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 phylogenic 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-senescing 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.*

	Men			Women		
Year	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_o) 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_o 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*

	Life span		
Name	Average (months)	Maximum (months)	Age at puberty (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 hydoxylase, 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, phenlyketonuria). 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 phenoype.

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, polydactally, and diabetes in human isolates illustrate