A Journey through the Interdisciplinary Landscape of Biodemography

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The biodemography of aging explores the population consequences of the biological etiology of disease and death for individuals. As a consequence, biodemographic research is inherently interdisciplinary—using theory and methodology from numerous disciplines to better understand and reveal the interwoven forces that are responsible for creating and shaping the biological, demographic, and social attributes that define a species. The primary purpose of this chapter is to describe the formation of our interdisciplinary collaboration and explain how this collaboration has allowed us to make scientific contributions to the emerging field of biodemography. We identify personal and professional challenges that emerge from collaborations in general and interdisciplinary research in particular. We then describe how we have attempted to resolve these problems over the course of a collaboration that is long-term and ongoing. A detailed examination of issues that arise from collaborations and research that are interdisciplinary is the underlying theme of this book. Nevertheless, we thought that it was important to also present a brief description of the intellectual foundation of biodemography, a short summary of our biodemographic research, a demonstration of the relevance that biodemography has to important issues of public policy, and a discussion of the ongoing expansion of biodemographic research across disciplines within the scientific community.

The Big Questions about Aging

Although an enormous amount of research on aging has been conducted, only a handful of truly big questions have emerged from this intensive effort. *Why do we age*—or, asked another way, why are we not immortal? *How do we age*—that is, what are the biological mechanisms that cause a fertilized egg to proceed along a path of growth and development that invariably leads to the effects of aging that can be seen in the mirror and a death that cannot be avoided? *When do we age*—that is, why do aging, disease, and death occur when they do, and why do they exhibit variation within a population?

The *why* question of aging has been the focus of research in the fields of evolutionary biology and genetics for over a century. The *how* question of aging has been actively pursued by scientists from a variety of disciplines, including epidemiology, genetics, histology, medicine, pathology, and molecular biology. The *when* question of aging has been addressed by actuaries, biostatisticians, demographers, and epidemiologists who have developed numerous methods of quantitative analysis for population data containing ages at death and information on the diseases and disorders that precede it.

The question of *how we age* often overshadows the *why* and *when* questions, particularly when it comes to public opinion and the policy decisions that arise from that opinion. Virtually everyone wants answers to the *how* question because of the universal desire to control the consequences of aging. As a result, the biomedical sciences devote an enormous effort to identifying age-related health effects and developing methods of intervention that either prevent or delay the expression of these effects. Physicians also have a keen interest in the *how* question because they are the ones who must deal with the consequences of an aging population on a daily basis.

By its very nature, the biodemography of aging is an interdisciplinary approach to the study of aging. Our contributions to the ongoing development of biodemography involved the development of answers to the *why* and *how* questions for individuals in order to address the question of *when* mortality occurs in populations, and to explore comparisons of age patterns of mortality across species. In seeking answers to these questions, we have combined traditional demographic analysis with theoretical and experimental elements from a variety of disciplines in which research relevant to aging has been conducted: anthropology, ecology, embryology, epidemiology, evolutionary biology, genetics, molecular biology, pathology, and population genetics. Two bodies of historic literature have had a particularly profound influence on the development of our conceptual framework for the biodemography of aging: the search for a "law of mortality" by actuaries, chemists, and biologists, and the attempts to answer the question of why we age that arose from within the field of evolutionary biology.

The Search for a Law of Mortality

The intellectual origin of our biodemographic perspective on aging can be traced to observations made by the British actuary Benjamin Gompertz (1825). In the beginning of the nineteenth century, Gompertz noticed that the age distributions of death for various human populations and time periods looked remarkably similar. In fact, the pattern of high early age mortality, a rapid decline in the risk of death from birth to sexual maturity, and an exponential rise in the death rate from sexual maturity to about age 60, was so invariant that Gompertz believed there must be some "force" responsible for this phenomenon. Gompertz speculated that the exponential rise in the risk of death that he observed following sexual maturity was the result of a "law of mortality," or state of nature, characterized by "a deterioration, or an increased inability to withstand destruction" as one grows older. Gompertz's speculations on the biological forces responsible for his demographic "law of mortality" make him an excellent candidate for being considered the intellectual father of biodemography.

In a series of articles published later in the nineteenth century, the famous actuary William Makeham (1860, 1867, 1872, 1889, 1890) noted that some "diseases depending for their intensity solely upon the gradual diminution of the vital power" (1867, p. 335) fit the Gompertz equation far more closely than a mortality schedule based on all causes of death combined (i.e., total mortality). Medical science, however, was not sufficiently advanced at that time to permit the partitioning of total mortality into its constituent elements (Makeham, 1867). Makeham modified the Gompertz equation by including a parameter that was intended to account for environmental forces of mortality that were unrelated to those associated with aging. Makeham's refinement of the Gompertz equation and his quantitative development of what he called partial forces of mortality are the origins of what today is called competing risk theory.

Early in the twentieth century, scientists began looking at patterns of mortality for species other than humans to determine whether they also conformed to Gompertz's law. Their goal was to extend the Gompertz law for humans to a universal law of mortality that applied to all living things. Their assumption was that mortality differences among species were simply a function of scale that were compressed within short time periods for some and expanded for others.

Several scientists in the early part of the twentieth century made insightful speculations on factors that could determine whether there is a law of mortality. For example, biologists Jacque Loeb and J. H. Northrop (1916, 1917a,b) theorized that a species' lifespan was determined either by the depletion of important biological substances or through the toxic buildup of damaging by-products of living. Biochemist Samuel Brody (1924) speculated on a biochemical basis for a law of mortality after demonstrating that several biological processes related to senescence could be described by an equation used to quantify changes in chem-

ical reactions over time. These early researchers were among the first to suggest that growing old was an intrinsically biological phenomenon.

The first scientist to empirically assess the pattern of death for more than one species was biologist Raymond Pearl. In a series of articles, Pearl and his colleagues (Pearl, 1921, 1922; Pearl and Minor, 1935) asserted that a fundamental biological law of mortality would be revealed if differences in lifespan were removed by superimposing two biologically comparable points within the life cycles of humans and *Drosophila* (fruit flies). After two decades of research using this scaling approach on an expanded repertoire of species, Pearl and Minor (1935) eventually declared that a universal law of mortality did not exist because the death curves for the animals studied remained different, even after adjusting for lifespan differences. In discussing their unanticipated failure, Pearl and Minor recognized what Makeham (1867) had identified 68 years earlier as the main problem with this effort: the inability to partition total mortality into its intrinsic and extrinsic causes of death. While Makeham's development of the theory of partial forces of mortality was designed to show how Gompertz's law would apply consistently among different subgroups of the human population, Pearl and Minor declared that partitioning total mortality into its constituent elements would extend Gompertz's law to other species. As you will see, the insights by Makeham and Pearl on why they failed to discover evidence for the universal law of mortality they believed must exist were fundamental to the contributions that we have made to the biodemography of aging.

After Pearl gave up his search in 1935, scientists shifted their focus to the development of mathematical models that more reliably characterized patterns of mortality (for example, see Deevey, 1947; Heligman and Pollard, 1980; Perks, 1932; Pollard and Streatfield, 1979; Pollard and Valkovics, 1992). Although these efforts advanced the understanding of the mathematics of mortality, biological explanations for why death occurs in a Gompertzian pattern for many forms of life (the *when* question about senescence) remained a mystery. Interestingly enough, the question of *why* senescence occurs (or perhaps more appropriately, why humans and other animals are not immortal) dates back to the pioneering work of evolutionary biologists; these theoretical developments took place independently at about the same time the law of mortality was being discussed by actuaries in the late nineteenth century.

Evolutionary Theories of Senescence

Evolutionary biologists from Darwin through the present have speculated on the biological origin of senescence, but they did this independent of knowledge of research on aging in the actuarial/demographic sciences that had taken place decades earlier. When we realized that these two groups of scientists were working on closely related questions of aging completely independent of each other for more than a century, the first pieces of the puzzle of our work on the biodem-

ography of aging fell into place. A brief summary of the evolutionary literature on aging will make it clear what led us down a particular theoretical and methodological path.

The origin of modern evolutionary theories of senescence dates back to the theory of aging set forth by biologist August Weismann (see Weismann, 1891). According to Weismann, the one aspect of life that could not be avoided was the inevitable exposure of the individual to external forces, which produced a constant barrage of small injuries to the body. Because the perfect repair of these injuries is not realistically possible, it became self-evident why older individuals should be replaced by new ones. This was the rationale supporting both the need for reproduction and the importance of death. Thus, even if immortality theoretically were possible, it could not be realized in the real world where the external force of injury was ubiquitous and unavoidable.

The modern evolutionary theory of aging was provided by Nobel laureate Sir Peter Medawar (1952), who was able to make extensive use of Mendelian genetics in his arguments. Like Weismann, Medawar invoked the importance of the ever-present external force of mortality, which was acknowledged to be the primary reason that most members of a population were unable to live long enough to experience senescence. Medawar's unique contribution to the evolutionary theory of senescence was the argument that genes arising from mutation and whose expression is related to time would affect a different number of people, depending on when in the lifespan it was expressed. If the gene was expressed early in the lifespan, a large number of individuals would be affected while only a few would be influenced if it was expressed later in the lifespan. By implication, natural selection would favor and bring early into the lifespan those genes that were advantageous, while figuratively pushing genes with damaging effects into later portions of the lifespan where fewer individuals would normally be affected. Under his paradigm, senescence arises from the accumulation of genes with damaging effects that have been pushed by natural selection into the postreproductive period of life (which Medawar referred to as the "genetic dustbin"), and the extended survival of individuals (through protection from external sources of mortality) into an age range where these diseases have the opportunity to be expressed. Williams (1957) provided an important extension of Medawar's view of aging when he hypothesized that some of the genes that have damaging effects later in the lifespan may have positive effects early in the lifespan. This made senescence a product not just of deleterious genes expressed later in life, but an inadvertent consequence of selection-favoring genes with early adaptive functions and late-acting damaging effects (referred to as pleiotropic genes).

One of the most recent extensions of the evolutionary theory of senescence appears in a series of articles published by Thomas Kirkwood and colleagues (see Kirkwood, 1977, 1992; Kirkwood and Holiday, 1979; Kirkwood and Rose, 1991). Like Weismann and Medawar, Kirkwood argues that the inevitable force of external mortality plays a crucial role in the timing of senescence. However, in this case, the logic supporting the existence of senescence is based more on its prox-

imate causes of differential energy investments in somatic and germ cells, with the time-dependent decline in somatic maintenance and repair serving as the underlying mechanism. Thus, species under the influence of high external forces of mortality would benefit from greater investment in early reproduction and lower investment in somatic maintenance. Species facing less pressure from external forces of mortality (such as humans, animals domesticated by humans, whales, elephants, and a few other species) could afford to delay their reproductive efforts. Under this paradigm, senescence is viewed as a product of accumulated damage to somatic cells that is managed biologically at a level that depends on the intensity of external forces of mortality that are present in the environment of an organism.

In summary, the argument that selection alters the genetic composition of a population through the differential reproductive success of individuals is a basic tenet of modern evolutionary biology. According to Medawar (1952) and Williams (1957), opportunities for selection to alter gene frequencies should be greatest before individuals begin reproduction, diminish as the cumulative reproductive potential of individuals is achieved, and become weak or nonexistent once reproduction has ceased. This age-based gradient for the effectiveness of selection permits the potential lifespan of organisms to be partitioned into biologically meaningful time periods: the prereproductive, reproductive, and postreproductive periods.

The modern evolutionary theory of senescence is based on the premise that selection is most effective in altering gene frequencies in the prereproductive period. When the normally high force of external mortality is controlled and survival beyond the end of the reproductive period becomes a common occurrence, senescence and senescent-related diseases and disorders have the opportunity to be expressed. If gene expression in the postreproductive period—whether favorable or deleterious—is beyond the reach of natural selection, then a genetic basis for either immortality or senescence resulting from the direct action of selection is not possible. Under this paradigm, senescent-related diseases and disorders observed in organisms not molded by selection for extended survival (beyond the genetically defined reproductive period) is an inadvertent consequence of selection pressures that shape the reproductive biology of species (Hamilton, 1966). As a consequence, investments in the biochemical machinery necessary to maintain the integrity of the organism should diminish as the reproductive potential of the individual is achieved. This is the fundamental biological explanation for why individuals senesce, and it is a critical element in our work on the biodemography of aging.

The Formation of a Scientific Collaboration

Our contribution to modern developments in the biodemography of aging began inadvertently in 1989. At that time we were working in different divisions at

Argonne National Laboratory (ANL), a research complex that originated with the Manhattan Project and is now managed by the University of Chicago and funded primarily by the Department of Energy (DOE). Olshansky was the director of the social sciences section in the environmental studies group, where he worked on large-scale environmental projects. For example, he was responsible for estimating population growth rates and levels near a proposed high-level nuclear waste facility in Nevada; he explored the demographic and health consequences of building the super-conductor super-collider in Texas; he used census data and worked with meteorologists to estimate levels of human exposure to noise at Air Force bases throughout the United States; and he estimated human death rates associated with accidental releases of chemical agents at chemical weapons facilities in the United States. Because Olshansky had access to vital statistics data from the United States through the ANL library system, he was also able to maintain an active research program in the field of aging during his spare time. As a demographer, his research interest was focused entirely on humans.

In 1989, Carnes was a staff scientist (biologist/statistician) in the division of biological and medical research at ANL, where he was conducting research on the biological consequences of exposure to radiation. Most of his time was spent using mortality data for exposed populations of either laboratory mice (Carnes, Grahn, and Thomson, 1989; Grahn, Lombard, and Carnes, 1992) or beagles (Carnes and Fritz, 1991, 1993) in order to develop quantitative models for the prediction of radiation-induced mortality risks. His ultimate goal was to develop a quantitative method of interspecies extrapolation for predicting the age-specific risks of radiation-induced mortality in humans from the Argonne animal data. Carnes took a significant step toward achieving this goal when he and his colleagues demonstrated that age-specific radiation-induced mortality in exposed populations of the beagle could be accurately predicted from a simple scaling of the hazard models used to describe the mortality experience of exposed mice (Carnes, Olshansky, and Grahn, 1998). The mortality and pathology data used by Carnes came from an extensive database developed and maintained at ANL for radiation biology studies conducted there between 1953 and 1992. These data include approximately 70,000 mortality records for 20 strains of laboratory mice (Grahn, 1994; Grahn, Wright, Carnes, Williamson, and Fox, 1995), detailed histopathology data for around 800 beagles (Carnes and Fritz, 1993), and an epidemiological study of humans (Carnes, Groer, and Kotek, 1997).

Olshansky developed an interest in the question of how long humans can live after he attended an interdisciplinary conference on "Estimating the Upper Limits to Human Life Expectancy" sponsored by the National Institute on Aging in 1988. Soon thereafter, he developed a simple mathematical approach that involved a unique twist to the traditional way that the question of limits to human life expectancy had been addressed in the past: a reverse engineering model designed to evaluate the magnitude of the reduction in death rates that would be required to raise life expectancy at birth from current levels to 120

years. Upon learning that life tables and survival analysis were the focus of research conducted by Carnes, Olshansky proposed a collaboration in conjunction with Dr. Christine Cassel, a physician/geriatrician from the University of Chicago. The result of this initial collaboration was a lead article in *Science* (Olshansky, Carnes, and Cassel, 1990), international attention from the scientific and lay press, and the beginning of a debate among scientists about prospective increases in human life expectancy that continues to this day.

Shortly after the publication of our *Science* article and following discussions with colleagues in the biological sciences, we developed a strong interest in searching for the underlying biology that we believed must be driving the statistics of a life table. However, this required a dedicated full-time research and training effort that neither of us could pursue while working at Argonne. At that time, Olshansky decided to make research on aging a full-time job. The best outlet that simultaneously permitted him to leave Argonne and work on the question of biology in the life table was a Special Emphasis Research Career Award (SERCA) (K01) from the National Institute on Aging (NIA). He submitted a K01 proposal to the NIA that was funded in 1992. The purpose of the SERCA was twofold: it enabled Olshansky to leave Argonne and move to the University of Chicago in order to make research on aging a full-time career, and it enabled him to pursue an independent course of study in the fields of evolutionary biology, molecular biology, epidemiology, and statistics as each field relates to aging. The SERCA and the research and training opportunities it created were instrumental in helping Olshansky and his colleagues contribute to the emerging field of biodemography.

Carnes received his formal training in general biology, population biology, theoretical ecology, and biostatistics. Because we worked closely together after our first collaboration in 1990, Carnes's background in the biological sciences was instrumental in helping Olshansky in his training program under the SERCA. It was from these first interactions that we developed the theoretical and methodological elements of our research on the biodemography of aging. Early in 1992, it became evident to us that our research involved a unique merging of the demographic and biological disciplines, something we had not seen very often in the historical literature. We began to view our research as contributing to the development of a new interdisciplinary approach to aging. Initially, we referred to our approach as *evolutionary demography* because it was from these two disciplines (evolutionary biology and demography) that our research hypotheses were primarily derived. We quickly realized, however, that the conceptual framework we were trying to create encompassed a far broader range of biological reasoning than was implied by the restrictive term *evolutionary demography*. After settling on *biodemography* as a more accurate description of our work, we searched the scientific literature to determine whether the term had already been used. Our search revealed that the term *biodemography* appeared in a 1948 article by the ecologist G. Evelyn Hutchinson and that it had also appeared in a paper written by the geneticist Ken Weiss (1990). We also discovered that several the-

oretical antecedents of the biodemography of aging appeared sporadically in the scientific literature between 1825 and 1925 (for details, see Olshansky and Carnes, 1997).

The Biodemography of Aging: From Individuals to Populations

Our initial effort to understand the biology of the life table led us to examine the forecasts of mortality and life expectancy that official government agencies like the Social Security Administration (SSA) and the Census Bureau had been making for decades. We wanted to see whether the numerical methods they used to make their forecasts were similar to ours, and whether they ever brought a biological perspective to their forecasts. We discovered that their approaches to forecasting relied primarily on the extrapolation of past mortality trends (observed during selected time periods) into the future. Although both agencies made assumptions about future trends for specific diseases, their decision-making process was not influenced by a biological understanding of aging and death.

The empirical, or nontheoretical, approach to forecasting death rates and life expectancy has been unreliable in both the short-term and long-term because the time periods used as a frame of reference for the projections led to both underestimates and overestimates of the future course of life expectancy as a consequence of trends in death rates that have been both volatile and unpredictable during the last half of the twentieth century (Olshansky, 1988). The main problem that we saw with the extrapolation method was that projected death rates must eventually approach zero when time frames with favorable mortality trends are used as a basis for extrapolating over long time periods. In our opinion, the death rates resulting from this extrapolation approach for long-term forecasts are both theoretically and biologically indefensible.

We set out to find a way to bring a biological understanding of aging and senescence to official forecasts of mortality and life expectancy. Specifically, we suggested that once death rates decline to the point where most members of a population have the opportunity to experience senescence, the biology of why and when senescence occurs must be incorporated into demographic and actuarial methods of forecasting mortality. The findings from our *Science* article led us to believe that this point had already been reached in the United States and other low mortality populations where the rise in life expectancy at birth had already begun to decelerate.

We came to realize that the theories of aging and senescence developed by evolutionary biologists contained a rationale that could be used to explain the consistent age patterns of death that researchers working independently within the actuarial sciences were trying to describe quantitatively. By combining theory with data, we thought it should be possible to test the mortality implications of evolutionary theories of senescence. Like many people working within the actu-

arial and demographic sciences, we had access to data on humans. However, we also possessed a truly unique data resource, the mortality data for laboratory animals used by Carnes. These data and our interdisciplinary collaboration made it possible for us to pursue a research path that simply was not available to other researchers.

What is the link between these two independent bodies of scientific research devoted to aging, and how can this link be used to make biologically defensible forecasts of life expectancy? It was our contention that the common age pattern of mortality first noticed for humans by Benjamin Gompertz in 1825, and subsequently identified for other organisms by other scientists early in the twentieth century, makes sense when the evolutionary theory of senescence is extended from individuals to populations. Evolutionary biologists did not make this linkage because the focus of their research was almost exclusively at the level of genes, sometimes individuals, rarely populations, and almost never applied to humans. The scientists working in the actuarial/demographic sciences were unable to make this linkage because (1) their attention was focused on finding empirical evidence for a law of mortality, (2) they were operating without knowledge of the evolutionary theories of senescence that had been developed during the previous 100 years, and (3) they admittedly did not have the appropriate data needed to test their hypotheses. It is only when these two bodies of literature are brought together that it becomes possible to understand how the ideas and concepts from one discipline may be used to explain a phenomenon (common age patterns of mortality across species) observed by scientists in other disciplines. In this case, evolutionary biology provides the biological rationale that Gompertz, Makeham, Pearl, and others believed was present to explain why consistent age patterns of death exist across species. What follows is a summary of how we merged the research of these disciplines, formed a series of testable research hypotheses, and in so doing contributed to the emergence of the biodemography of aging.

We hypothesized that the logic from evolutionary biology that establishes links between natural selection and reproduction and between reproduction and senescence for individuals has a direct bearing on *when* senescent mortality should occur in a population. The logic is as follows. The timing of genetically determined processes such as growth and development are driven by a reproductive biology that evolved under the direct force of natural selection, molded by the necessity for early reproduction, which, in turn, is driven by the normally high external force of mortality. If individual senescence is an inadvertent consequence of these developmental processes as predicted from the evolutionary theory of senescence, then patterns of *intrinsic* (biologically related) causes of death in a genetically diverse population should also be calibrated to element(s) of a species' reproductive biology. Furthermore, given that a hostile environment is the critical driving force of natural selection for most species, the linkage between reproduction and the timing of death in a population should be consistent across species. Although individuals within a population are responding to a common set of hostile evolutionary pressures, we suggest that genetic heteroge-

neity among individuals and a stochastic "environmental" component of senescence should inevitably lead to a distribution of senescent-related deaths across the age structure. In other words, populations of all sexually reproducing species are composed of individuals with a wide range of inherent and acquired senescent mortality risks that lead to early mortality for some and late mortality for others.

If the genetic composition of a population remains stable over time, then we predict that an age pattern of senescent (intrinsic) mortality should exist for every species that remains invariant, even under conditions where mortality pressures from extrinsic causes of death differ. We called this consistent age pattern of death an *intrinsic mortality signature* because it is believed to be as characteristic of a species as the more traditional morphological traits used by taxonomists. However, changes in the intrinsic mortality signature of a population would be expected when forces of selection acting to maintain the genetic composition of a population are disrupted (e.g., environmental challenges such as modified reproductive schedules; see, Luckinbill et al., 1984; Rose, 1984), or indirectly by "manufacturing" survival time through (among other means) medical interventions that extend life for some individuals who have approached or reached their potential lifespan. In the published literature we have suggested that this has already occurred in low mortality populations (Olshansky, Carnes, and Grahn, 1998).

We then hypothesized that the full array of potential senescent processes, their consequences, and the intrinsic mortality signature itself can be revealed only under the "unnatural" condition of survival beyond the age of sexual maturity by a significant proportion of a birth cohort—a scenario that Medawar (1952) suggests is necessary to observe the senescence of individuals. This rarely happens for animals living in the wild because, as evolutionary biologists emphasize, death almost always precedes senescence in a hostile environment. However, for species living under controlled environments where extrinsic (nonbiologically related) causes of death are dramatically reduced (e.g., humans, household pets, and zoo and laboratory animals), we suggest that each species' intrinsic mortality signature should become visible for the first time. Since there are common forces (extrinsic mortality) responsible for molding the reproductive biology of species, a common pattern of intrinsic mortality—*an evolutionary imprint*—may also become visible when species are compared on a biologically comparable time scale. These are the basic hypotheses that we initially set forth in our work on biodemography, they are the main hypotheses we subsequently proposed to test under funding from the Social Security Administration, and in the end, this is the point at which evolutionary arguments for why senescence exists can be used to test for the existence of the Gompertz/Makeham/Pearl law of mortality. The evolutionary theory of why senescence occurs at the level of individuals may also be used to provide a biological rationale for explaining why there are age patterns of intrinsic mortality in humans and other species—that is, the "vital force" in Gompertz's rationale.

Earlier it was noted that the SSA had a tradition of forecasting mortality that dates back to the origin of the Social Security trust fund in 1935 (Olshansky, 1988). The SSA's predictions about age patterns of death in populations have public policy implications that are not just theoretical, but applied. When life expectancy at birth approaches higher levels as large proportions of birth cohorts have the opportunity to survive to older ages, the main force influencing death rates will be biomechanical features of the human body that influence the expression of fatal diseases (Olshansky, Carnes, and Butler, 2001). If this is true, then forecasting models and the assumptions that drive them would benefit from a biological perspective. Specifically, the presence of an intrinsic mortality signature would suggest that there are biological forces that influence how high life expectancy can rise, and if the SSA forecasts death rates that are below these levels, then strong justification must be provided for why this will occur.

Based on the evolutionary theory of senescence, we developed the following testable research hypotheses:

1. The age of lowest intrinsic mortality will always be at puberty.
2. The intrinsic death rate at puberty will serve as the launching point for exponentially rising death rates throughout most of the age structure.
3. The rate of increase in death rates from intrinsic causes following puberty will be calibrated to the length of the reproductive period.
4. Age patterns of intrinsic mortality will remain largely unchanged across time and population subgroups.
5. Attributes of intrinsic mortality will be present across sexually reproducing species (universal law of mortality).

The last of these hypotheses, if confirmed, represents evidence for species-specific intrinsic mortality signatures and biologically related limits to declines in death rates and a rise in life expectancy.

The main problem that scientists have faced in testing for the presence of a law of mortality ever since Gompertz involves stringent requirements on data. Both Gompertz in 1825 and Pearl in 1935 recognized the importance of distinguishing between intrinsic and extrinsic causes of death, but both realized they did not have the data that would permit such partitions. Makeham modified the original Gompertz formula as a way to partially take into account the important force of extrinsic mortality, but even his modification was not actually based on observed differences in causes of death among people. Evolution biology has based its theory of senescence on the ever-present high force of extrinsic mortality that shapes reproduction, and indirectly, death, but scientists in this field have had no need to perform a partition of mortality in a real population. In order to empirically test for the existence of a universal law of mortality, accurate information on cause of death is needed for more than one species.

We soon realized that Carnes worked with and was responsible for what was perhaps one of the only sources of mortality data in the world that was intentionally designed for making mortality comparisons between species. Mortality data for control populations of humans, dogs, and dozens of strains of mice had been carefully collected and maintained. Most individuals in these studies were autopsied by veterinary or human pathologists in order to determine why death occurred. In addition, like humans, the laboratory animals were raised within controlled living environments that limited extrinsic causes of death. In other words, the conditions had been met for observing and analyzing senescence in different species. It was our expectation that the quantitative attributes of the intrinsic mortality signatures for the three species that we studied would be relatively insensitive to assumptions made about future changes of total mortality (derived either from empirical or epidemiological models).

For this chapter, it is not important to provide details about the results of the research funded by the Social Security Administration and the National Institute on Aging. Those details are provided in most of our scientific papers published since 1995. For now, it is important to emphasize that the biodemographic paradigm of aging and mortality provides scientific evidence supporting the existence of a law of mortality as originally proposed by Gompertz/Makeham/Pearl: it led to practical public policy implications for forecasting mortality that were used by the Social Security Administration; it led to a series of testable research hypotheses on the biodemography of aging (Carnes, Olshansky, and Grahn, 1996) that are being evaluated by other investigators and graduate students in the United States and abroad who have acquired an interest in this field; and it has spawned a series of new research projects that incorporate elements of other scientific disciplines such as molecular biology and anthropology.

Key Findings, Conclusions, and Implications

A number of key findings follow from the interdisciplinary perspective provided by the biodemography of aging. In a manuscript we published in *Scientific American* entitled "The Aging of the Human Species," we described how population aging, a traditionally demographic phenomenon, could and should be examined and understood within the context of evolutionary biology (Olshansky, Carnes, and Cassel, 1993). In the light of evolution biology, population aging is the product of an acquired ability to alter the forces of natural selection that have been operating on humans for thousands of years, resulting in an experiment in life that extends survival well beyond the reproductive period for a significant portion of successive birth cohorts. The public policy implications of this perspective were immediately obvious to the scientists and trustees of the Social Security Administration (SSA), who then invited Olshansky and other demographers to participate in a debate about the future course of human mortality. When our research was subsequently funded by the SSA, that was the first time any government

agency had formally supported research devoted exclusively to work on the biodemography of aging. Numerous scientific publications were the direct products of this research (Bennett and Olshansky, 1996; Carnes and Olshansky, 1997; Carnes et al., 1996, 1998; Olshansky and Carnes, 1997; Olshanskyet al., 1998, 2001). The SSA-funded project served as the launching point for a series of scientific publications and research that continues to this day.

The first explicit mention of biodemography in the scientific literature after Weiss (1990) was in a pair of articles that we published in *Population and Development Review* (Carnes and Olshansky, 1993; Olshansky and Carnes, 1994). In our 1993 article, we set out to describe the evolutionary theories of senescence to the demographic community and to present the literature from evolutionary biology that had, for more than half a century, focused on issues of human aging and longevity from a perspective that social scientists were not generally familiar with. In our follow-up to that article published in the next issue of *Population and Development Review* in early 1994, we then applied reasoning from evolutionary biology to examine the plausibility of various demographic methods of forecasting mortality that led some investigators to conclude that life expectancy at birth in the United States will rise above 100 years. Our conclusion was that some methods of forecasting mortality currently in use by scientists and government agencies include assumptions that, from a biological perspective, yield forecasts that are mathematically correct but are biologically implausible.

The full development of the biodemography of aging that we originally proposed included a detailed discussion of its theoretical and empirical roots, the specification of 10 testable research hypotheses, and the results of our efforts to empirically test several of these hypotheses—all of which was published in an article in *Population and Development Review* (Carnes et al., 1996). This article was the main product of the SSA-funded project on biodemography in which we provided empirical evidence favoring the existence of a "law of mortality." Findings from this research imply that there are consistent biological forces that operate in largely the same way across species that regulate age patterns of death in genetically heterogeneous populations. Unless these biological forces of mortality are altered, there is reason to believe that death rates cannot decline significantly below the intrinsic mortality schedule for a species—a finding that has a direct bearing on forecasts of mortality and life expectancy made by actuaries at the Social Security Administration.

After publication of our 1996 paper outlining the biodemography of aging, some researchers rejected the idea that there is an "intrinsic" (or biologically based) force of mortality. Instead, it was their belief that nearly all causes of death are inherently modifiable by altering either behaviors or the environments within which humans live. The suggestion that there is no such thing as intrinsic mortality was surprising, given that scientists from a variety of disciplines had recognized the distinction between intrinsic and extrinsic mortality for more than a century. In response to the initial rejection by some of the importance of intrinsic mortality or the 170-year old search for a "law of mortality," we pub-

lished two separate manuscripts that were designed to address these issues head on. In the first (Olshansky and Carnes, 1997), a history of biodemographic thinking dating back to a detailed discussion of Benjamin Gompertz and the century-long debate about a "law of mortality" was presented. In the second (Carnes et al., 1999), we summarized the historical reasoning developed independently from within several biological disciplines that supports the presence of intrinsic mortality. The main problem among scientists who reject the idea that intrinsic mortality exists is a tendency to equate intrinsic mortality with an unmodifiable risk of death (i.e., if it is intrinsic, they reason, then it is biologically determined and therefore unmodifiable). We suggest that intrinsic mortality is inherently modifiable because there can be no genetically determined death programs fashioned by natural selection. However, the fact that intrinsic mortality can be modified does not mean that it does not exist.

Elements of the biodemographic paradigm in one form or another has made its way into all of the publications resulting from our interdisciplinary collaborations (Bennett and Olshansky 1996; Carnes and Olshansky, 1997; Carnes et al., 1996, 1998; Olshansky and Carnes, 1997; Olshansky et al., 1998, 2001). It is not necessary to go into further detail at this point on exactly how the biodemography of aging has appeared in all of our subsequent research and writing. The relevant papers are referenced in this article and the reader is invited to explore these publications in depth.

Modern Biodemography

The rebirth of biodemography in the early 1990s was an important development. The work of Gavrilov and Gavrilova (1991) was initially focused on a general examination of age patterns of death across species, but has since narrowed in on the link exclusively in humans between parental age at conception and adult onset of age-related diseases in offspring. The work of Weiss and colleagues was focused more narrowly on the genetics behind age patterns of death in humans, although Weiss (1990) should be credited with merging elements of demography and anthropology and bringing back the notion of biology contained within the life table as originally theorized by Gompertz.

Our collaboration that resulted in the development of the biodemographic paradigm of aging ignited a spirited debate among scientists in the social and biological sciences. Although the debate about human longevity continues to this date, perhaps what is more important is that the biodemography of aging surfaced at a time when other successful collaborations between biologists and social scientists also had been established. As it turns out, during the decade of the 1990s, a number of different research teams were conducting research in what is now known as biodemography, although the term itself was not initially associated with their work. In the paragraphs that follow, we describe how our own research program on biodemography has developed from the initial ideas developed in

1992, to a much more broadly defined program that is being embarked on today. In addition, we discuss how biodemography has since branched out well beyond the study of aging and mortality to include other critically important elements of the life cycle of humans.

Several important developments have been made on the biodemography of aging since the publication of our initial findings. When we demonstrated in 1996 that the age patterns of death overlapped for different species, we noticed that at very old ages humans fared better than the laboratory animals. At first this was puzzling, given our prediction that the mortality schedules would overlap perfectly, but it later became clear why this occurs. The laboratory animals were permitted to die from life-threatening conditions. In other words, no heroic medical measures were used to extend their lives. By contrast, humans go through considerable effort to extend life through biomedical interventions. We concluded that humans are capable of "manufacturing" survival time for enough people to increase life expectancy marginally beyond its biologically related limits. Details of this hypothesis are presented in Olshansky et al. (1998).

A second development in our biodemographic work involves an extension of our previous research to evaluate other attributes of the mortality schedule of humans. For example, Medawar (1952) theorized about the age when inherited diseases should be expressed and how they should accumulate within the post-reproductive period of the lifespan. Although his theories have not been tested in vertebrates, information coming from the human genome project offers intriguing opportunities to study the demography of inherited diseases. We believe that this work has important implications for public policy because it will enable us to define our previously identified intrinsic mortality schedule with far greater pathologic specificity. Efforts to get this work funded have not met with success for reasons that will be discussed in the next section. Despite these setbacks, we are persisting in our struggle to merge scientific disciplines in order to address both scientific and public policy issues.

A third development in our biodemographic work involves an effort to bring molecular biology directly into our research paradigm. We have proposed to work with a molecular biologist to establish a transgenic mouse model for the purpose of exploring the role of antioxidants in the aging process, and to use this animal model to test predictions from biodemography regarding the onset and age progression of intrinsic mortality. In this unique example of interdisciplinary collaboration, we will establish the research protocol, and a colleague (molecular biologist, Alan Diamond) would produce a genetically engineered strain of mouse that produces elevated levels of a specific antioxidant (the cytosolic form of selenium-dependent glutathione peroxidase, or Gpx). In effect, this project would test for changes in the "rate of aging" at the molecular level in relation to attributes of the species' reproductive schedule—a phenomenon that we have explored indirectly through our use of mortality statistics for populations.

These are just three of many examples of how our work on the biodemography of aging has already led to several other research projects that involve

scientists from other disciplines. In addition to these projects, we have worked with a postdoctoral student from France on the concept of manufactured time; we are working with an epidemiologist from Australia (and his graduate student) to refine our definition of intrinsic mortality using data from their country; and we are working with a geneticist and anthropologist to explore a possible association between longevity of offspring and parental age at conception.

One particularly important development in biodemography is that it is no longer restricted to the study of aging. In an excellent book entitled *Between Zeus and the Salmon* (Wachter and Finch, 1997), a number of authors discuss interdisciplinary collaborations involving the application of biodemography to other attributes of the life cycle. For example, geneticists Thomas Johnson and David Shook combine evolutionary theory and demography as they explore how genes are associated with longevous phenotypes. Entomologists James Carey and Catherine Greunfelder use data from nonhuman species to develop a theoretical and empirical foundation for their argument that the elderly of many species contribute more to reproductive fitness than is currently believed. Evolutionary biologist Steven Austad explores how menopause and postreproductive survival in species other than humans can influence the behavior of offspring. Economist Ronald Lee explores the economic flow of resources and knowledge between generations as a basis for explaining the utility of a postreproductive population; this is a particularly novel approach that links longevity to intergenerational transfers.

As it turns out, many other forms of biodemography have appeared throughout the literature during the past 170 years, although the term "biodemography" was never directly associated with these projects. These include studies based on biochemistry (Brody, 1924; Brownlee, 1919; Greenwood, 1928; Loeb and Northrop, 1916), interspecies comparisons of age patterns of mortality (e.g., see Deevey, 1947; Pearl, 1922; Pearl and Minor, 1935), physiologically based models that were at times based on the experimental use of senescence accelerators (e.g., see Brues and Sacher, 1952; Failla, 1958; Lorenz, 1950; Mildvan and Strehler, 1960; Sacher, 1956; Sacher and Trucco, 1962; Szilard, 1959), medical and demographic models that use multiple risk factor simulations for human populations (e.g., see Manton, Stallard, and Tolley, 1991), studies of age patterns of mortality of nonhuman species (e.g., see Brooks, Lithgow, and Johnson, 1994; Carey, Liedo, Orozco, and Vaupel, 1992; Fukui, Xiu, and Curtsinger, 1993), and life history models from the fields of ecology and evolutionary biology (e.g., see Orzack and Tuljapurkar, 1989; Tuljapurkar, 1990).

Obstacles to the Biodemography of Aging

Pursuing research on an interdisciplinary subject like biodemography requires collaboration between scientists. These collaborations can be extremely beneficial

because the interactions between researchers from different disciplines often generate novel insights that would not have been revealed had the scientists been conducting the same research on their own—a synergy that can most easily be observed in the enhanced quality of publications. Although the participating scientists benefit from these collaborations, the greatest beneficiaries are the graduate students who are being exposed to the broader perspective offered by interdisciplinary research.

Initially, technical communication was the biggest problem that we had to overcome. Although both of us worked with life tables, numerous misunderstandings arose over the different terminology and mathematical formulas that we use to describe the same life table concepts. Although the problem was initially frustrating, the universal language of mathematics made this a relatively easy problem to solve. The technical jargon of biology also created communication problems at first. Fortunately, the SERCA award from NIA gave Olshansky the time and freedom to pursue training in the biological sciences, greatly accelerating his learning curve. Within a relatively short time, he was able to read classic papers on aging from journals in the biological sciences and then discuss them with Carnes. At the same time, Olshansky provided Carnes with key papers on aging from the demographic/social sciences. This creative and interactive research environment would have been nearly impossible to achieve without the intellectual freedom that was made possible by the SERCA award from NIA.

A potential problem that we never faced in our collaborations was how to initiate research projects and carry them through to the publication of manuscripts. Olshansky is skilled at visualizing the broad implications of a research problem, and Carnes excels at seeing interconnections between the technical details of a research problem. Olshansky often generates the first draft of manuscripts and proposals. However, once Carnes weaves in his independent views, the expanded second draft usually bears little resemblance to the initial draft. After numerous iterations, a final document emerges that completely blends our individual contributions. Invariably, our collaborative papers are broader in scope and more clearly written than any document that either of us could have produced on our own. Although we have become progressively more interdisciplinary in our thinking and writing, we still depend on each other to ensure the substantive accuracy of information content from our respective disciplines of biology and demography.

Our collaborative team has been able to develop a cooperative and equal partnership within a working environment of mutual trust. Without this trust, we would not have been able to maintain a collaboration that has persisted for over a decade. Maintaining collaborations even over a short term requires overcoming serious obstacles, especially when the collaborations involve scientists. The generation of grant money and publications are key measures of productivity that are often used to make salary, tenure, or promotion decisions for scientists. This means that problems can easily arise over such issues as "ownership" of

ideas, distribution of effort, professional recognition (within an organization, as well as among peers), distribution of senior authorship on papers, identifying a principal investigator on proposals, and the distribution of grant money.

Interpersonal issues are a challenge, but the greatest impediments to creating and sustaining a successful collaboration are publishing papers and obtaining funds, especially when the collaboration is interdisciplinary. Both impediments have a common cause. Review panels at journals and funding agencies usually do not have an interdisciplinary composition. As a consequence, papers and proposals of an interdisciplinary nature easily can be misunderstood, criticized, and put at a severe competitive disadvantage relative to their more traditional counterparts.

By definition, interdisciplinary research and the manuscripts generated from this research will involve subject matter from different disciplines—disciplines that may not share theories, methodology, technical jargon, or literature. Although expanded intellectual scope is a real strength of interdisciplinary research, it also causes problems when trying to publish interdisciplinary research papers. Most professional societies, the journals they spawn, and the people chosen to review manuscripts come from either a single discipline or a fairly narrow range of related disciplines. This means that an interdisciplinary manuscript is likely to contain some subject matter that goes beyond the technical expertise of any reviewer. We have routinely experienced reviews at journals in the social sciences where one or more of the reviewers did not appear to know or understand the biological terms, concepts, or literature needed to properly review the submitted manuscript. Our solution to this problem has been to submit large manuscripts with a careful definition of terms, extensive background information, and a large literature citation section. Despite these precautions, almost every biodemography paper that we have tried to publish in the demography literature has been an exhausting and often frustrating process—although every paper submitted has been published.

Funding is by far the biggest impediment that we face in trying to maintain our interdisciplinary collaboration, and this problem continues to this day. Just as with journals, study sections or their equivalents at funding agencies are invariably composed of reviewers who come almost entirely from a single discipline. Once again, a lack of familiarity with technical language, concepts, and literature has been a serious problem. Our colleagues in the biological sciences who have considerable experience serving on study sections will often give the biological components of our biodemography proposals a strong positive endorsement, just as our colleagues in the demographic and actuarial sciences will endorse the demography components. However, when submitted to a social sciences study section, the proposals have come under severe criticism. We have tried to counter this problem by pursuing an active agenda of publishing peer-reviewed papers that address the specific issues raised by the reviewers. This has obviously been time consuming, and, as yet, this strategy has been only partially successful—each of us has received Independent Scientist Awards (K02) from the NIA, but

neither of us has yet had a biodemography R01 funded. The only real solution to developing and maintaining a biodemography program will be for funding agencies like the National Institutes of Health and the National Science Foundation to create interdisciplinary study sections to review and fund interdisciplinary grant proposals.

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