Evolutionary Perspectives on Human Senescence

Bruce A. Carnes; S. Jay Olshansky

Population and Development Review, Volume 19, Issue 4 (Dec., 1993), 793-806.

Stable URL:
http://links.jstor.org/sici?sici=0098-7921%28199312%2919%3A4%3C793%3AEPOHS%3E2.0.CO%3B2-T

Evolutionary Perspectives on Human Senescence

BRUCE A. CARNES
S. JAY OLSHANSKY

FOR THE 100,000 YEARS THAT HUMANS have inhabited the earth, intense mortality selection pressures have produced a consistent long-term pattern of high unstable death rates that resulted in very high attrition at younger ages. Historically, only a small but robust subgroup of the human population has been able to survive into older ages. This persistent pattern of mortality was abruptly changed early in the twentieth century when marked reductions in infant, child, and maternal death rates occurred—a product of improved living conditions and medical technology. More recently, unexpected reductions in middle-age and old-age mortality have been observed in countries with low death rates. As a result, survival into older ages has become commonplace in the developed world[1]—leading scientists to hypothesize about how much lower death rates can decline and how much higher life expectancy can increase.

To comprehend the importance of recent trends in human longevity, it is useful to place them in historical perspective. The dramatic transition in the pattern of human mortality has occurred only within the last one to two hundred years—a blink of an eye on the evolutionary time scale. As we began to control the high unstable death rates present at younger ages, the prevailing forces of natural selection operating on our species were profoundly altered. The subsequent combination of stable low mortality and lagging high fertility led to rapid population growth, as predicted by Malthus. A less recognized but perhaps more important demographic change also began at this time—a transformation of the human age structure from a pyramidal form that existed for at least 100,000 years to a rectilinear form, or old-age structure (Olshansky, Carnes, and Cassel, 1993a). Thus, changes in the demographic profile of our species are already having a profound impact on many aspects of human society, not the least of which is the financial stability of age-based entitlement programs.

In this note we introduce some of the basic elements of evolutionary theories of senescence in an attempt to familiarize researchers outside the biological sciences with these important concepts. Indeed, we contend that the evolutionary model of senescence can provide a theoretical framework for demographers in their development or evaluation of models of human mortality.

A biodemographic paradigm

The fields of biogerontology and molecular biology are replete with empirical studies describing the physiological and morphological changes that occur in living organisms with the passage of time (see Arking, 1991; Shock, 1983). Evolutionary biologists have proposed theories to address the most basic questions of why senescence occurs. Most of the information generated by these disciplines has not been incorporated into basic demographic models of human mortality and senescence, nor has this information been considered when demographers forecast mortality. Instead, demographic approaches to modeling and forecasting mortality typically rely on short-term trends in death statistics,[2] assuming that the future will be some variation of recently observed historical trends (for example, see Bell, Wade, and Goss, 1992; Day, 1992).

The field of demography has been a leader in the development of sophisticated quantitative methods for manipulating mortality data. However, demographers typically do not receive training in the basic biology of the organism upon which their mathematical models are applied—humans. We contend that the study of human senescence and mortality, and in particular the issue of forecasting longevity, is an exemplar of a scientific endeavor that requires an interdisciplinary approach. Specifically, we argue in this note that demographic estimates of future human longevity should be considered within the context of the basic biology of the organism and the historical forces that have shaped the evolution (and survival) of our species (Weiss, 1990). Further, scientists involved in forecasting should recognize that recent trends in human mortality represent a dramatic departure from the patterns of mortality that must have existed for the past 100,000 years.

The terminology of evolutionary biology is quite different from that of demography. For this reason we provide the following definitions.

Natural selection is the primary mechanism through which evolution occurs. It is characterized by differences in the survival and reproductive success of individuals with different genetic (heritable) traits.

Fitness is the quantification of an individual's genetic contribution (reproductive success) to subsequent generations relative to other individuals in the population.

Pleiotropy is the phenomenon of genes either being involved in more than one biological process, or having different effects when expressed at different times in the life cycle.

Soma are the cells of an organism other than those involved in reproduction. Somatic cells are distinguished from germ cells (gametes), which include only sperm, eggs, and their progenitors.

Life history strategy is the collection of physical attributes and behavioral characteristics that delineates a species' response to its environment. A life history strategy for a species is largely fixed and includes such characteristics as fecundity, length of reproductive period, gestation period, rate of development, and parental care. For example, the life history strategy of humans includes a high parental investment in raising offspring, a developmental strategy (and supporting physiology) that leads to maturation in the second decade of life, and relatively fixed ages at menarche and menopause.

Reproductive period is a portion of time within the lifespan of a species that includes reproduction, childrearing, and for some species a time frame during which parents contribute to the reproductive success of their offspring.

Senescence is the time-dependent accumulation of damage at the molecular level that begins at fertilization and is eventually expressed as nonspecific vulnerability, impaired function, disease, and ultimately death. The rate of senescence is influenced by a combination of stochastic events, genetic makeup, cell type, personal behaviors, and environment. Senescence may be viewed most easily as the passage of biological time.

Aging is the passage of chronological time. This definition is included only to distinguish between chronological aging and senescence (or biological aging). Henceforth, in referring to the latter concept, we use the term senescence.

Evolutionary theories of senescence

Theories that have addressed the question of why senescence occurs were formulated by evolutionary biologists in the early part of the twentieth century and have been empirically tested only within the last quarter-century. Unlike molecular biology, in which numerous theories about the mechanisms of senescence have been formulated (Dice, 1993; Hayflick, 1985; Medvedev, 1990), evolutionary biology has one main hypothesis, with variations on a central theme.[3] One of the basic concepts—referred to as "antagonistic pleiotropy"—was initially set forth by Fisher (1930) and Haldane (1941), formulated more clearly by Medawar (1946, 1952) and Williams (1957), and empirically tested by Hamilton (1966), Charlesworth (1980), and Rose (1982), among others. The "disposable soma" theory of senescence, originally formulated by Kirkwood (1977, 1981) and Kirkwood and Holliday (1979), represents an extension of antagonistic pleiotropy.

An understanding of the evolutionary model of senescence first requires an appreciation of the key ingredients of any evolutionary argument. Foremost among these is the identification of the most basic unit of evolution—the gene.

Individuals exist for only a short time: the gene is the one irreducible unit of biologic information that has the capacity to be immortal. Even the unique arrangement of genes on the chromosome of an individual is not preserved when gametes (eggs and sperm) are produced.

We can now ask how genes persist through time. For brief periods, assemblages of genes maintain residence within individual organisms—individuals with finite lifespans. Only through reproduction are genes able to escape the limitations imposed by the finite lifespans of individuals. The variety of potential solutions (strategies) employed by organisms to solve the problem of reproduction is reflected by the incredible diversity of life on earth. In this note, however, we restrict our discussion to sexually reproducing organisms.

Species are populations of individuals with the capacity to interbreed and produce viable offspring. All species, past and present, can be thought of as experiments in the propagation of genes through time (Dawkins, 1976). Each species is a unique lifeform with a matrix of adaptive strategies employed by members of the species to survive long enough in a hostile world to reproduce successfully. Nature's penalty for an unsuccessful life history strategy is the extinction of the species.

Despite the diversity of life on earth, a few common themes emerge when the life history strategies of species are compared. The critical point in the present context is that reproduction invariably occurs early in the life cycle of all sexually reproducing species. Early reproduction is a common strategy because a ubiquitous component of the environment must have been the presence of exogenous (i.e., nonsenescent) mortality. Apparently, individuals that reached sexual maturity earlier had a greater likelihood of surviving to reproduce than individuals reaching sexual maturity later. Natural selection must have favored a shift toward earlier sexual maturity until an evolutionarily stable strategy was reached between the benefits of early reproduction and the costs associated with accelerated development. At the point of equilibrium the life history of a species is set and the genetic link between reproduction and senescence is fixed in the genome. For humans, the point of equilibrium is characterized by a concentration of fertility in the second and third decades of life. This reproductive strategy represents a legacy of our response to environmental conditions that must have existed at the time the human species arose.

The concentration of reproduction early in the life cycle strongly suggests that extremely high mortality at younger ages has been a common demographic characteristic among all forms of life. As such, survival into older ages has been an improbable event limited to a small fraction of the population. The combination of high attrition at younger ages and a low probability of survival to even modest ages explains why senescence is such a rare event in nature.

Our progression of logic from the immortality of genes to the evolution of reproductive strategies was intended to lay the biological foundation for the following discussion of theories of why senescence arose.

Antagonistic pleiotropy

Antagonistic pleiotropy is a theory of senescence with roots in evolutionary theory. This theory depends on the proposition that the intensity of natural selection declines with age. The logic behind this proposition requires clarification.

Evolution, in its simplest form, means changes in the genetic composition of a population (gene pool) through time. In the collective sense, the ability of a specific gene to persist in a population through time depends on the reproductive success of the individuals who possess the gene. In sexually reproducing species, every individual carries a unique assemblage (genotype) of the available genes in the population. The gene pool of the population changes through the differential survival and reproductive success of genetically different individuals. The arbiter of reproductive success is natural selection. However, from an evolutionary perspective, the time before the reproductive period ends is the only opportunity for natural selection to alter gene frequencies. Differential mortality occurring after the reproductive period can have no effect on the genetic composition of subsequent generations. Thus, the force (effectiveness) of natural selection is strongest before reproduction begins, diminishes as the cumulative reproductive potential of individuals is achieved, and is weak or nonexistent after the reproductive period ends.

If survival beyond the reproductive ages is required for senescence to be expressed and if one accepts the role and effectiveness of natural selection in the process of evolution, then it is hard to imagine how senescence could be an evolved element of any life history strategy. Instead, it must have arisen as a by-product of selection operating on something else—such as fertility. According to Medawar (1952) and Kirkwood and Rose (1991: 16), senescence might have arisen indirectly through the accumulation of deleterious mutations that act only later in life (especially after reproduction), when the force of natural selection is either weak or nonexistent.

Williams (1957) postulated that some genes designed to enhance reproductive success early in life could have deleterious effects later in life if the somatic environment changes—hence the origin of antagonistic pleiotropy. Since the force of natural selection must decline once reproduction begins, a gene conferring reproductive advantages early in life could proliferate in the population even if it had a deleterious effect after the reproductive period. This apparent contradiction occurs because natural selection alters gene frequencies through differential reproduction, and must, therefore, be blind to differential mortality occurring after reproduction has been accomplished. Hence, genes whose deleterious effects are expressed late in life could accumulate in the gene pool because of their beneficial effects early in life.

Under this theory, many of the genes involved with growth and development early in life could be indirectly responsible for the phenomenon we call

senescence late in life. For example, the genes associated with Huntington's Disease and the growing list of genes implicated in cancer (oncogenes) may have accumulated in the human genome because their deleterious effects only arise after the reproductive period, when natural selection is weak or nonexistent. Senescence is probably a multigenic process that is intimately tied to the basic developmental characteristics of a species, and whose expression arose indirectly as a by-product of natural selection operating to enhance reproductive fitness. It is important to emphasize that to observe the deleterious consequences of the expression of these late-acting genes, survival into older ages is required.

The epidemiologic transition of the twentieth century has created an opportunity to observe whether the evolutionary theory of senescence applies to humans. As predicted from evolutionary theory, for survivors beyond the reproductive period there has been a proliferation of what we now call the fatal and nonfatal degenerative diseases of senescence. Age-related changes in body composition, physiological function, disease expression, and ultimately death may be the inadvertent consequence of the deleterious effects of genes expressed late in life.[4] What we call senescence may simply be the inevitable biological consequence of survival beyond the reproductive period. Other mechanisms have also been proposed to augment and extend the concept of antagonistic pleiotropy.

Disposable soma

One such extension, the disposable soma theory, has roots in physiological ecology. Kirkwood (1992: 1192S) maintains that there is no programmed senescence, but neither is there an active genetic program for immortality. In short, organisms have evolved varying physiological defense, maintenance, and repair mechanisms that work only efficiently enough to ensure evolutionary fitness. Once reproduction is achieved (possibly including a period of parental care for some species), the soma is "disposable." Since there is no need for a perfect mechanism for somatic maintenance, under this theory senescence is inevitable.

Senescence results from a conflict between the necessary allocation of energy to maximize reproductive fitness and the energy investment required to maintain the soma. An investment of resources sufficient to ensure immortality could only be achieved at the expense of reproductive success and, thus, evolutionary fitness. Not only would this be difficult to achieve, it is also not necessary to ensure the continuity of the germ line and thus the survival of the species. An optimum strategy for allocating energy resources is one that permits the organism to live only long enough to ensure reproductive success. The push toward maximizing evolutionary fitness inadvertently results in the progressive accumulation of unrepaired somatic damage, which translates into what we observe as senescence (Kirkwood and Rose, 1991: 17). While the nature of the

differential allocation of energy resources between reproduction and somatic maintenance is the focus of the disposable soma theory, the actual molecular mechanisms involved remain poorly understood.

The variety of potential investment strategies for somatic maintenance and reproduction is reflected in the nearly endless array of mortality patterns observed for organisms living in the wild. For organisms living in artificial environments where predation is eliminated and infectious and parasitic diseases are controlled, mortality patterns associated with senescence reflect the species-specific reserve capacity for post-reproductive somatic maintenance, repair, and therefore survival.[5] Different species would be expected to have unique lifespans based on their allocation of resources between somatic maintenance and reproduction—allocation strategies representing responses to environmental conditions that prevailed when each species arose. Life history strategies are a legacy of the evolutionary process itself, moulding the basic biology and pattern of senescence for every species, including Homo sapiens (Hamilton, 1966).

Gene disregulation

Antagonistic pleiotropy and the disposable soma theory can be linked through what Cutler and Semsei (1989) called the disdifferentiative hypothesis of "aging"—an effort on their part to use gene disregulation as a mechanistic link between cancer and senescence. A potential relationship between cancer and senescence is relevant because statistical models have been proposed to examine how anticipated medical advances against cancer (and other diseases that are prevalent in older ages) might influence life expectancy (Chiang, 1968). The hypothesized mechanism for both cancer and senescence is the time-dependent and stochastically influenced disregulation of genes.

Gene disregulation can also be used to link the antagonistic pleiotropy and disposable soma theories into a potentially unified concept of disease and senescence. The logic is as follows. Gene expression is carefully regulated and the products of gene action are typically involved in multiple, often interacting, processes (pleiotropy). Further, the normal regulation of gene activity can be disrupted by the gradual accumulation of random damage that occurs through the inevitable passage of time. Because of pleiotropy, a cascade of deleterious consequences may follow when the regulated state of genes is disrupted. The severity of the consequences will depend on how critical the affected processes are at the time of disregulation and on the ability of the organism either to compensate for or to repair the damage.

Under this paradigm, when the damage involves the regulation of cell growth or differentiation, cancer results. In other cases, the gene product itself may be unaffected but the appropriate temporal expression of the gene may become disregulated. For example, a gene whose activity was absolutely essential early in life may be expressed inappropriately later in life with resulting

deleterious effects (i.e., antagonistic pleiotropy). Senescence occurs when the repair and maintenance functions of cells are impaired, leading to a gradual degradation of physiologic function with time (i.e., disposable soma). The source of the damage leading to gene disregulation can be either internal (endogenous) or external (exogenous). For example, endogenous damage could arise when inadvertent errors occur during the transcription, replication, or translation of DNA. Potential sources of exogenous damage include chemicals in the environment (natural or manmade) and natural radiation (solar radiation; radioactivity in soil).

Radiation-induced damage is relevant because of its potential link to both cancer and senescence. Radiation has always been a ubiquitous component of the environment, and when radioactive particles interact with water and other molecules, destructive compounds known as free radicals are produced. Since 80 percent of living matter is composed of water, free radicals represent a component of the cellular environment that has been present since the beginning of life on earth. The biological importance of these highly reactive compounds that are produced through many mechanisms (principally normal metabolism) is reflected in the fact that virtually all living organisms have evolved the ability to either scavenge for or repair the damage caused by free radicals. Damage caused by free radicals has been linked to cancer as well as other disorders associated with senescence (Harmon, 1981, 1992). The time-dependent loss of gene regulation, including maintenance and repair, may represent one mechanism by which the damage produced by free radicals brings forth a cascade of changes in living organisms that we generally identify as senescence.

A biologically defensible linkage can be made between the time-dependent accumulation of somatic damage, the deleterious effects of free radicals, molecular mechanisms for disease, and theories of senescence. The common thread is the argument that disease and senescence may be the inadvertent results of deleterious pleiotropic effects caused by gene disregulation. In turn, the disregulation of genes may be the product of an organism's sacrifice of somatic maintenance for investment in reproduction. This tradeoff leads to an inevitable degradation of maintenance and repair mechanisms that mediate the accumulated damage to genetic information caused by, among other things, free radicals. It is suggested here that some of the theories of senescence could be combined such that the damage caused by free radicals is viewed as simply one modality for gene disregulation, and gene disregulation serves as a mechanism through which pleiotropic effects cause senescence.

The stochastic (or random) nature of the breakdown in gene regulation should be clarified. The insults that can lead to genomic damage are neither directed toward specific gene targets nor restricted to specified periods of the lifespan. While the insults themselves may be stochastic, recent evidence suggests that there may be regions of the genome that are inherently unstable and, therefore, more susceptible to mutation that may lead to the disruption of gene regulation (Boulikas, 1992; Lindahl, 1993). It also appears that some types of

damage to segments of DNA (genes) undergoing active transcription are preferentially repaired (Boulikas, 1992). Thus, while the insults may be stochastic, the cellular response of the organism is anything but random.

If genes currently active are preferentially repaired, this implies that nonactive genes may accumulate unrepaired genomic changes over time. Alterations to genes not being expressed may be of little importance, while changes to sequences of DNA that control gene expression (regulatory genes) may be critical. For example, even the inappropriate temporal expression of a normal gene through loss of regulation could have severe consequences. It may be no accident that most oncogenes have been linked to regulatory functions (e.g., cell growth, differentiation)—processes critical during early growth and development (Brugge et al., 1991). The inherent parsimony of DNA repair processes is consistent with the tradeoff between somatic maintenance and reproduction predicted by the disposable soma theory.

When accumulated damage occurs in somatic cells, disease or senescence, or both, may occur. Damage to the germ cells (eggs and sperm) ranges from causing immediate cell death to leaving viable gametes capable of passing on the genetic changes to the next generation. The division between somatic and germ cells is not mutually exclusive, in that propensities toward disease and competency of somatic maintenance and repair are probably heritable.

Although there may be a biological clock that begins ticking when the sperm fertilizes the egg, it is likely to be driven by the inevitable passage of time rather than predetermined by a date of death encoded in the genes. These observations suggest that it may be only a matter of time before it becomes possible to manipulate disease processes at the molecular level and intervene to alter the rate of senescence and thus the average lifespan of a species. Just how far the average lifespan of a species might be extended by altering the rate of senescence through genetic intervention (directly through genetic engineering or indirectly with pharmaceuticals) is the subject of much speculation and debate. According to the theories presented here, the genetic manipulation of a species to favor extreme longevity may require altering a substantial portion of the genome—a genome that evolved to enhance reproductive fitness through accelerated development, with senescence resulting only as an inadvertent consequence of extended survival. Because gene effects are often pleiotropic and gene expression is carefully regulated, manipulating the genome to favor a single trait such as increased longevity could easily generate adverse secondary consequences. The physiological, morphological, and behavioral ramifications of manipulating the normal expression of the human genome are currently unknown.

The evolutionary paradigm applied to humans

If the evolutionary model of senescence is correct, one would predict that natural selection would have favored somatic maintenance and repair mechanisms in

humans that remain operative at a high level of efficiency for approximately the first 30–40 years of life (Cutler, 1985). This time frame corresponds to the probable life expectancy for the majority of our existence as a species, but more importantly it reflects the biological response to environmental forces that were present when our species first arose. With reproduction likely to have been concentrated in the second and third decades of life, 30–40 years also represents a time frame for humans when our ancestors could have been grandparents (i.e., when the reproductive success of offspring would have been determined). Beyond this age range, the force of natural selection should decline, additional gains in fitness should be minimal, and the increase in senescent-related mortality should become evident.[6]

In fact, despite rapid declines in mortality during the twentieth century, the death rate for humans has doubled every eight to nine years beginning in the second decade of life (Finch, 1990: 15).[7] The presence and intransigence of mortality rate doubling times (MRDT) has also been observed in other species (Finch, 1990). While it may be possible through medical technology to modify the MRDT for subgroups of the population, it is also possible that an unyielding MRDT represents a fundamental demographic characteristic of our species.[8]

The evolutionary arguments suggest that senescence is inevitable for any sexually reproducing species. Dramatic declines in age-specific mortality over the last century are a tribute to the progress humans have made toward controlling the extrinsic forces that act on our species. As survival continues to extend beyond the period of reproduction, however, opportunities for further declines in mortality should diminish as the intrinsic mortality associated with the inevitable accumulation of damage to maintenance and repair mechanisms is revealed. Under this logic, further extensions of survival should, at some point, be associated with a never-ending and progressively more difficult battle against the disorders of senescence. This represents a biologically based law of diminishing returns.

At the population level, when death rates at younger and middle ages have declined to levels that permit most of the population to survive into older ages (as is already the case in low-mortality countries), mortality declines and gains in life expectancy should begin to decelerate—a well-documented phenomenon known as entropy in the life table (Horiuchi, 1989; Keyfitz, 1985; Lee and Carter, 1992; Olshansky, Carnes, and Cassel, 1990). Under these conditions, the age structure of a stationary population will become rectilinear for the first time, and the combined effect of population aging and extended survival into older ages could result in rapid increases in the prevalence of morbidity and disability—and possibly even increases in their rate of occurrence (for example, see Crimmins, Saito, and Ingegneri, 1989; Olshansky et al., 1991; Robine et al., 1991; Verbrugge, 1984). These trends may also be accompanied by a simultaneous increase in the frequency of transitions to improved health status by others who survive to older ages (Rogers, Rogers, and Belanger, 1990).

Although an evolved genetic program for senescence and death probably does not exist, evolutionary theories imply that effective bounds on longevity exist and are determined by inevitable age-related declines in somatic maintenance and repair. Progress against today's fatal diseases will probably lead to further declines in mortality at older ages. However, as each new medical success or improvement in health status at the population level leads to incremental increases in survival, evolutionary theory implies that new or infrequently observed diseases and disorders associated with senescence should replace those in decline. As long as the fundamental rate of decline in somatic maintenance remains unaltered, the driving force behind age-related disorders will also remain unchanged.

Conclusions

The concept of diminishing returns as applied to future life expectancy increases for humans has been associated with entropy in the life table. Evolutionary theories of why senescence arose imply that other forces of diminishing returns might act to limit declines in mortality and gains in life expectancy—the inherent vulnerability of the genome and the possible accumulation of pleiotropic genes expressed late in life as lethal and disabling senescent diseases. The legacy of senescence for every species is determined by the link between reproduction and senescence that was established by the evolutionary process—a legacy that has been fixed in the genome. As such, once survival beyond the reproductive period has been achieved for the majority of the human population, inevitable declines in physiological mechanisms designed to maintain the soma should result in diminishing longevity benefits from further modifications to the environment (such as risk factor modification). Further declines in old-age mortality should also permit the full expression of the senescent pattern established by the evolutionary process as a legacy for humans—a legacy that should become more evident as life expectancy increases.

The evolutionary theories of senescence outlined here do not represent the full spectrum of thought from this discipline.[9] We have tried to present key points of the logic used in these theories for the purpose of introducing these concepts to scientists outside the field of evolutionary biology. Also missing from this discussion are the many theories concerning possible mechanisms of senescence that have arisen from the field of molecular biology. Knowledge at the molecular level is growing rapidly, but linkages to the predictions made by evolutionary biologists are few. In subsequent articles we will discuss mechanisms of senescence at the molecular level, examine the demographic implications of evolutionary theories of senescence, and attempt to identify quantitative features of senescent mortality patterns. The main point here is that theories of why senescence arose provide demographers and other interested scientists with what we believe is a useful paradigm both for interpreting historical trends in

mortality and for predicting mortality and morbidity trends in the future. It is premature to expect definitive answers to emerge from any single discipline about the causes or future of human mortality. In fact, we argue that before reliable quantitative models for predicting human mortality can be developed, input from several disciplines will be required to characterize the biological nature of the complex process of dying out.

Notes

Funding for this work was provided by the National Institute on Aging (NIH/NIA Grant No. AG-00577-01 for S. J. Olshansky) and the Department of Energy Office of Health and Environmental Research (contract No. W-31-109-ENG-38 for B. A. Carnes). The authors thank the following individuals for their review of an earlier draft: Felicity Bell, Neil Bennett, Jacob Brody, Michael Carnes, Christine Cassel, Caleb Finch, Sylvia Furner, Steve Goss, Shiro Horiuchi, Tom Kirkwood, Marty McCarthy, Richard Rogers, Jeff Schwartz, Greg Spencer, Fred Stevens, and Gayle Woloschak.

1 A majority of the human population lives in developing countries, where intense mortality selection pressures still preclude survival into older ages for most persons. Other species living in the wild also remain subject to the intense mortality pressures that have always been present as a primary force of natural selection.

2 Because the pattern of human mortality has not changed much during the 100,000 years that humans have inhabited the earth (with the exception of about the last 200 years), mortality trends observed during the past century are considered short-term. However, most official forecasts of mortality made by US government agencies have based their forecasts on trends in mortality observed during the 15–20 years preceding the forecasts.

3 Excellent reviews of the evolutionary theories of senescence have been published by Kirkwood (1992) and Kirkwood and Rose (1991).

4 We are not arguing that genes or inappropriate gene expression is the sole cause of disease expression and mortality. Personal behaviors and stochastic events throughout the life cycle can also influence the rate of senescence and therefore disease expression. Unanswered questions include what the baseline rate of senescence is and the extent to which longevity can be influenced by nongenetic factors once extended survival has been achieved in a population. It is hypothesized here that in low-mortality populations where survival beyond the reproductive period has been achieved by most persons, the longevity benefits associated with risk factor modification diminish and mortality becomes dominated more by genetic than by environmental factors.

5 Such underlying cause-of-death patterns may also provide some indication of what may be expected for humans as we gain similar control over our environment. In other mammals raised in controlled environments, the primary causes of death are cancer and "cause of death unknown" (probably multiple organ failure).

6 The age at which the mortality rate from endogenous causes begins to double for humans could possibly be extended through medical technology—a testable hypothesis. According to evolutionary theories of senescence, however, delaying that age for humans should become progressively more difficult with extended survival, eventually reaching a point of diminishing returns. At that time further delays could be achieved only by modifying the genome itself. Identifying the mathematical properties of that age for humans and its potential modifiability is an example of how demographers can begin testing evolutionary theories of senescence.

7 The doubling time for endogenous mortality (MRDT) should be lower than 8–9 years in low-mortality populations. The esti-

mate of senescent-related MRDTs for humans is the subject of ongoing research by the authors of this note. Horiuchi (1993) has already shown that in Japan the MRDT (for all causes of death) may have remained constant in recent decades at about 6–7 years. Several other studies have been published on the Gompertzian nature of cause-specific mortality in humans (Riggs 1990a, 1990b).

8 A recent study of old-age mortality in low-mortality populations indicates that mortality rates may level off at very old ages (Wilmoth, 1993). The MRDT may represent a species-specific mortality signature that applies only to a heterogeneous population (Olshansky, Carnes, and Cassel, 1993b). Once genetic heterogeneity is reduced by earlier attrition, a different Gompertz (or other) distribution would be expected to apply to the remaining survivors. However, declining old-age mortality could also maintain genetic heterogeneity into older ages, thereby extending the age span for which the MRDT applies.

9 For a list of the theories of aging from evolutionary and molecular biology see Medvedev (1990). Also, see citations in note 3.

References

Arking, R. 1991. *Biology of Aging: Observations and Principles.* Englewood Cliffs: Prentice-Hall.

Bell, F. C., A. H. Wade, and S. C. Goss, 1992. "Life tables for the United States Social Security Area 1900–2080," Actuarial Study No. 107. Social Security Administration, SSA Publication No. 11–11536.

Boulikas, T. 1992. "Evolutionary consequences of nonrandom damage and repair of chromatin domains," *Journal of Molecular Evolution* 35: 156–180.

Brugge, J., T. Curran, E. Harlow, and F. McCormick (eds.) 1991. *Origins of Human Cancer: A Comprehensive Review.* Plainview: Cold Spring Harbor Laboratory Press.

Charlesworth, B. 1980. *Evolution in Age-Structured Populations.* Cambridge University Press.

Chiang, C. L. 1968. *Introduction to Stochastic Processes in Biostatistics.* New York: Wiley.

Crimmins, E. M., Y. Saito, and D. Ingegneri. 1989. "Changes in life expectancy and disability-free life expectancy in the United States," *Population and Development Review* 15: 235–267.

Cutler, R. G. 1985. "Evolutionary perspectives of human longevity," in R. Andres, E. L. Bierman, and W. R. Hazzard (eds.), *Principles of Geriatric Medicine.* New York: McGraw-Hill, pp. 22–29.

——— and I. Semsei. 1989. "Development, cancer and aging: Possible common mechanisms of action and regulation," *Journal of Gerontology* 44: 25–34.

Dawkins, R. 1976. *The Selfish Gene.* New York and Oxford: Oxford University Press.

Day, J. C. 1992. *Population Projections of the United States, by Age, Sex, Race, and Hispanic Origin: 1992 to 2050,* Current Population Reports, Series P-25, No. 1092.

Dice, J. F. 1993. "Cellular and molecular mechanisms of aging," *Physiological Reviews* 73: 149–159.

Finch, C. E. 1990. *Longevity, Senescence, and the Genome.* Chicago: University of Chicago Press.

Fisher, R. A. 1930. *The Genetical Theory of Natural Selection.* Oxford University Press.

Haldane, J. B. S. 1941. *New Paths in Genetics.* London: George Allen and Unwin.

Hamilton, W. D. 1966. "The moulding of senescence by natural selection," *Journal of Theoretical Biology* 12: 12–45.

Harmon, D. 1981. "The aging process," in *Proceedings of the National Academy of Sciences* 78: 7124-7128.

———. 1992. "Free radical theory of aging," *Mutation Research* 275: 257–266.

Hayflick, L. 1985. "Theories of biological aging," in R. Andres, E. L. Bierman, and W. R. Hazzard (eds.), *Principles of Geriatric Medicine.* New York: McGraw-Hill, pp. 9–21.

Horiuchi, S. 1989. "Some methodological issues in the assessment of the deceleration of the mortality decline," in L. Ruzicka, G. Wunsch, and P. Kane (eds.), *Differential Mortality: Methodological Issues and Biosocial Factors.* Oxford: Clarendon Press, pp. 64–78.

———. 1993. "Sex differentials in the life table aging rate," paper presented at the Annual Meeting of the Population Association of America, Cincinnati, 1–3 April.
Keyfitz, N. 1985. *Applied Mathematical Demography,* 2nd edition. New York: Springer.
Kirkwood, T. B. L. 1977. "Evolution of ageing," *Nature* 270: 301–304.
———. 1981. "Repair and its evolution: Survival versus reproduction," in C. R. Townsend and P. Calow (eds.), *Physiological Ecology: An Evolutionary Approach to Resource Use.* Oxford: Blackwell Scientific Publications, pp. 165–189.
———. 1992. "Comparative life spans of species: Why do species have the life spans they do?" *American Journal of Clinical Nutrition* 55: 1191S–1195S.
——— and R. Holliday. 1979. "The evolution of ageing and longevity," *Proceedings of the Royal Society of London B: Biological Sciences* 205: 531–546.
——— and M. R. Rose. 1991. "Evolution of senescence: Late survival sacrificed for reproduction," *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 332: 15–24.
Lee, R. D. and L. R. Carter. 1992. "Modeling and forecasting United States mortality," *Journal of the American Statistical Association* 87: 659–671.
Lindahl, T. 1993. "Instability and decay of the primary structure of DNA," *Nature* 362: 709–715.
Medawar, P. B. 1946. "Old age and natural death," *Modern Quarterly* 2: 30–49.
———. 1952. *An Unsolved Problem of Biology.* London: Lewis.
Medvedev, Z. A. 1990. "An attempt at a rational classification of theories of aging," *Biological Reviews* 65: 375–398.
Olshansky, S. J., B. A. Carnes, and C. Cassel. 1990. "In search of Methuselah: Estimating the upper limits to human longevity," *Science* 250: 634–640.
———, et al. 1991. "Trading off longer life for worsening health: The expansion of morbidity hypothesis," *Journal of Aging and Health* 3: 194–216.
———, B. A. Carnes, and C. Cassel. 1993a. "The aging of the human species," *Scientific American* (April): 46–52.
———, B. A. Carnes, and C. Cassel. 1993b. "Fruit fly aging and mortality" (letter), *Science* 260: 1565–1566.
Riggs, J. E. 1990a. "Longitudinal Gompertzian analysis of adult mortality in the U.S., 1900–1986," *Mechanisms of Ageing and Development* 54: 235–247.
———. 1990b. "Longitudinal Gompertzian analysis of stroke mortality is the natural consequence of competitive deterministic mortality dynamics," *Mechanisms of Ageing and Development* 55: 235–243.
Robine, J. M., et al. 1991. "Healthy life expectancy: Evaluation of global indicators of change in population health," *British Medical Journal* 302: 457–460.
Rogers, R., A. R. Rogers, and A. Belanger. 1990. "Longer life but worse health? Measurement and dynamics," *Gerontologist* 30: 640–649.
Rose, M. R. 1982. "Antagonistic pleiotropy, dominance, and genetic variation," *Heredity* (London) 48: 63–78.
Shock, N. W. 1983. "Aging of physiological systems," *Journal of Chronic Diseases* 36: 137–142.
Verbrugge, L. M. 1984. "Longer life but worsening health? Trends in health and mortality of middle-aged and older persons," *Milbank Quarterly/Health and Society* 62: 475–519.
Weiss, K. M. 1990. "The biodemography of variation in human frailty," *Demography* 27, no. 2: 185–206.
Williams, G. C. 1957. "Pleiotropy, natural selection and the evolution of senescence," *Evolution* 11: 398–411.
Wilmoth, J. 1993. "Are mortality rates falling at extremely high ages?" paper presented at the Annual Meeting of the Population Association of America, Cincinnati, 1–3 April.