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Biodemographic Perspective

A BIOLOGICALLY MOTIVATED PARTITIONING OF MORTALITY

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Abstract—For over a century, actuaries and biologists working independently of each other have presented arguments for why total mortality needs to be partitioned into biologically meaningful subcomponents. These mortality partitions tended to overlook genetic diseases that are inherited because the partitions were motivated by a paradigm focused on aging. In this article, we combine and extend the concepts from these disciplines to develop a conceptual partitioning of total mortality into extrinsic and intrinsic causes of death. An extrinsic death is either caused or initiated by something that originates outside the body of an individual, while an intrinsic death is either caused or initiated by processes that originate within the body. It is argued that extrinsic mortality has been a driving force in determining why we die when we do from intrinsic causes of death. This biologically motivated partitioning of mortality provides a useful perspective for researchers interested in comparative mortality analyses, the consequences of population aging, limits to human life expectancy, the progress made by the biomedical sciences against lethal diseases, and demographic models that predict the life expectancy of future populations. © *1997 Elsevier Science Inc.*

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INTRODUCTION

SINCE ITS creation, the Gompertz model (Gompertz, 1825) has remained an influential paradigm for the mathematical analysis of mortality data (Olshansky and Carnes, 1997a). Researchers have either tried to improve the Gompertz model (Makeham, 1867) or were motivated by it to propose alternative quantitative theories of mortality (e.g., Sacher, 1956; Failia, 1958; Szilard, 1959; Strehler and Mildvan, 1960; Sacher and Trucco, 1962; Brown, 1974; Juckett and Rosenberg, 1990). The development of non-Gompertzian models (e.g., Rosenberg *et al.*, 1973; Economos, 1982; Tyurin *et al.*, 1995) has been stimulated by the apparent failure of the Gompertz paradigm to explain patterns of age-specific mortality observed at older ages (e.g.,

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Strehler and Mildvan, 1960; Economos, 1982; Pakin and Hrisanov, 1984; Cary *et al.*, 1992; Fukui *et al.*, 1993; Perls, 1995). Discussions on the merits of these models have often involved the physiological implications of their mathematical assumptions (e.g., Mildvan and Strehler, 1960) and/or their ability to accurately describe age patterns of total mortality (all causes of death). Gompertz (1825) also introduced an idea, later extended and formalized by Makeham (1867), that there are fundamental differences among the causes of death that compete for the lives of individuals. One goal of this article is, therefore, to review some of the important historical attempts to partition total mortality into biologically meaningful categories. Intriguing common themes, but no consensus, emerge from the logic used by researchers from the actuarial and biological sciences to create their mortality partitions. The existence of biologically meaningful partitions of total mortality could have important implications. For example, conclusions concerning the relative merits of mathematical models of mortality may not be relevant if they were derived from analyses of total mortality. As another example, the relevance of demographic models of total mortality used to forecast longevity and predict the consequences of population aging to establish governmental policies for entitlement programs may need to be examined. As such, the primary purpose of this article is to propose a biologically motivated partitioning of mortality that takes advantage of current knowledge to unify and extend the interdisciplinary efforts of the past.

Historical efforts to partition mortality

The earliest organization of mortality information in tabular form can be traced to the actuarial tables of the Romans in the third century A.D. (Hutchinson, 1978). Edmund Halley (1694), the astronomer, is credited with constructing the first life table in modern form organized by age (Hutchinson, 1978). The attempts to quantify the population effects of plagues and war and the calculation of insurance annuities chronicle a historical recognition of the importance of mortality. From the construction of these mortality tables it is also evident that there was a public and an academic interest in the incidence and age pattern of specific causes of death.

The eminent ecologist G. Evelyn Hutchinson (Hutchinson, 1978, p. 5) suggested that "scientific demography" may have begun in 1662, when the British haberdasher John Graunt used information from the published Bills of Mortality for London to make demographic predictions. Scientific demography flourished during the 18th century under such notables as Dr. Benjamin Franklin (1706–1790) and Rev. Thomas Malthus (1766–1834)—both of whom focused on the dynamics of population growth. Although the notion of geometric increase was applied to population growth as early as 1677 (Hutchinson, 1978), it was not until 1825 that the British actuary Benjamin Gompertz applied this concept to mortality. In a now classic article, Gompertz (1825, p. 514) noted that a "law of geometrical progression pervades, in an approximate degree, large portions of different tables of mortality."

Gompertz made two observations in his 1825 work that would have a profound influence on future investigations of mortality. First, he concluded that "I derive the same equation from various published tables of mortality during a long period of man's life, which experience therefore proves that the hypothesis approximates to the law of mortality during the same portion of life . . ." (p. 519). Second, he proposed a physical explanation for his law by suggesting that "death may be the consequence of two generally coexisting causes; the one, chance, without previous disposition to death or deterioration; the other, an unspecified force that destroyed the material of organization necessary for life" (p. 517). In other words, Gompertz

not only detected a regularity in the age pattern of mortality across different populations but he also provided a biological explanation for why that regularity might exist.

The next 150 years saw refinements to Gompertz's law (Makeham 1867; Brownlee, 1919; Greenwood, 1928), questions over whether a law of mortality exists (Pearl and Minor, 1935), generalizations of the law to species other than humans (Pearl, 1922; Brody, 1924; Deevey, 1947), and continued research on the biological basis of such a law (Weismann, 1891; Loeb and Northrop, 1916; Medawar, 1952; Williams, 1957; Hamilton, 1966). Makeham's (1867, p. 332) theory of "partial forces of mortality" is representative of a general theme that pervades the post-Gompertz literature. Makeham (1867, p. 335) noted that "some diseases depending for their intensity solely upon the gradual diminution of the vital power" fit the Gompertz law far more closely than a mortality schedule based on all causes of death combined (i.e., total mortality).

Gompertz made a distinction between two kinds of mortality but he proffered only the vague notion of "an unspecified force that destroyed the material of organization necessary for life." Makeham took the Gompertz concept an important conceptual step forward. Makeham (1867) linked the "diminution of the vital power" to biologically determined causes of death, but did not believe that the current state of medical knowledge was sufficient to identify them. He broke new ground by analyzing a collection of diseases less inclusive than total mortality but more than single causes of death considered separately. In terms of modern survival analysis, Makeham recognized the importance of what is now commonly known as competing risks (Chiang, 1991) and developed a biologically motivated approach to censoring (Carnes *et al.*, 1996).

Makeham (1867) did not know how many "partial forces" of mortality existed but he noted (p. 335) that those following the Gompertz law most closely embraced "all the principal vital organs of the body." The first serious attempt to identify the factors responsible for the age distribution of what became known as "natural death" was made by Raymond Pearl (Pearl and Miner, 1935). After initially identifying five factors "concerned in death and its time distribution," Pearl and Miner (1935, p. 77) hypothesized that their classification could be distilled to "but two fundamental biological variables" and one environment variable that was "not necessarily or essentially biological in its nature." A decade later, in reference to Pearl's classification, Deevey (1947, p. 283) noted that "the environmental determinants of life duration cannot, at least as yet, be disentangled from such biological determinants as genetic constitution and rate of living." The work of these researchers (and many others cited by them) reflect an ongoing effort across several scientific disciplines to refine Gompertz's notion of an "unspecified force that destroyed the material of organization necessary for life" and to determine whether his law had applicability to species other than humans (Carnes *et al.*, 1996).

Historical efforts to gain insight (biological as well as demographic) into this "unspecified force" and its mortality consequences invariably involved a biologically motivated partitioning of total mortality. Clarke's (1950) bioactuarial approach to forecasting death rates continued this tradition. For example, Clarke (1950, pp. 14–15) partitioned total mortality into *anticipated deaths* ("accident, disease or any other cause, which are anticipations of the natural termination of life"), and *senescent deaths* (principally "arteriosclerosis, cardiovascular diseases, renal diseases, bronchitis and bronchopneumonia, and senile decay"). He argued that the timing of senescent deaths were genetically determined and, therefore, not susceptible to postponement. When it became difficult to assign specific diseases to the senescent category with confidence, Clarke made the assumption that the proportion of total mortality attributable to senescent causes increased from 5% at age 20, to 100% above age 80. Benjamin (1959), on the other hand, decided that no deaths before age 55, and all deaths after age 76 would be classified as

senescent. Others have made similar efforts (e.g., Juckett and Rosenberg, 1990; Gage, 1991). Beginning with Gompertz, there has been a progression in the focus of research on mortality from all deaths combined (total mortality), to so-called "natural" deaths, to aging-related or senescent deaths.

The gerontologist Bernard Strehler (1959) was interested in the process of aging and its effect on the age distribution of mortality. Strehler's notion of senescent death was a modern rendition of Pearl's concept of "natural" death. Like Pearl, his focus on mortality and aging led him to a set of criteria (i.e., universality, intrinsicality, progressiveness, and deleteriousness) intended to distinguish between processes of "normal aging" and the "consequence of deleterious agents in the environment." Strehler's basic premise (p. 124) was that "there exist gradual changes in the structure of organisms which are not due to preventable diseases or other gross accidents and which eventually lead to the increased probability of death of the individual with advancing age." As Strehler noted (p. 125), while his "criteria appear reasonable from the biologist's standpoint, their application to specific phenomena is not a simple matter."

Strehler and Mildvan (1960) used the concept of physiological decline to develop a quantitative theory of mortality and aging based on the Gompertz equation. The radiation biologist, George Sacher (1956; Sacher and Trucco, 1962), also developed a Gompertz based theory of mortality. A discussion of mathematical models of mortality is not, however, the purpose of this article (see Mildvan and Strehler, 1960, for a critique of competing models developed during this period). What is important for this article is that these investigators viewed death as arising from fluctuations in the physiologic state that escape the homeostatic control of the organism. In other words, they argued that death is an inherently physiological process.

Evolutionary importance of extrinsic mortality

The work of the actuaries, demographers, and biologists discussed so far was focused on the need to partition total mortality into discrete categories to identify better quantitative models to describe the age pattern of death. Yet at the same time this work was underway, a parallel line of theory and research had already been developed by evolution biologists who addressed the related question of why organisms grow old and die. Scientists in these two disciplines were largely unaware of each others work. As it turns out, a rationale for partitioning total mortality into discrete biological and nonbiological categories was developed by scientists from both disciplines. The rationale of the evolution biologists will be described here because it provides additional insight into why distinguishing between causes of death might be useful.

August Weismann (1891) was one of the first biologists to ponder the question of why organisms grow old and die. He felt that it benefitted a species to eliminate the old, who were competing with the young for limited resources. Weismann (1891, p. 33) was also one of the first to recognize that "an undying succession of reproductive cells" meant that the individual carrying these cells was disposable once the perpetuation of the species had been ensured. An inevitable degradation of the individual through the unavoidable accumulation of injuries by forces external to the organism led Weismann (1891) to argue for the necessity of reproduction and the utility of death.

A modern Darwinian perspective on aging was first provided by Medawar (1952). Whereas Weismann focused on external sources of mortality, Medawar focused his attention on natural causes of death. He reasoned (p. 4) that because natural deaths were "in some degree influenced by heredity," the genes responsible for these deaths "should be subject to those forces, of natural selection, that discriminate between the better and the genetically less well endowed." Under his

paradigm, senescence and age-related mortality arise from an accumulation of deleterious genes whose time of expression has been pushed by natural selection into the postreproductive period of life. Senescence becomes observable when individuals are sheltered from external sources of mortality such that survival is extended into the postreproductive period, where the delayed effects of deleterious genes have an opportunity to be expressed.

Kirkwood and colleagues (see Kirkwood, 1977; Kirkwood and Holiday, 1979; Kirkwood and Rose, 1991; Kirkwood, 1992; Kirkwood and Franceschi, 1992) also argue that external mortality has played a crucial role in the evolution of senescence. Their reasoning is that external mortality forces organisms to divert physiological resources into reproduction that could have been otherwise spent maintaining the body (soma) of the organism. Thus, species that experience high levels of external mortality should invest in early reproduction rather than somatic maintenance. In this economic view of life, senescence and the disposal of the soma (death) are viewed as inadvertent byproducts of physiological investments in reproduction, necessitated by high levels of external mortality that make investments in somatic maintenance a poor use of finite resources.

Partitioning mortality

The researchers that dealt with life tables (Makeham, 1867; Clarke, 1950; Benjamin, 1959; Bourgois-Pichat, 1978) were vague about the biological forces responsible for age-related mortality but were, by necessity, explicit in their partitions of total mortality. By contrast, the evolution biologists trying to explain the existence of senescence developed more sophisticated biological arguments but had no need to operationally define external mortality. For our purposes, two important points emerge from these largely independent bodies of literature. First, the gerontologists recognized, whether explicitly or implicitly, that reliable quantitative models for the age distribution of death could not be achieved with the use of total mortality. Second, evolution biologists used the notion of external forces of mortality to explain the existence of senescence. In each case, the researchers partitioned total mortality into two conceptually distinct categories—generically summarized as aging and environmental mortality. In this article we are proposing an alternative partitioning of mortality based on the merging of concepts from both biology and demography.

Causes of death that have been most often characterized as external forces of mortality in humans and other animals include accidents, homicides, infectious and parasitic diseases, natural disasters, predation, suicide, and poisoning. The first thing to notice is that this is a large category of death, accounting for approximately 15% of all deaths in the United States in 1990 (National Center for Health Statistics, 1994). Second, this category contains both biological and nonbiological agents of death. Finally, deaths arising from these external causes occur at an earlier age than would have been predicted from the physiological state of the organism had the external force of mortality not existed. From these observations, we have constructed a category of death called *extrinsic* mortality. Extrinsic mortality is defined as a death that is either caused or initiated by something that originates outside the body of an individual.

Intrinsic mortality is the opposite of *extrinsic* mortality—namely, a death that is either caused or initiated by processes that originate within the body. It is important to emphasize that intrinsic mortality is not synonymous with the kinds of mortality implied by the terms aging or senescence. A modern definition of senescence will help to see why this is so. Recall first that the term senescence was used by gerontologists to avoid the confusions of meaning that had come to be associated with the term aging (Martin, 1996a). A definition with a demographic

orientation has been provided by Finch (1990, p. 5), where senescence refers to "age-related changes in an organism that adversely affect its vitality and functions, but most importantly, increase the mortality rate as a function of time." Rose (1991, p. 19) provides an evolution-oriented definition of senescence (with an emphasis on evolutionary fitness)—defined as "a persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration."

As intended, these definitions of senescence capture successfully the notion of diseases and disorders that are commonly associated with growing older (e.g., lethal diseases such as vascular diseases, malignant neoplasms, kidney and liver failure, and dementia, and nonlethal disorders such as sensory impairments and arthritis). However, an infant dying of a congenital malformation, a teenager dying from early onset diabetes or early childhood leukemia, or a 40-year-old dying of ALS (amyotrophic lateral sclerosis) are deaths that do not fit well in a senescence-based classification of mortality. Deaths arising from these familial (inherited) diseases lack the age-related physiological deterioration implicit in either of the definitions of senescence provided earlier.

Intrinsic mortality incorporates both senescent and inherited diseases (e.g., Huntington's chorea, ALS, multiple sclerosis, ataxia, and early onset diabetes), thereby avoiding the problems of a classification based only on age-related (senescent) mortality. The modern concept of senescent mortality that captures the "unspecified force" referred to by earlier investigators is simply a subset of intrinsic mortality. Many of these genetic diseases are already known and more will be revealed as molecular biologists and geneticists working on the Human Genome Project continue to identify a rapidly expanding list of inherited diseases expressed at ages throughout the life span. The specific components of intrinsic mortality will also become better known as biomedical researchers improve their understanding of the genetic mechanisms that are either responsible for or closely linked to such causes of death as cancer and heart disease.

Cancer and heart disease require closer scrutiny because they are generic labels for a host of disease syndromes. Each syndrome has an etiology that can be influenced by genetic and environmental factors (Claus, 1995; Perera, 1996). Deaths caused by some of these syndromes, like the virus-associated cancers (Mueller, 1995; WHO, 1996) and smoking-related illnesses (e.g., lung cancer, emphysema), would be classified as extrinsic mortality. Deaths arising from the familial forms of these diseases (McKusick, 1992) would fall into the intrinsic component of mortality. Some syndromes of these diseases fall into a gray area where the manifestation of disease in genetically predisposed individuals must be triggered by additional events (e.g., lifestyle choices, childhood disease, exposure to mutagens or carcinogens) that occur after fertilization (e.g., Malkin, 1995; Roberts, 1995). Still other forms of these diseases are thought to arise from genetic damage that is acquired (rather than inherited) through the course of living (Harman, 1992; Holmes *et al.*, 1992). Ironically, this later component of intrinsic mortality may be the consequence of a cooperative arrangement forged between organisms in the early history of life on earth that permitted the evolution of multicellular life (Harman, 1993).

Mitochondria are microscopic organelles inside cells that are responsible for the final transformation of food into the form of energy used by cells. It has been suggested that without the energy provided by mitochondria, multicellular life would not be possible. The notion of a symbiotic relationship arises from the observation that mitochondria have their own DNA, independent of the nuclear DNA. In the process of creating stored energy that can be used for work by the cell, mitochondria produce molecules called free radicals. Metabolic free radicals are considered a significant (but not the only) source of damage to DNA that occurs thousands of times every day in every cell (Ames and Gold, 1991; Ames and Shigenaga, 1992). Fortu-

nately, the vast majority of this damage is repaired with great efficiency. However, the complex surveillance mechanisms that exist within cells to maintain the functional integrity of DNA are not perfect (Vijg, 1990; Boulikas, 1991; Lindahl, 1993). The result of this biological imperfection is that unrepaired damage to DNA begins to accumulate over time, beginning with the first cell formed by the union of egg and sperm (Holmes *et al.*, 1992).

Acquired genetic damage from free radicals has been implicated in the aging process (Gensler *et al.*, 1987; Ames and Shigenaga, 1992; Holmes *et al.*, 1992) and the free radical hypothesis of aging (Harman 1956, 1992, 1993) continues to hold a prominent position in the scientific community. This subcomponent of intrinsic mortality is also consistent with the disposable soma theory in evolution (Kirkwood and Rose, 1991), which views the imperfect maintenance of the soma (body) as an inevitable consequence of the physiological investment in reproduction that an organism must make in an environment characterized by high mortality pressures from extrinsic causes of death.

Acquired genetic damage also incorporates Cutler and Semsei's (1989) disdifferentiative hypothesis of aging, which posits the loss of gene regulation as a mechanism that links cancer and aging. Under this paradigm, cancer occurs when genes regulating cell growth and differentiation become damaged. The gene disregulation concept of Cutler and Semsei (1989), when coupled to the biological effects of free radicals, provides a mechanism (Anderson, 1996; Martin, 1996b,c) for a phenomenon called antagonistic pleiotropy (Williams, 1957). Williams (1957, p. 410) suggested that deleterious effects (i.e., senescent diseases) associated with genes expressed after the "period of maximum reproductive probability" can arise from the action of natural selection if these same genes are involved in processes that confer reproductive advantages early in life.

The distinction between inherited, genetically predisposed, and acquired genetic damage is less clear for cancers like Li-Fraumeni syndrome, retinoblastoma, and Wilm's tumor, where an individual inherits a subset of the multiple genetic changes required for the disease to be manifested (Weinberg, 1991). Reasonable arguments could be made for classifying these kinds of diseases into either intrinsic or extrinsic categories, regardless of where the source of additional damage originates. Deaths caused by the growing list of inherited diseases, on the other hand, must be considered unambiguous examples of intrinsic mortality. Any lethal disease linked to the damage caused by metabolic free radicals (e.g., Rosen, 1993; Schapira, 1995) would also be classified as intrinsic because the etiology of the disease arose from processes that originate within the body. Genetic damage and its imperfect repair acquired during the course of living may be the modern version of what the earliest investigators called "an unspecified force that destroyed the material of organization necessary for life" and later researchers envisioned as aging or senescence.

Our motivation for partitioning total mortality into extrinsic and intrinsic categories of death was an interest in capturing the biology believed to be hidden within a species' life table. The formal definitions provided here were based on an attempt to capture the intent of both the applied and theoretical partitionings of total mortality in the demographic and biological literature. As such, our partitioning will not be a perfect match with any of the classification efforts of the past. More to the point, we felt that the classifications of mortality from the demography/gerontological literature were focused primarily on the senescent diseases while neglecting the lethal diseases linked in the biological literature to heredity.

Although our partitioning of total mortality was biologically motivated, it should not be construed (as in the Strehler, 1959, classification) that intrinsic mortality is biological and extrinsic mortality is not. Recall that extrinsic mortality contains many biological causes of

death (e.g., infectious and parasitic diseases, predation). Nor should extrinsic mortality be viewed as unimportant just because our research focus (Carnes *et al.*, 1996) has been on the intrinsic component of mortality. This is, however, an easy conceptual trap to fall into, because individuals dying of extrinsic causes of death would be censored in modern methods of survival analysis (e.g., Kalbfleisch and Prentice, 1980). Censored observations, by virtue of not being the death events of interest, have the connotation of being a nuisance that is adjusted for by the quantitative procedures. As will be seen, extrinsic causes of death have played a central role in determining the age distribution of intrinsic deaths.

Biodemography: linking extrinsic and intrinsic mortality

As mentioned earlier, we have attempted to bring together biological and demographic arguments for partitioning mortality into intrinsic and extrinsic components. As yet, an explanation has not been provided for why a distinction between these two types of mortality is important in understanding why and when death occurs today. The argument has been made (Carnes *et al.*, 1996) that extrinsic mortality has been a driving force in determining why individuals die when they do from intrinsic causes of death. Notice that this statement has been made more specific through the inclusion of the terms extrinsic and intrinsic, and a causal relationship between extrinsic and intrinsic mortality has been implied.

How can extrinsic mortality influence intrinsic mortality when more and more people are dying from intrinsic causes of death at increasingly older ages? To begin with, what people die from today is misleading because humans are living in extremely unusual times for our species. Consider that 2000 years ago, life expectancy at birth in Rome was estimated to be about 25 years (MacDonell, 1913) and was probably less than that throughout most of human history. By the turn of this century, life expectancy at birth had doubled to 50 years of age. As the new millennium is approached, life expectancy in places like the United States and Japan has climbed up to and even beyond 80 years of age. The point is that from a historical perspective, the vast majority of our ancestors did not survive to ages that would be considered "old age" today.

These dramatic gains in life expectancy during the 20th century reflect significant changes in the mortality schedules of successive human cohorts over an extremely brief time frame. However, from an anthropological or biological perspective, humans as a species have changed very little over far greater time periods than a mere century. By implication, the rapid fluctuations (declines as well as increases) in mortality that have occurred throughout most of human history must have been due to changes in extrinsic mortality rather than intrinsic mortality. The historical record suggests that our ancestors had a much different mortality profile than is observed today. That is, while some of our ancestors died from the same diseases that kill most people today (e.g., heart disease, cancer, and stroke), the vast majority died from infectious and parasitic diseases. In the context of the mortality classification scheme presented here, there has been a transition in the major causes of death from extrinsic mortality to intrinsic mortality. Further, this mortality transition has shifted the age distribution of death from the young to the old. Major components of this rapid transition in mortality most certainly include such things as improvements in hygiene, living conditions, and public health, and the discovery and use of antibiotics.

To appreciate the implications of this mortality transition, it is useful to broaden the discussion to include mortality in species other than humans. Ecologists (e.g., Promislow, 1991) have argued that senescence is rarely seen in the wild. For example, in studies of the population

dynamics of prairie mice, it is extremely rare to catch the same mouse for more than about six months. Yet if these same species of mice are brought into the protected confines of a laboratory, they are capable of surviving three or four years. The reason for this huge discrepancy in survival is that just about everything eats mice—snakes, owls, hawks, stray cats, and coyotes. Old mice are not found in nature because they do not survive long enough to grow old. The fate of prairie mice is not an exception. Most animals, whether they be predator or prey, tend to die at young ages from extrinsic causes of death.

Thus, for most of recorded history, the mortality experience of humans has been no different than any other species. The conclusion to be drawn from these observations is that the environment is and has always been a hostile place, leading to high mortality rates from extrinsic causes of death at young ages for all species. From a biological perspective, the most important implication of a hostile environment is that if an organism delays reproduction it runs a very high risk of not reproducing at all. The longer reproduction is delayed, the more likely it is that the organism will die from an extrinsic cause of death—predation, accident, or infectious or parasitic disease.

If all organisms are challenged in a similar way by a hostile environment, early reproduction should be a common biological trait among a broad variety of different kinds of animals. By early reproduction, we mean early relative to potential lifespan (even though, as the earlier mouse example illustrates, very few animals in nature come anywhere close to achieving their potential lifespan). To be more specific, most species of mice are capable of reproducing within 30 to 40 days after birth even though they can live three to four years in the protected confines of a laboratory environment. With a few caveats, a general survey of the animal kingdom shows that early reproduction is nearly a universal pattern in nature (Finch, 1990).

A number of sea birds that make their nests in rocky cliffs by the ocean are an apparent exception. When compared with other birds of comparable size, these species begin reproducing at later ages. The explanation normally provided for this phenomenon is that the nesting habits of these birds provide excellent protection from predators (Ricklefs, 1973). In other words, their nesting habits protect them from an important source of extrinsic mortality and afford them the opportunity to delay reproduction. However, even among these species, their period of reproduction occurs early relative to their potential life span.

A corollary to early reproduction is the relative maturity of the young at birth. For example, species that are predators tend to have young that are born helpless and mature slowly. Species like chimpanzees and humans that provide lots of parental care for their young also appear to be in no great rush to achieve sexual maturity. Prey on the other hand, have young that are very precocious and mature rapidly. For example, the young of herbivorous animals like impala, giraffes, horses, and warthogs are up and mobile within hours of birth. It is clear, therefore, that ecological factors such as how a species makes a living, the intensity of predation pressure, and the social organization of the species all influence this notion of early reproduction.

Early reproduction implies that after fertilization there is a developmental race to reach the age of sexual maturity. Most species sprint to this age, some appear to jog, but almost no species crawl to sexual maturity. The fact that human females giving birth at 11, 12, and 13 years of age tend to have premature babies and medical problems is an indication that humans, like other species, are reproducing about as early as is biologically feasible.

Evolution biologists have suggested that organisms have a biology (e.g., physiological processes of growth and development) that has been moulded by the forces of extrinsic mortality to attain the age of sexual maturity as soon as possible (e.g., Hamilton, 1966; Kirkwood, 1977; Austad, 1993). Once sexual maturity is attained, there is a window of time within which

reproduction must occur if it is going to occur at all. This window of reproductive opportunity is a probability window where the chance of surviving to the next day becomes progressively smaller (Williams, 1957). It has been hypothesized that this tension between the biological imperative to reproduce and the probability of dying from an extrinsic cause of death has had a profound impact on the very biological nature that defines an organism, including the age pattern of intrinsic mortality following sexual maturity (Carnes and Olshansky, 1993; Carnes *et al.*, 1996).

The incredibly complex choreography of cell divisions and differentiation called growth and development needed to attain sexual maturity is too critical to leave to chance alone. For that reason, the developmental process from fertilization to sexual maturation is under considerable genetic control. Developmental events are supposed to occur at specific times and locations within the body, and the biological clocks that govern these processes are ticking to a rhythm scripted by genes (Nathanielsz, 1996). The genetic uniqueness of individuals ensures that the timing of these developmental events will vary somewhat from individual to individual. It is, however, not the variability but the regularity of when these events occur that is remarkable. For example, after determining when conception occurred, doctors are able to estimate a date of birth quite reliably. Once born, a child passes through a predictable series of developmental events (e.g., rolling over, crawling, standing, walking) at predictable ages. The complex series of developmental milestones that all organisms pass through on their way to sexual maturity appear to be events whose timing responds to genetic instructions that have been dictated by a need to reproduce in an environment made hostile by a broad range of extrinsic causes of death.

For most animals, the postreproductive period of life is brief (Austad, 1994). This implies that the biology of these animals has remained in balance with an environment not too dissimilar from that of their ancestors. Humans, on the other hand, are now in the nearly unique position of having a prolonged period of postreproductive life (see Austad, 1994, for a discussion of postreproductive survival of humans in paleolithic cultures). This implies that humans alive today have inherited a biological legacy from our ancestors that is out of synchrony with the world in which we live. As Medawar (1952, p. 13) noted, this biological legacy is being revealed in the form of senescent and some inherited diseases "only by the most unnatural experiment of prolonging an animal's life by sheltering it from the hazards of its ordinary existence."

The pitfalls of partitioning

The concept of extrinsic and intrinsic mortality described in this article was biologically motivated, is consistent with concepts from an evolving multidisciplinary effort to understand senescence and its effect on the age distribution of death, and avoids some of the problems of an age-based method of classifying mortality. In the real world, however, it is not possible to avoid Strehler's (1959, p. 125) dilemma—"criteria appear reasonable from the biologist's standpoint, [but] their application to specific phenomena is not a simple matter." There are reasons why any partitioning of mortality, no matter how well justified, must remain imprecise and inaccurate in practice.

Classifying mortality into extrinsic and intrinsic components would benefit from pathology information—information most reliably obtained from autopsies. The reality is that very few autopsies are performed. In practice, this means that cause of death is rarely determined by a trained pathologist. The lack of pathology information contributed to Pearl and Miner's (1935) inability to disentangle the environmental from the biological determinants of death. However, as studies involving laboratory animals illustrate, difficulties in the classification of mortality

persist even when pathology information is available for every animal (Holland, 1978). One reason for this difficulty is that pathologists do not always agree on a diagnosis of what killed an animal. Unless uniformity is imposed by a pathology protocol, philosophical differences between pathologists can have dramatic effects on the analysis of pathology data (Kodell *et al.*, 1982). A further complication is that advances in veterinary pathology over time lead to changes in the specificity of coding used to classify cause of death. The problems observed in controlled animal studies are amplified in the case of humans (e.g., Yamamoto *et al.*, 1978) because (1) attending physicians with varying backgrounds determine cause of death; (2) with few exceptions, it is not possible to acquire the biological material needed to review pathology diagnoses made in the past; and (3) many people dying at older ages have multiple illnesses.

Probably the single biggest source of classification error occurs because the etiology of the disease process is rarely known. Cause of death is most often determined at the time of death and the biological manifestations of disease can be similar for completely different reasons (Fry *et al.*, 1978). Consider two individuals that die of pneumonia. One person acquires pneumonia from an infectious disease, while the other acquires it from an infection made possible by a tumor in the lung. Presuming that the lung tumor was spontaneous, the former death should be classified as extrinsic, while the later death should be classified as intrinsic. In our present classification scheme, all pneumonia deaths are classified as extrinsic. Problems like these cannot be avoided because the etiology of the disease process leading to death can only rarely be determined from a death certificate.

Age-based classifications

Partitioning deaths into extrinsic and intrinsic categories could also be criticized because it ignores the physiological state of the victim. For example, consider a frail old woman with diminished equilibrium who dies after accidentally falling down a flight of stairs. Under the classification scheme presented here, accidental deaths (regardless of age) would be classified as extrinsic mortality. It could be argued, however, that the woman's physiological state, degraded by aging, was the principal reason for her fall. Equating physiological state with aging in this way suggests that her death should be classified as intrinsic. There is no doubt that the race between extrinsic and intrinsic causes of death competing for the life of an individual, especially at older ages, has been a photo finish in many cases. Perhaps the woman would have had a massive stroke (an intrinsic cause of death) the next day if the fall had not killed her first. The point, however, is that her physiological state just prior to death allowed her to be in a position to fall down the stairs. In all probability, someone closer to an imminent encounter with an intrinsic death would not have been on those stairs in the first place.

Classification errors caused by age-related patterns in extrinsic mortality are, in some cases, a trivial issue. For example, less than 5.5% of all extrinsic deaths combined occur past age 65 in the United States (National Center for Health Statistics, 1994). Of these, only a small fraction are likely to have been influenced by the physiological state of the victim (i.e., intrinsic events). In developed nations, the mortality experience of humans is becoming more like that observed for laboratory animals that have been protected from sources of extrinsic mortality. The need to distinguish intrinsic mortality from total mortality diminishes as the force of extrinsic mortality becomes progressively weaker. Conversely, whenever comparisons of mortality are being made between populations that differ in the intensity of extrinsic mortality, the distinction between intrinsic and total mortality becomes more critical.

It should be emphasized that we are not suggesting that age-related mortality is unimportant.

Teenagers are charged higher automobile insurance premiums because their risks for accidents and death are known to be high. Alaskan wolves prey on caribou that are either very young or very old. Bald eagles carry away puppies in the Northwoods. Most deaths in airline crashes occur among working-aged adults. Even the victims of natural disasters fall within predictable age ranges. However, suggesting that the assignment of causes of death into extrinsic and intrinsic categories is a false partitioning because age-related patterns of mortality exist in both categories is like declaring that one cannot distinguish between black cats and black dogs. The solution is to use criteria other than color to distinguish between them.

For mortality classifications, the problem is that the probability of dying from almost any cause of death (whether intrinsic or extrinsic) can be related to an individual's age. As such, if senescence and age-relatedness are the only criteria used to partition mortality, then the classifications can become (1) subjective because of arbitrary age cutoffs (Clarke, 1950); (2) tautological because age decisions are being used to study age-related mortality (Benjamin, 1959); and (3) incomplete because, as previously argued, such an approach ignores deaths caused by inherited diseases that are not associated with physiological decline.

Modifying intrinsic mortality

Manipulating the biology of another species is far easier than modifying our own. As a consequence, humans have been able to exert considerable influence over the forces of extrinsic mortality. Historically, the disease processes associated with intrinsic causes of death have been far less easy to manipulate. The last quarter century has, however, given rise to a remarkable array of medical interventions that have prolonged the time between the age of onset of an intrinsic disease and the age when death occurs. It is probable that survival time will continue to be manufactured (Olshansky *et al.*, in press) as the biological mechanisms responsible for intrinsic causes of death become progressively better understood.

Indeed, the notion that the "reclassification of processes from endogenous to exogenous is occurring with increasing frequency owing to rapid increases in scientific knowledge" (p. 622) has been used by some demographers (e.g., Manton *et al.*, 1991) as a justification for the hypothetical elimination of major causes of intrinsic death. Other demographic approaches (see reviews by Olshansky and Carnes, 1994, 1996, 1997), effectively eliminate intrinsic diseases by extrapolating into the future, the declining trends in total mortality that have been observed over brief time periods. All of these purely demographic approaches to the analysis of mortality contain unstated biological assumptions. From a biodemographic perspective, the biological assumptions implied by these methods are implausible, even though no mathematical or statistical assumptions have been violated.

One strong assumption implied by these demographic models is that biomedical technology will overcome a number of significant biological obstacles. For example, technology must eliminate or control the effects of countless defective genes that are only now beginning to be identified—something that natural selection over the approximately 130,000 year history of anatomically modern humans (Foley and Lahr, 1992) has been unable to accomplish. Selection has only managed to push the age of expression for some of these genes toward the postreproductive period of life.

According to these models, technology will also overcome one of the most basic biological costs of being a multicellular organism—genetic damage acquired during the conversion of food to useable energy. Further, if evolution theory is correct, technology will have to compensate for the imperfect maintenance and repair of a soma made disposable by sexual

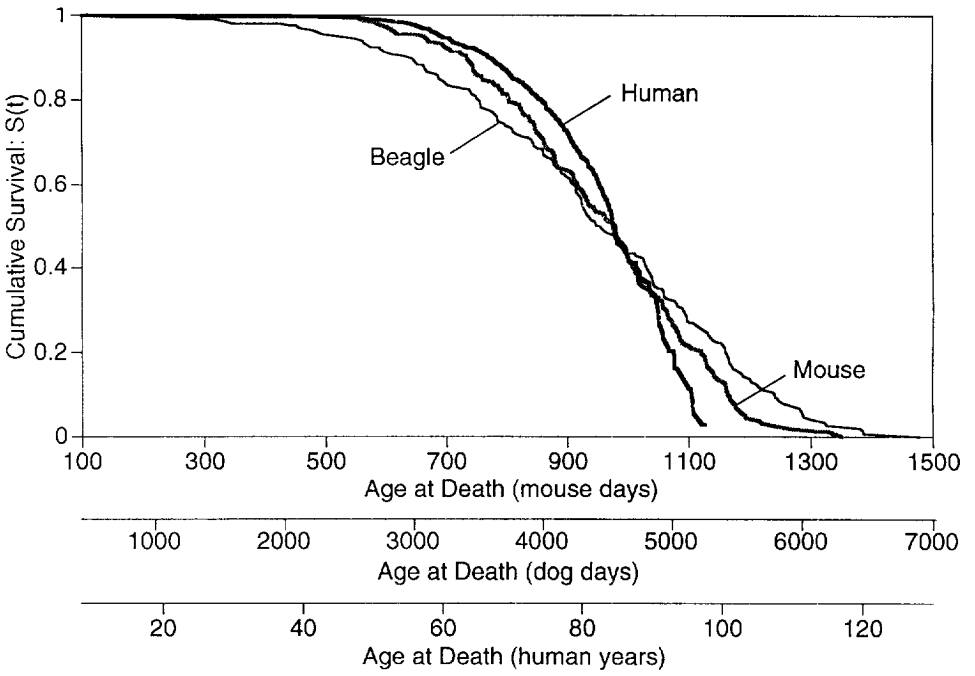

FIG. 1. Cumulative survival curves of intrinsic mortality for the B6CF1 mouse, beagle, and human. (Reprinted with the permission of the Population Council, from B.A. Carnes, S.J. Olshansky, and D. Grahn, "Continuing the search for a law of mortality," Population and Development Review 22, 231–264, 1996.)

reproduction in a hostile environment. Learning to control these most intrinsic of biological processes will remove many of the biological barriers to immortality. All that will remain is for technology never to lose the escalating arms race between humans and their primary source of extrinsic mortality—infectious and parasitic disease. At present, the biological reality is that no intrinsic cause of death has ever been eliminated. Intrinsic diseases may still be occurring at the same ages (e.g., Enriquez-Sarano *et al.*, 1996) with medical treatment and lifestyle modification simply altering their expression by delaying the age when death occurs (Olshansky and Ault, 1986; McGovern *et al.*, 1996; Hunink, 1997).

CONCLUSION

Benjamin Gompertz (1825) was so struck by how similar the age pattern of death appeared across different populations of humans that he invoked a "law of mortality" to explain it. Raymond Pearl (1922; Pearl and Parker, 1921) devised scaling methods to adjust for life span differences to extend the Gompertz law to species other than humans. These early attempts to reveal a general law of mortality that applied across different species failed (Pearl and Minor, 1935). We hypothesized that their failure to reveal a law arose from an inability to adjust for expected differences between species in the intensity of extrinsic mortality. When the contaminating influence of extrinsic causes of death was removed from the mortality schedule, it was demonstrated that populations of laboratory mice, beagles, and humans shared a common pattern of intrinsic mortality (Fig. 1) a result consistent with the concept of a law of mortality

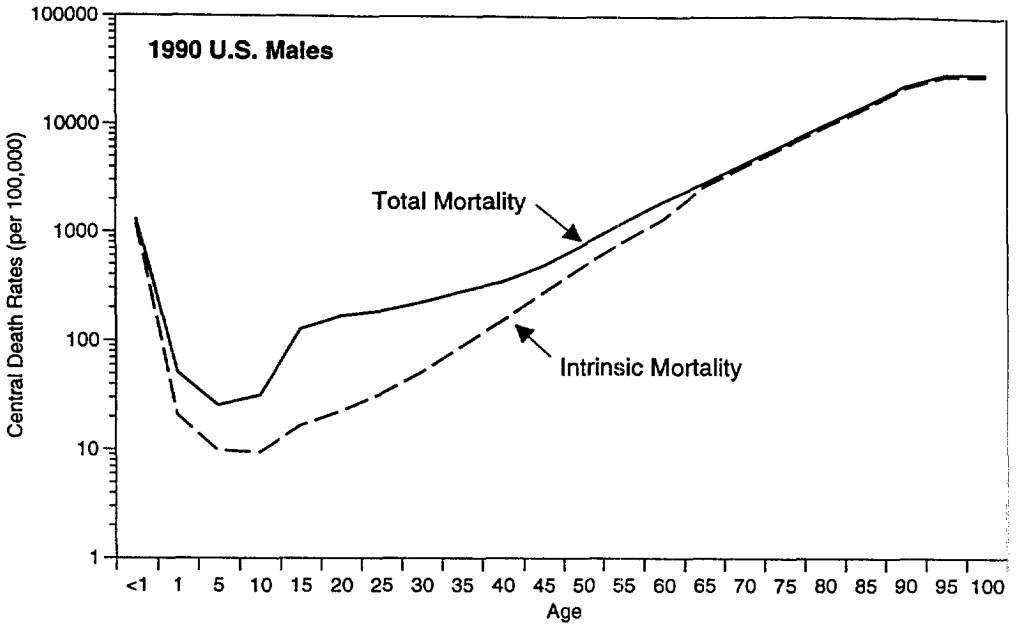

FIG. 2. Central death rates for total mortality and intrinsic mortality in 5-year age intervals for the 1990 U.S. males.

as originally proposed by Gompertz and extended by Pearl (Carnes *et al.*, 1996).

For some human populations and a small number of other species protected from the forces of extrinsic mortality, the contamination of the all-cause mortality schedule by extrinsic causes of death may not be severe—particularly beyond the age of sexual maturity. This caveat does not pertain, however, to the entire mortality schedule or to human populations outside developed countries. For example, when the mortality schedule for the 1990 U.S. population is decremented for such extrinsic causes of death as accidents, homicide, suicide, and infectious and parasitic diseases, the well-known mortality hump observed at younger ages in human populations is eliminated (see Fig. 2). As predicted from biodemographic theory (see Carnes and Olshansky, 1993; Carnes *et al.*, 1996), what remains is a constant progression in the force of intrinsic mortality that begins at the age of sexual maturity and extends to extreme old ages.

SUMMARY

For over 100 years, actuaries and biologists working independently of each other have attempted to develop a rationale for a biologically motivated partitioning of total mortality. The partitioning arguments made by biologists, while primarily theoretical, were intended to apply to all sexually reproducing species. Only the actuaries and demographers made explicit attempts to assign specific causes of death to their mortality partitions. Their efforts, however, were focused on aging and restricted exclusively to humans. In this article, a conceptual partitioning of total mortality into intrinsic and extrinsic components is presented that combines and extends concepts from both biology and demography. It is argued that demographers must not ignore the biology of the organism they study. A biodemographic approach to the study of human mortality provides a valuable perspective on such important demographic issues as population aging and

projections of future life expectancy. A biologically motivated partitioning of total mortality is an essential element of the biodemographic approach to comparative studies of mortality. Unfortunately, incomplete and flawed pathology data, converging disease etiologies, multiple disease processes competing for the lives of individuals, and an imperfect understanding of the biological basis for even major causes of death means that an error-free partitioning of mortality is impossible. It is, however, the premise of this article that even an imperfect partitioning of mortality, when biologically motivated, is preferable to a mortality schedule contaminated by extrinsic causes of death.

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