post-maturational changes brought about by the processes of senescence. Both disciplines are predicated on the assumption that there are particular biological processes that underlie changes commonly observed with increasing age. There are two major views as to the genetic bases for these biological processes of senescence: (1) they constitute a specific genetic program for senescence (Clark 1999), or (2) they are an artifact or byproduct of evolutionary forces acting to maximize reproductive success and inclusive fitness in sexually reproducing organisms (Rose 1991). The next chapter will examine evolutionary models of senescence and the molecular and genetic bases of senescence while exploring how these fundamental concepts relate to human senescence and life span.

Senescence and aging

Another fundamental division in gerontology is between aging (to become old: to show the effects or characteristics of increasing age) (Webster's Unabridged, 1983, p. 22) and senescence (the process of becoming old: the phase from full maturity to death characterized by an accumulation of metabolic products and decreased probability of reproduction and survival) (adapted from Webster's Unabridged, 1983, p. 1055; see also Rose 1991) – terms so frequently

used incorrectly as synonyms that their individuality is sometimes unclear. All things age, whether living or not. Bottles of wine improve, while rocks and socks weather and wear with age (Harper and Crews 2000). Only the living may senesce. As humans know so well, many physiological phenomena show age-related change, but these are not all senescent changes. Senescence is a biological process of dysfunctional change by which organisms become less capable of maintaining physiological function and homeostasis with increasing survival. This leads to a reduced probability of reproduction and an increased susceptibility to death from both exogenous and endogenous causes. Aging is an elusive term carrying multiple sociocultural and political connotations. Aging best describes social, cultural, biological, and behavioral variability occurring over the life course *that does not directly increase the probability of death*. The areas of social gerontology, death and bereavement, and life course development generally are studies in aging, although some social factors, such as loss of a spouse, are associated with an increased probability of death. Senescence better serves current scientific discussion of mechanisms that preclude continued reproduction and survival in sexually reproducing organisms (Finch 1994; Cristofalo *et al.* 1999).

Researchers and disciplines often define senescence and aging differently (Crews 1993a; Harper and Crews 2000). For example, Comfort (1979) defined senescence as "... a deteriorating process, with an increasing probability of death with increasing age ..." (p. 8). Fifteen years later, Finch (1994) refined this definition to include "... age-related changes in an organism that adversely affect its vitality and function ... (Associated with an) increase in mortality rate as a function of time" (p. 5). Rose (1991) faulted earlier definitions for not including any aspect of reproduction, an essential component for an evolutionary definition of senescence, defining aging as "... a persistent decline in age-specific fitness components of an organism due to internal physiological deterioration" (p. 20). In a recent review of molecular aspects of aging, Kirkwood (1995) defined aging as "... a progressive, generalized impairment of function resulting in a loss of adaptive response to stress and in a growing risk of age-related disease" that ultimately leads to an increased probability of death, while senescence was defined as "the process of growing old". In the same volume, Johnson *et al.* (1995) provided very different working definitions: "Aging is a naturally occurring, post-developmental process. Senescence is a progressive impairment of function resulting eventually in increased mortality, decreased function, or both." The view of Johnson *et al.* (1995) is that most "but not all, degenerative diseases would thus be manifestations of senescence."

Aging *per se* is simply the fact of existence through time, the phenomenon of becoming older. Senescence is a progressive degeneration following a period of development and attainment of maximum reproductive potential that leads to

an increased probability of mortality. Quoting one last definition: "... with the passage of time, organisms undergo progressive physiological deterioration that results in increased vulnerability to stress and an increased probability of death. This phenomenon is commonly referred to as aging, but as aging can refer to any time-related process, a more correct term is senescence" (Cristofalo *et al.* 1999, p. 8). "Aging" and "senescence" are not used interchangeably here. Since animate and inanimate objects alike become older, aging is reserved for such processes and the social, behavioral, cultural, life style, and biological changes that occur as individuals grow older in particular social settings but that do not in and of themselves increase the probability of dying. Biologically, since only certain living forms senesce, senescence is reserved for those detrimental processes that occur secondarily to biological and physiological alterations occurring over the life span that leave individuals less capable of reproducing and more susceptible to extrinsic and intrinsic stresses, and which increase the probability of death.

From a scientific viewpoint, human senescence represents an evolutionary problem to be solved, while, medically, it represents a process to be avoided, halted, or delayed. To do either, senescence must be understood within the context of natural selection. This requires both a better understanding of the evolutionary biology of theories on senescence (reviewed in Chapter 2) and examination of the patterns of life history (changes through which an organism passes in its development from its primary stage of life (gametes) to its natural death) among humans, their closest relatives, and their immediate ancestors. Human life history includes copulation, fertilization, embryogenesis, fetal development, birth, infancy, childhood, adolescence, reproductive adulthood, menopause, post-reproductive survival of women and late-life survival of men, and senescence; each of these is affected by numerous intrinsic (i.e., inborn, biological/genetic) and extrinsic (i.e., not intrinsic) factors. Extrinsic factors include environment, diet, population density, culture, and society (Finch 1994; Wood *et al.* 1994; Finch and Rose 1995). For most natural populations, life history factors are difficult or impossible to measure, thereby limiting the accuracy of available data and their usefulness for comparisons (Finch 1994). Data that are available suggest that rates and patterns of senescence, perhaps even the basic mechanisms of senescence, may differ within and between phylogenetic classes and across environmental contexts even within the same species (Finch 1994; Finch and Rose 1995; Johnson *et al.* 1995).

One arguable, but ultimately unfruitful, position is that the processes of senescence are so uniquely individualized and species specific that they are neither interpretable nor understandable. Another is that, as with height, weight, skin color, or blood pressure, human senescence is just another type of phenotypic variation (Johnson *et al.* 1995) and amenable to research. Although its

precise method of measurement is unclear, viewing senescence as an individual phenotype is supported by the large amount of interindividual variation in life span (Shock 1984, 1985), the lack of data showing any specific genetic program for senescence (Gavrilov and Gavrilova 1991; Rose 1991; Beall 1994; Wood *et al.* 1994; Arking 1998; Gavrilov and Gavrilova 2001; Mangel 2001), and senescence's multifactorial (where the etiology includes both environmental and genetic factors) and polygenic (an etiology including multiple genetic factors) nature. Common experience tells us that the processes of senescence and death differ between persons. Recognition of this fact is crucial for the diagnosis and treatment of patients. This variation complicates applications of higher order theories to senescence in living individuals. Still, there are consistent patterns within and across populations, suggesting that, as with other complex phenotypes, although there is a wide range of variation, senescence can be measured and experimentally manipulated. Wide variation also suggests that neither life span nor senescence may be subject to strong selective pressures in wild (natural) populations. In this book, senescence is viewed as a multifactorial and detrimental physiological process affecting all organs and bodily systems that, although accelerating with increasing age, is itself time independent and increases individual risk of death.

Although senescence is an individual phenomenon, different in its details across somas, certain generalizations are true. Senescent changes are encountered in most organisms (Finch 1994) and apparently are universal in sexually reproducing species (Rose 1991). No non-senescent sexually reproducing species has been reported. A broad range of organisms show mortality (or survival) curves that indicate an increasing vulnerability to death with increasing time of survival – the hallmark of senescence (Comfort 1979) – many also display similar and specific changes in proteins and DNA along with accumulations of lipofuscin and mitochondrial DNA (mtDNA) mutations with increasing survival time (Reff 1985; Wallace 1992b). Such broad similarities across species suggest that at least some common biological processes and genetic factors underlie individual and species manifestations of senescence. Current research is directed to finding such root causes of senescence and physiological dysfunction and to determining their relevance for each species.

Longevity and life span

In addition to aging/senescence, inconsistency characterizes many additional terms found in the gerontological literature (Crews 1990a; Olshansky *et al.* 1990; Finch 1994; Olshansky and Carnes 1994; Harper and Crews 2000). Terms such as longevity, life span, average and maximum life span, life expectancy,

Table 1.1 *Male and female life expectancy (in years) at birth, age 40, and age 85 in the U.S.A.*

Year	Men			Women		
	Birth	Age 40	Age 85	Birth	Age 40	Age 85
1900	46.6	68.0	88.8	48.7	69.1	89.1
1910	48.6	67.7	88.8	52.0	69.2	89.1
1920	54.4	69.1	89.0	55.6	69.9	89.1
1930	59.7	69.1	89.0	63.5	71.6	89.8
1940	62.1	69.9	89.0	66.6	73.0	89.3
1950	66.5	71.2	89.4	72.2	75.7	89.8
1960	67.4	71.6	89.3	74.1	77.1	89.7
1970	68.0	71.9	89.6	75.6	78.3	90.5
1980	70.7	74.0	90.0	78.1	80.1	91.3
1990	72.7	75.6	90.2	79.4	81.0	91.4
2000	74.3	76.9	90.4	80.9	82.0	91.7

Data from Wright, 1997.

maximum achievable life span (MALs), mortality rate doubling time (MRDT), and maximum life span potential (MLSP/MLP) all have very specific meanings, but like aging and senescence are not always used appropriately. Expectation of life at birth or life expectancy at birth (e_0) is a demographic measure of average life span resulting from the all-cause mortality of a cohort (a group of individuals born in the same year). Expectation of life (e_x) at any age (x) is a well-defined basic life table (an actuarial table based on mortality statistics that follows an entire cohort from birth to death) function. Although well defined, life expectancy data may be used misleadingly in aging research because they are based on both child and adult mortality rates and are influenced by prevailing sociocultural, political, economic, and environmental factors (Olshansky *et al.* 1990; Olshansky and Carnes 1994). For example, comparing e_0 of populations in very different cultural or ecological settings, where one group experiences high and the other low infant and child mortality, reflects sociocultural and environmental factors associated with preventable diseases and illnesses, rather than processes of senescence. However, e_x calculated for ages other than birth may provide more meaningful comparisons between populations and time periods (see Table 1.1 to examine e_0 , e_{40} , and e_{85} for the U.S. population between 1900 and 2000).

MLSP and MALs are closely related theoretical concepts commonly defined as the longest known life span or the oldest living individual of a species or the maximum predicted life span (Weiss 1981; Hoffman 1984; Harper and

Table 1.2 *Estimated average and maximum life spans and ages at puberty for selected mammalian species*

Name	Life span		Age at puberty (months)
	Average (months)	Maximum (months)	
Human	849	1380	144
Gorilla	—	472	—
Chimpanzee	210	534	120
Rhesus	—	348	36
Cow	276	360	6
Swine	192	324	4
Horse	300	744	11
Elephant	480	840	21
Cat	180	336	2
Dog	180	408	2
Whale	—	960	12
Mouse	18	42	1.5
Rat	30	56	2
Guinea pig	24	90	2

From Table 2, Finch and Hayflick (1997), p. 9.

Crews 2000). Maximum life span is commonly estimated based on captive and domestic samples. Some researchers have suggested that the MALS represents the genetic capacity of a species for long-term survival (Cutler 1980; Fries 1983; Hoffman 1984; Susser *et al.* 1985). However, both life expectancy and current maximum life span are sensitive to environmental influences, vary widely between different populations of the same species, and are easily modulated in controlled laboratory settings (e.g., dietary restriction, temperature variation) (Finch 1994). Among extant lineages, MALS is thought to have increased over evolutionary time and to have changed over the course of evolution of multiple species. Unfortunately, documentation of such change cannot be obtained directly from the fossil record. There is no direct measure of either e_o or MALS for extinct species such as dinosauria, dryopithecines, australopithecines, or erectines. Rather, allometric relationships between life spans and either body or brain size established for extant, often domestic, species are used to estimate MALS for fossil specimens (see Table 1.2 for estimates of average and maximum life spans and age at puberty for some modern species).

Longevity (long-lived, a long duration of individual life) is an individual phenomenon, identical to life span. The individual with the greatest longevity (maximum life span) in any particular environment is an outlier, a unique individual.

The maximum verified age for any human is over 122 years (Jean Calment of France), which is 7 years above the maximum life span reported in Table 1.2 for humans, and 2 years beyond the MALS for humans predicted by proponents of a limited life span model (Fries 1980; Fries and Crapo 1981; Fries 1983, 1984, 1988). Available data on maximum life span from zoo specimens or capture–recapture studies in the wild (such as are presented in Table 1.2) do not provide sufficient information to assert anything regarding either patterns or rates of senescence in natural populations. What they do illustrate is that maximum life span is often much greater than the average. Paraphrasing Finch (1994, pp. 12–13), little evidence about the role of senescence in limiting life span is garnered from such comparisons. However, similar comparisons of the same species in different environmental settings do show that average and maximum life spans of most lengthen in response to simple environmental modulations that include improved nutrition, reduced disease, and lack of predation. These data illustrate that most wild species have a potential for long life not often expressed in their natural ecological setting. The domestic cat (*Felis catus*) provides a clear example. When kept as a house cat without access to the outdoors, the life expectancy of *F. catus* is about 15 years. Conversely, a feral cat's life expectancy is only about 18–36 months. Extended life expectancy among domestic house cats results without change in genes or biology. Rather, improved nutrition, negligible predation, and reduced disease (an altered environmental setting produced by human culture) lead to improved survival, and, if not surgically controlled, greatly enhanced reproductive success.

Evolutionary biology

Fundamental to grappling with the complex biology of senescence is a basic understanding of the terminology and principles of evolutionary biology. The basic hereditary unit, DNA, is composed of four nucleotides – thymine, adenine, guanine, and cytosine. In humans, DNA molecules form 46 linkage groups (chromosomes) sequenced into about 30 000 coded subunits called genes (a segment of DNA that can be translated into RNA, a locus). Loci provide RNA templates for proteins and differ in DNA sequence across chromosomes. Each DNA variant at a specific locus is a unique allele. Such coding loci are separated by intervening nucleotides (perhaps 90% of all human DNA, but only about 10% in flying mammals and birds); these are not known to code for RNA. Each allele codes for a specific RNA molecule, but the same RNA molecule and thus protein may be coded for by a variety of possible alleles. For most loci and segments of intervening DNA (iDNA), many different sequences of DNA nucleotides (alleles) are available to occupy the locus.

Genetic traits and conditions (e.g., the ABO blood group, the enzyme phenylalanine hydroxylase, albinism, Huntington's disease, sickle cell anemia) are due to the inheritance of different alleles at a specific locus. Any alleles that differ from the wild type (the most common allele in the wild population) represent mutations (change in DNA sequence) of the supposed original allele in the founding population. Loci with but a single common allele are monomorphic, which is an uncommon situation. Loci generally show two or more common alleles. These are polymorphic (many types) when the second most common allele occurs more frequently than its mutation rate, or is above 1%. Alleles occurring at low frequencies (1/1000 or 1/10 000) cause a variety of detrimental phenotypes (e.g., Duchenne muscular dystrophy, hemophilia, cystinuria, cystic fibrosis, phenylketonuria). These are frequently termed mutants compared with alleles predisposing to what are considered 'normal' phenotypic outcomes. In such cases, normal and mutant may include a variety of specific alleles producing either phenotype.

DNA alleles are the raw material acted on by the forces of evolution (natural selection, mutation, gene flow, and genetic drift). Mutation creates entirely new DNA sequences by small (base pair (bp) substitutions that change one nucleotide, e.g., A $\rightarrow$ T) and large steps (insertions and deletions covering a few or a few hundred of bases, e.g., a 9 bp deletion of mtDNA or a 240 bp deletion of the angiotensin converting enzyme (ACE) locus). Natural selection, flow, and drift only shape this variability. Natural selection limits the reproductive success and inclusive fitness of individuals carrying mutations less viable in the current environment. In a constant environment, natural selection may lead to organisms remarkably well adapted to a specific ecological niche (e.g., koala bears in eucalyptus forests, giant pandas in bamboo forests). Most environments are not so stable nor are most organisms so highly specialized. Eating almost anything, surviving in a range of habitats, and using culture to manipulate the environment, humans may be included among the most generalized of species, along with, for example, other primates, rodents, and insects.

Gene flow and drift act to spread/mix and eliminate genetic variation. Flow is simply the exchange of gametes (DNA) between populations, such that variants arising in one area may migrate throughout an entire species if not eliminated by natural selection or genetic drift. In highly mobile organisms such as humans, the spread of novel alleles with reproductive or survival benefits may be very rapid (Lasker and Crews 1996). Alleles with no (or very little) effect on fitness and reproductive success are selectively neutral. These may be lost or become fixed through chance alone as their frequencies change from one generation to the next in relatively small populations through, random genetic drift. High frequencies of conditions such as Huntington's disease, pseudohermaphroditism, xeroderma pigmentosum, polydactyly, and diabetes in human isolates illustrate

the power of random genetic drift, through Founder's effect, to alter allele frequencies. During phases of hominid evolution when local populations (demes) were smaller and more dispersed, drift was more influential on human variation and likely contributed to the variety of human types found around the globe.

Genetic influences developed under the influence of evolutionary forces structure multiple quantitative aspects of human phenotypic variation. To the degree genetic variability influences human life history, these same evolutionary forces have structured human senescence and life span. Mutation continually alters the DNA of all organisms. This provides new alleles that potentially enhance or retard senescent processes. Clearly, many alleles contributing to rapid loss of function and lower fitness have already been culled from the human gene pool, or we would not survive twice as long as other large-bodied primates. Such culling continues today. The pace at which detrimental alleles are eliminated depends on their penetrance (degree to which genotype is expressed in the phenotype), and any established dominant–recessive, pleiotropic, and epistatic interactions. Alleles neutral with respect to fitness (including early life survival, growth and development, reproductive success, and the fledging of offspring) but carrying senescence-enhancing or -reducing effects have, over most of hominid and human existence, been most affected by random drift. Alleles that retard or enhance senescence are likely to be widely dispersed and represent a genetic reservoir of senescence-delaying allelic propensities available to not only humans, but also most wild species.

Several additional terms related to evolutionary biology are frequent in discussions of senescence. Phenotype or phenotypic traits are the observed manifestations of human form and function. Phenotypes result from the interplay of genotype (the sum of nuclear and mitochondrial alleles carried by or the specific allele(s) at one (or more) locus in an individual) with the cellular and external environment, and, in humans, the sociocultural environment. Some phenotypes are quantifiable characteristics – height, weight, blood pressure, glycemia, visual acuity, enzyme activity, skin reflectance, number of children produced, and observed life span – while others are qualitative – amino acid sequences of proteins, eye color, and sex. Many are difficult to measure – for example, rate of senescence, psychological inclinations, culture/ethnicity, stress response, and personality type. Throughout life, from the cytoplasm of the ova that becomes our zygote, to our mother's uterus and internal physiology, birth, and ultimately death, the genotype constantly interacts with the environment. Natural selection and numerous random factors determine how well phenotypes produced through this process survive and reproduce. If the phenotype does not reproduce, the entire genotype is lost without representation in future generations.

Today, in more cosmopolitan (cultures that look outward and are not bounded by local customs and beliefs, the antithesis of traditional) settings, genotypes

producing phenotypes that survive through birth generally also survive to reproductive age. The force of natural selection falls less heavily on them during infancy and childhood than on members of populations living more traditional (cultures that look inward and are bounded by local customs and beliefs) life styles or those who were conceived and survived to birth during earlier epochs of human evolution. Throughout hominid evolution, natural selection, through high fetal, infant, and childhood mortality rates, likely eliminated many alleles and genotypes that today allow their carriers to survive to maturity. Today, in privileged settings, differential pre-reproductive survival is very low (<5%) and likely to be secondary to differential reproduction in changing the gene pool (the sum total of alleles represented in a breeding population).

History of research on senescence and longevity

Alfred Russel Wallace (1823–1913), who along with Charles R. Darwin (1800–1882) first developed the concept of evolution by natural selection among variable phenotypes, was also the first naturalist to propose an evolutionary theory of senescence. His original formulation appeared in an unpublished note written between 1865 and 1870, and was quoted in a footnote to an 1889 translation of an 1881 essay by August Weismann (1834–1914) entitled “The Duration of Life” (for a review of Wallace’s comments see Rose 1991, pp. 4–5). It was Weismann (1891; for a review see Kirkwood and Cremer 1982), however, who articulated the most substantive evolutionary theory of senescence prior to the twentieth century. Weismann (1891) proposed that death was an adaptation which arose when an infinite life span became disadvantageous to the species, such as when old and decrepit, yet immortal, individuals take the place or resources of those who are healthy. The notion that death would be the direct result of natural selection and, thus, an adaptation is not supported by available data and few today accept Weismann’s explanation for senescence as an outcome of group selection. However, Weismann was among the first to examine senescence from the viewpoint of evolutionary biology and natural selection, to see the separation between the mortal soma and the potentially immortal germ cells, to observe that there was no fixed relationship between size of the soma and length of life, and to propose that the “rate at which animal lives, influences duration of life” (Weismann 1891, p. 8).

Weismann (1891) also observed that larger animals tended to have greater difficulty obtaining sufficient food and need additional calories to reproduce than smaller ones. Thus, larger animals exhibit slower rates of reproduction. He further noted that the rate of living influenced longevity “not because of rapid consumption of the body” but rather because the “...increased rate at

which vital processes take place permits more rapid achievement of the aim and purpose of life, viz., the attainment of maturity and reproduction of the species" (p. 8). Thus, Weismann proposed that growth and development of the soma, reproduction, and life span shared common evolutionary origins. Weismann did not believe that physiological factors alone could determine length of life; rather, he found that "duration of life is really dependent upon adaptations to external conditions . . . determined by precisely the same mechanical process of regulation as that by which the structures and functions of an organism are adapted to its environment" (p. 10). Based on these postulates, Weismann suggested " . . . that, as a rule, life does not greatly outlast the period of reproduction except in those species which tend their young" (p. 11) and that evolutionarily there is a "necessity for as short a life as possible" (p. 23). Furthermore, he refers "the question as to the means by which the lengthening or shortening of life is brought about . . . to the process of natural selection" (p. 20). Weismann saw long life as a "luxury without an advantage" (p. 25), but knew that death was not "an absolute necessity, essentially inherent in life itself" (p. 26). Rather, death " . . . is an adaptation that first appeared when, in consequence of a certain complexity of structure, an unending life became disadvantageous to the species" (p. 111). He based this assertion on phenomena that first Medawar (1952) and later Kirkwood (1977) would use to develop further the evolutionary theory of senescence. Weismann proposed that the " . . . limited duration of Metazoan life may be attributed to the worthlessness (of individuals) . . . liable to wear and tear . . . (and that the) perishable and vulnerable nature of the soma was the reason why nature made no effort to endow this part of the individual with a life of unlimited length" (p. 156). Finally, Weismann clearly understood that: "As the soma becomes larger and more highly organized, it is able to withstand more injuries, and its average duration of life will extend . . . (Such) lengthening of life is connected with an increase in the duration of reproduction . . . (thus) there is no reason to expect life to be prolonged beyond the reproductive period; so that the end of this period is usually more or less coincident with death."

In a series of writings early in the twentieth century, Raymond Pearl (Pearl 1922, 1928, 1931; Pearl and Pearl 1934), following closely Weismann's work, suggested that longevity resulted as an epiphenomenon of other aspects of life history (e.g., metabolic rate, body size, and reproduction; see also Comfort 1979; Finch 1994). Among mammals, smaller forms tend to have higher basal metabolic rates and shorter life spans than larger animals and metabolic rates tend to co-vary with brain weight and body size (Harvey and Bennet 1983; Hoffman 1983), while both body and brain size show positive associations with life span (Cutler 1975, 1980; Sacher 1980; Hoffman 1983; Finch 1994). The basic premise for metabolic control of senescence or rate-of-living theories is that smaller animals have more rapid metabolic rates, expend their life's

allotment of energy more rapidly, and die more quickly than larger animals with slower metabolic rates. However, not all species conform to this model. For instance, bats live longer than other rodents of comparable body size and metabolic rates, while birds live longer than comparably sized mammals or reptiles. Weismann noted this latter phenomenon and suggested that the “long life of birds . . . (was) compensation for their feeble fertility and great mortality of their young . . .”. However, it may also be related to lower rates of extrinsic mortality from predation in adults of species that can fly, which then allows such feeble fertility to be a successful evolutionary strategy.

About a quarter of a century after Pearls’ writings, Medawar (1952) elaborated an evolutionarily based theory of senescence. He demonstrated that the force of natural selection decreases with age and that this decline holds not only for organisms that senesce, it also decreases in theoretical populations of immortal individuals with unlimited reproductive capability. Medawar showed that, given real, life-threatening hazards (e.g., illness, predation, accidents) that act to limit reproductive success, the force of natural selection always decreases with increasing age. Weismann (1891) previously had recognized that the susceptibility of the soma to accidents would diminish an organism’s reproductive ability; however, he did not develop a model that showed why this must ultimately be true. Eventually, Hamilton (1966) and Charlesworth (1994) both provided rigorous mathematical proofs of Medawar’s intuitive results. Between them, they proposed and mathematically proved what today is regarded as the ultimate evolutionary cause of senescence and death: regardless of the physical capabilities of the organism to prevent internal degeneration of the soma, or its continued capability to reproduce, the force of natural selection decreases with age.

Population genetics shows that the force of natural selection decreases throughout most of one’s adult life. This was first parameterized by R.A. Fisher (1930) as: “reproductive value”, or $v(x)$, representing the relative reproductive contribution individuals aged x can expect to make to the next generation. Fisher hypothesized that this variable would be proportional to the force of natural selection at age x . Of primary interest for gerontology is the maximum value of $v(x)$, the point at which the force of natural selection begins to decline, for this is when senescent changes may begin to emerge. The age at which $v(x)$ is maximum is expected to vary across populations; however, for the Australian women Fisher used as an example, maximum $v(x)$ was reached at about 19 years of age. Similar results are cited for Taiwanese men and women by Hamilton (1966), Chilean, German, and American women by Keyfitz (1968), and American women by Goodman (1969). Thus, among humans, the process of senescence likely begins at a relatively early age (one-sixth of the maximum known life span) as the force of natural selection and reproductive value reach

their maximum and begin to decline after about two decades of life. Rather than occurring exclusively in the elderly, senescence is a long-term process occurring over many decades of life (Harper and Crews 2000).

In addition to remarking on the role of declining natural selection with age, Medawar (1952) proposed that the age-specific actions of genes and mutation accumulation were basic components of the senescent process. Because natural selection diminishes with age, mutant alleles producing deleterious effects at ages beyond that of maximum reproductive potential, but with little or no effect at younger ages, may remain in the gene pool unaffected by natural selection. When sufficient mutations with late-acting, detrimental effects accumulate, broad senescent changes may result. Recently, Martin *et al.* (1995, 1996) suggested that any alleles that accumulated in this fashion should be “private” (alleles that segregate only in specific families/kindreds), as opposed to “public” (alleles found in broad segments of the population) alleles. Since natural selection is negligible for any such neutral mutations, their ultimate frequencies are presumed to be dictated by genetic drift alone (Martin *et al.* 1995, 1996). Evolutionary theory suggests that gene flow, mutation rates, and, specifically for alleles with post-reproductive influences on senescent processes, linkage (when loci are found close together on the same chromosome) to non-selectively neutral alleles – a specific form of genetic drift – would determine the fate of these late-acting alleles. Martin *et al.* (1995, 1996) suggest that such late-acting genes should aggregate in certain lineages, but they do not anticipate that they will be responsible for population-level senescent processes. However, given linkage, gene flow, variable mutation rates across populations and environments, and local selective forces, such alleles, particularly if they are linked to other alleles with positive influences on reproduction, are likely to spread widely across the population and ultimately to be represented throughout the species (Lasker and Crews 1996).

Medawar (1952) saw that both pleiotropy (when the product of one locus has multiple effects on physiology or phenotype) and linkage to beneficial early-acting alleles could lead to an increased representation of alleles with late-acting detrimental effects on survival at late ages. However, G.C. Williams (1957) was the first to develop fully the theory that pleiotropy might be an important determinant of senescence. Williams proposed that genes exhibiting pleiotropy could have early-life beneficial effects but later-life detrimental effects. Such late-occurring detrimental effects could then account for multiple senescent changes observed in various species. Clearly, natural selection favors alleles that increase vigor and vitality at young ages, including any alleles that enhance acquisition, utilization, or retention of the resources needed for growth and development or that lead to the optimal use of resources whose scarcity may have limited reproductive success during earlier phases of human evolution

(Crews and Gerber 1994; see Chapter 2). Natural selection also favors any mutations that postpone undesirable pleiotrophic effects of valuable early-acting alleles to ages beyond the point of maximum reproductive potential. Dubbed “antagonistic pleiotropy” because of the counteracting pleiotropic effects such alleles have during different phases of the life course, natural selection is the major factor in this model. In Martin and colleagues’ (1995, 1996) jargon, antagonistic pleiotropy is a “public” mechanism and, as such, should explain senescent processes which are common across a wide variety of life forms.

Fisher’s (1930) model showing reproductive value as proportional to the force of natural selection at any given age was refined by Hamilton (1966) who demonstrated that under very specific conditions $v(x)$ may increase at the same time as the force of natural selection decreases. Hamilton proposed a slightly different concept, “expected reproduction beyond age x ”, where $w(x)$, is an explicit formulation of “reproductive probability” as defined by Williams (1957). Hamilton’s equations more precisely estimate the changing force of natural selection with age (see Rose 1991, p. 14). However, the relationship between reproductive potential and natural selection in humans may be approached more intuitively. Maximum reproductive potential (MRP) may be defined as “the point in life at which an organism is sufficiently mature to not only bear/sire offspring, but also best able to rear and fledge any offspring produced with maximum efficiency” (Crews and Gerber 1994; Gerber and Crews 1999; Harper and Crews 2000). In species with large investments of parental care in offspring, the fledging process is as important as the ability to reproduce. Natural selection will have less influence on alleles carried by individuals who have passed their MRP as their expected genetic contributions to future generations decrease with time (both $v(x)$ and $w(x)$ may have declined prior to MRP and generally will continue to decline). MRP differs from either $v(x)$ or $w(x)$ because sexual maturity and thus reproduction may occur before future parents are physically, emotionally, or behaviorally prepared to fledge successfully any offspring produced. Neither the onset of reproduction nor the maxima of either $v(x)$ or $w(x)$ signal the point of MRP. Total “reproductive probability” (Williams’ terminology) and reproductive value (Fisher’s terminology) generally decline following sexual maturity, favoring maximization of reproductive potential at about the same time. In humans, the effectiveness of natural selection decreases slowly after the attainment of MRP. Incipient senescent changes are slower while reproductive potential remains high, increasing only slightly through ages needed for continued reproductive effort (e.g., mating, gestation, birth, rearing, and fledging multiple offspring). Thereafter, senescent processes proceed in a random and time-independent, but seemingly synchronized, fashion. Senescent dysfunction increases rapidly in those with enhancing, and more slowly in those with retarding, propensities. This leads to some having short (45 years) and others

long (>100 years) life spans, while the majority falls in the mid-range (70–75 years).

Williams (1957), Charlesworth (1994), Rose (1991), and others have described how synchronicity may have come to characterize multiple aspects of senescence. Over evolutionary time, human life history, reproductive processes, patterns of growth and development, and senescence have responded to multiple evolutionary pressures in a similar way to all other existing species. Most populations that have ever existed, including hominids, probably experienced relatively high mortality rates throughout most of their life spans (recall Malthus and Darwin). Such high mortality would necessarily have limited the effectiveness of natural selection beyond early adulthood. This suggests that multiple senescent changes should coalesce just beyond the average life expectancy of a species in the wild (Williams 1957). Hominid evolutionary history may provide one example. Australopithecines and early *Homo* species are estimated to have averaged only about 15–20 years of life over the 280 000–350 000 generations they prowled the earth (Cutler 1976; Weiss 1981, 1984, 1989a), while over 400 generations of early agriculturists and nomadic pastoralists could expect to live only about 25 years (Weiss 1981, 1984, 1989a). Only over the last ten or so generations has life expectancy increased from 43 to 75 years (Deevey 1950; Weiss 1981, 1984, 1989a). Given such brief life expectancies among our ancestors, it is likely that multiple adult-onset, age-related declines in function result from the actions of alleles that, due to their infrequent expression and exposure to natural selection in earlier hominid and human ecological settings, have been retained in humanity's gene pool. Increases in life expectancy among humans in recent generations have followed cultural elaborations and novel environmental adaptations among our recent ancestors, rather than any major biological innovation, also supporting this model. For humankind, and our domesticated animals, culture has added an extra dimension of variation to senescence.

Originally introduced by Weismann (1891), the disposable soma theory of senescence was later further elaborated by Kirkwood (1977, 1995). Both Weismann and Kirkwood observed that the decreasing force of natural selection and the corresponding loss of reproductive potential with increasing age ultimately cause senescence. Although the disposable soma theory is fundamentally related to both antagonistic pleiotrophy and the age-specific action of alleles, Kirkwood (1990) proposes an additional direct relationship between evolutionary theories of aging and physiological descriptions of senescence in organisms with a distinct soma and germ line. In sexually reproducing species, available resources – most importantly energy – may be used either to preserve the soma or reproduce the germ line. Because death due to environmental mishaps, accidents, and hazards remains inevitable, once sexual maturation is complete natural selection favors investment in reproductive success over

somatic maintenance. Attainment of MRP demarcates the timing of this change to investment in reproduction. Kirkwood (1977, 1981) suggested that senescent changes result from insufficient development of maintenance and repair mechanisms in somatic tissues, leading to their ultimate decline and failure. Decline and failure are closely linked to the number and fidelity (accuracy of function) of redundant sub-units (cells, sub-units) in somatic tissues (Gavrilov and Gavrilova 1986, 2001). Based on the disposable soma theory of aging, multiple candidate alleles for antagonistic pleiotropy will directly or indirectly mediate processes of cellular, organ, and organism generation, maintenance, repair, and protection. The disposable soma theory fits well with observations that the physiological manifestations of senescence often appear to result from “wear and tear”, manifesting as physical damage to cells, organs, and organisms (Kirkwood, 1990).

The disposable soma theory is a broad evolutionary model that places natural selection in the position of a prime mover and details how tradeoffs between reproduction and maintenance of the soma ultimately result in somatic instability, dysfunction, and death. Numerous additional theories describe the mechanisms by which somatic damage, or a lack of repair thereof, may occur and accumulate. Prevalent among these is the oxidative damage theory of aging, in which naturally occurring oxidants impart functional damage to proteins, nucleic acids, lipids, and carbohydrates (Mead 1976; Sevanian 1985; Davies 1987; Richter *et al.* 1988; Stadtman 1992; Fridovich 1995; Newcomb and Leob 1998; Luciani *et al.* 2001; Sozou and Kirkwood 2001). Although the human organism has several enzymatic and non-enzymatic antioxidant defenses, the age-related increase of markers of oxidized protein and oxidized DNA suggests a long-term imbalance in oxidant production and defense (Martin *et al.* 1995, 1996). “Oxidative damage” subsumes Harman’s (1956, 1981, 1984, 1999) free radical theory of aging, since only a portion of damaging oxidative processes result from free radicals *per se* (Swartz and Mader 1995). The more inclusive term for such molecules is “reactive oxygen species” (ROS) (Swartz and Mader 1995).

Not only oxidative processes cause somatic damage. Senescence also may result from long-term, low-intensity stressors, including, in addition to oxidative damage, temperature, physical trauma, radiation, diet, and toxic agents, which cannot be perpetually counterbalanced by protective and repair processes without some damage accumulating (Masoro 1996). Other proximate theories of senescence include intrinsic cellular aging, protein error catastrophe, and somatic DNA mutations (Vijg and Wei 1995). These all assume gradually accumulating damage to DNA, proteins, or cells and declining somatic function with increasing survival times. In a general way, senescence results from accumulating somatic damage and impaired function as the body’s maintenance, protective, and repair processes gradually become overwhelmed. Damage results from

a variety of basic mechanisms – ROS, wear and tear, toxic agents, error accumulation, temperature extremes, trauma, loss of repair capability, metabolism, and mtDNA mutations – and is cumulative. The common outcome of these multiple processes is somatic damage, which is the key connector between senescence and chronic degenerative conditions (CDCs) (Esser and Martin 1995).

A modern revival of Pearl's (1928) rate-of-living and Kirkwood's (1977) somatic damage theories followed observations of cellular damage due to the byproducts of metabolic processes, in particular ROS (highly reactive charged molecules such as O⁻, COH⁻, H⁻) (Harman 1987; Adelman *et al.* 1988; Cutler 1991). Although rate-of-living theories have been popular in gerontology and age-related changes in physiology are closely correlated with life span, experimental data refute their applicability to senescence (Hart and Tuturro 1983; Rose 1991; Austad 1992; Finch 1994). Comparative life spans in birds and mammals illustrate these problems (Austad 1992). Rate-of-living theories predict that in both birds and mammals metabolic rate should decrease with increasing size. At any given body size, birds show about twice the metabolic rate of mammals. Therefore, one would expect that, at any particular body size, mammals should live about twice as long as birds. This is not true: birds generally live much longer than same-sized mammals. Based on exhaustive review of many body systems, from whole body metabolism to cellular and biochemical levels, Finch (1994) demonstrated that there are neither strong nor consistent relationships among body size, metabolism, and life span. Weismann had suggested this based on his review of avian life spans in 1891. Primates, our nearest phylogenetic relatives, provide another example. Folivorous primates have lower metabolic rates than their body sizes would predict. This could be because they have relatively smaller brains than frugivorous species, or perhaps because the leaves they eat are energy poor and require greater processing (Harvey and Bennet 1983). Relationships between body sizes, metabolic rates, and life span are affected by multiple aspects of diet, ecology, habitual activity, and phylogeny. In addition, there is no reason why the rate of senescence must be related to length of life. Selection pressures are likely to vary for these traits (e.g., Pacific salmon). Why we senesce and why we live a certain life span are two related, but separate, questions. Rate-of-living theories address the questions of how, not why, we senesce, and may apply to senescence in specific organisms or organ systems composed of variable numbers of redundant sub-units.

Age-related, age-determined, and senescent

“Age-related” changes are changes in physiology, structure, or function that show an increase in the probability of occurrence with increasing age. These

need not manifest in all individuals at the same age or even occur in all prior to death. “Age-determined” changes include events that are invariable and universal aspects of a species’ life history, but which may occur across a range of ages with an accepted mean. These would include such human universals as loss of juvenile, and eruption of adult, dentition, closing of cranial sutures, attainment of puberty and reproductive function, decreased hormone production in later life, accumulation of lipofuscin, menopause and the lessening of reproductive potential in men, graying of hair, loss of skin elasticity, enlargement of the prostate, and decreased visual acuity with increasing age. Although the precise age at which such changes will occur is variable, they will occur in all individuals who survive sufficiently long. Age-related changes include those alterations that occur more frequently with the passage of time – loss of teeth and hair, hyperglycemia, decreased ability to complete activities of daily living (ADLs) and instrumental activities of daily living (IADLs), decreased bone density, hypertension, and hypercholesterolemia – but which may not affect all individuals. These increase in frequency with age, but show variable age patterns of onset. As with the distinction between disease and senescence, the distinction between “age related” and “age determined” is arbitrary and to a great degree related to our current lack of knowledge of the multiple causal pathways linking a chronological variable, age, to a physiological process, senescence, in a complex adaptive system.

Many physiological systems show age-related alterations; not all of these alterations are senescent. Attempts have been made to enumerate characteristics required for an age-related change to be an aspect of senescence (i.e., it increases the hazard of mortality). Arking (1998, following Strehler 1982) suggests some combination of cumulative, progressive, intrinsic, and deleterious. Additional criteria might include irreversible or degenerative. Criteria such as Strahler/Arking’s provide a baseline for evaluating age-related change as senescent or not. Although such criteria may change with additional research (Arking (1998) dropped universal from his 1991 list (Arking *et al.* 1991)), they provide a guide for determining if a specific age-related change may be a senescent alteration. Currently, it is difficult to assess processes or delimit early alterations representing senescence. For many CDCs/senescence, early stages are insidious and progressive – such as the build-up of plaque in arteriosclerosis or the uncontrolled cell proliferation in neoplastic disease – but almost undetectable with current technologies. Many age-determined changes seem to have little impact on the survival probabilities of individuals; conversely, many age-related changes significantly alter survival probabilities with increasing age.

Given exceptions to every generalization, numerous age-related changes in humans appear to be senescent alterations – e.g., progressive dementia, lowered