Continuing the Search for a Fundamental Law of Mortality

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ABSTRACT

For 170 years, scientists have attempted to explain why consistent temporal patterns of death are observed among individuals within populations. Historical efforts to identify a "law of mortality" from these patterns ended in 1935 when it was declared that such a law did not exist. These empirical tests for a law of mortality were constructed using mortality curves based on all causes of death. We predicted patterns of mortality consistent with the historical concept of a law would be revealed if mortality curves for species were constructed using only senescent causes of death. Using data on senescent mortality for laboratory animals and humans, we demonstrate patterns of mortality overlap when compared on a biologically comparable time scale. These results are consistent with the existence of a law of mortality following sexual maturity. The societal, medical, and research implications of such a law are discussed.

The search for a "law of mortality" that describes the characteristic pattern of death observed within populations of sexually reproducing organisms dates back to the pioneering work of British mathematician Benjamin Gompertz (1,2). In 1825, Gompertz discovered for humans that a "law of geometrical progression pervades...large portions of different tables of mortality" -- a law described by a simple equation [$\lambda(t)=\alpha\exp(\beta t)$] (3). Perhaps more importantly, Gompertz endeavored to find a physical cause for his law by suggesting that "death may be the consequence of two generally co-existing 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" (2).

Subsequent efforts to identify a law of mortality using other species have failed because researchers have been unable to reveal common patterns of mortality for the species being compared. Further, explanations for why a law of mortality for populations should even exist have not been provided -- an issue originally raised by Gompertz himself.

The search for a law of mortality begins with the master principle upon which life depends -- the propagation of genetic information across time. One implication of the germ line's ability to escape the bounds of time is that immortality is not only possible, it has already been achieved (4). Unfortunately, for sexually reproducing organisms, the price paid for an immortal germ line is that its carriers -- individuals -- are disposable (5-8).

In hostile environments where causes of death extrinsic to the biology of the organism abound, natural selection has favored a common survival strategy for sexually reproducing organisms -- early reproduction -- a strategy locked into the genome of each species. According to evolutionary theory, natural selection is highly effective before reproduction begins but becomes progressively weaker throughout the reproductive period. This apparently simple concept may be the key to why

senescence occurs and to why survival beyond the age of sexual maturity is necessary to observe its expression. As Medawar (7) noted, senescence can be revealed "only by the most unnatural experiment of prolonging an animal's life by sheltering it from the hazards of its ordinary existence."

Evolutionary theories of senescence, when extended to populations, may provide a framework for predicting age-related increases in senescent mortality -- patterns that we contend are a consequence of biological processes calibrated to attributes of a species' reproductive strategy. We intend to determine whether: 1) a relationship exists between the onset and length of the reproductive period and the time course of senescent mortality, 2) a characteristic schedule of age-specific death rates associated with senescent mortality exists for a species, and 3) a common pattern of senescent mortality is revealed when species are compared on a biologically comparable time scale. It will be argued that a common pattern of senescent mortality identified for a taxonomically diverse group of species represents an imprint of shared evolutionary forces. The mathematical properties of this evolutionary imprint define what may be the operating rules for a law of mortality.

The Historical Search for a Law of Mortality

Early visions of a law of mortality have remarkable similarities to modern concepts concerning mechanisms of senescence. For example, Loeb and Northrop (9) hypothesized that the duration of life might depend on "the presence of certain substances which were used up during life" (analogous to the concept of vitality) (10), or by the "cumulative injurious effects of certain products of metabolism" (similar to the free radical hypothesis of aging) (11). Loeb and Northrop identified a temperature coefficient for the duration of life of *Drosophila* that was consistent with chemical reactions observed in vitro -- suggesting a biochemical basis for senescence (12,13).

Brownlee (14) was one of the first scientists to link the basic biology of humans with major quantitative elements of the life table. He suggested that mortality attributable to senescent causes should first be expressed at about age 12, become the dominant force of total mortality by age 30, and advance at an exponential rate from ages 12 to 85. Brownlee recognized that if a law of mortality existed, it was likely to be obscured by non-senescent mortality, and that a single Gompertz distribution does not apply to the entire life table.

Using data from the field of animal husbandry, Brody (15) attempted to characterize quantitatively the "kinetics of senescence." Brody extended Loeb's (9,12,13) observations by demonstrating that the changes through time for a variety of biological responses and organisms, could be described by a simple equation for exponential decline -- the "law of monomolecular change in chemistry." Brody suggested that death rates by age and underlying cause provided a quantitative description of senescent mortality.

Another perspective on the "order of dying-out" in a population was presented by Greenwood (16), who suggested that a life table was a reflection of underlying biological processes rather than just a useful working tool for actuaries. He concluded that "we have no sound reason for thinking that the force of mortality of mice increases with age more nearly geometrically than the force of mortality in men" nor is there any "reason to think that any more complex formulation of a physiological law would describe the observed facts better than Gompertz's century-old simple formula."

Pearl (17) demonstrated that the mortality patterns of species with different lifespans could be compared by superimposing two biologically comparable points within the life cycles of humans and *Drosophila*. Initially, he argued that his scaling approach would reveal a "fundamental biological

law" of mortality. However, after two decades of minimal success, Pearl and Minor (18) declared that a universal law of mortality does not exist. This conclusion was based on their acknowledged inability to separate all cause (total) mortality into its intrinsic (senescent) and extrinsic (non-senescent) components.

The intensive search for a "law of mortality" essentially ended after Pearl and Minor's declaration. Since then, researchers have instead attempted to classify (19) or develop mathematical models (20-23) to better describe the temporal nature of the dying out process.

Attempts to reveal a law of mortality and identify its properties have been hampered by several difficulties. Initially, reliable mortality data were rare and did not include information on underlying causes of death because the need for detailed pathology was not recognized as important. Even had pathology data been available, the theory and quantitative tools for using this information were not developed until recently. Revealing a law of mortality may also require access to data that is rarely available -- detailed reproductive histories for females maintained within environments that shelter them from non-senescent causes of death.

Finally, senescence is a multidimensional process involving many levels of biological organization (24). The underlying mechanisms responsible for senescence are poorly understood, and the interdisciplinary approach required to bring coherency to this process is difficult to achieve in an age of scientific specialization. We will attempt to integrate a biological explanation for why senescence occurs at the individual level, with the implications this has for the onset and age progression of senescent mortality at the population level following sexual maturity -- a conceptual framework referred to as "biodemography" (25,26).

Biodemography: Evolutionary Background

By extending to populations the logic employed by evolutionary biologists to explain why senescence occurs at the level of individuals, biodemography attempts to discover a biological pattern to the dying out of individuals within a population (26). Why do organisms senesce -- why can't individuals be immortal? Explanations begin with the simple observation that causes of death extrinsic to the basic biology of the organism are, and probably have always been, ubiquitous and unavoidable. For most species, even if senescence did not exist, survival beyond the age of reproduction is an extremely rare event with most deaths for a cohort occurring just after birth. At these ages, the vast majority of deaths result from forces of mortality that are unrelated to senescence (e.g., predation or infectious and parasitic diseases).

In hostile environments where death almost invariably precedes senescence, early reproduction (relative to potential lifespan) has become an essential element in the reproductive strategy of species (27). Consistent patterns of growth and development (ontogeny) observed within species suggests that the reproductive biology of organisms alive today represents a genetic legacy of responses to environmental conditions that prevailed during the early evolutionary history of each species.

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. Opportunities for selection to alter gene frequencies (Figure 1) 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 (8,28,29). This age-based gradient for the effectiveness of selection permits the potential lifespan of organisms to be partitioned into biologically meaningful time periods -- the pre-reproductive, reproductive, and post-reproductive

periods (30). For this discussion, the reproductive period includes the production and nurturing of offspring, and for some species, a grand parenting period where parents contribute to the reproductive success of their offspring.

Restricting the effectiveness of selection to the time before the end of the reproductive period leads to explanations for how senescence might have arisen. According to a theory appropriately named antagonistic pleiotropy, Williams (8) argued that genes with damaging effects late in life (when selection is weak or nonexistent) could accumulate in a population if they were involved in processes critical to survival and reproductive success early in life. These damaging effects would not ordinarily be observed because survival beyond the reproductive period is a rare event. Medawar (7) even suggested that the post-reproductive period was a genetic "dustbin" for the allelic forms of genes whose deleterious expression during this period fall beyond the effective reach of selection.

If gene expression in the post-reproductive 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 should not be possible. Instead, senescent-related diseases and disorders observed in organisms not moulded by selection for extended survival (beyond the genetically defined reproductive period) may be an inadvertent consequence of selection operating uniformly on reproduction (29).

Indeed, this is the perspective on senescence provided by evolutionary biologists (5-8,28,29,31-33). For example, Kirkwood (5,6) argues that perfect maintenance of an organism (immortality) is not necessary or even desirable if the resources required to extend survival are not translated into reproductive output (fitness). 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. In a world where successful reproduction is restricted to an early portion of the lifespan, senescence may be an inadvertent consequence of surviving into the post-reproductive period where the individual is disposable.

Biodemography: Individuals to Populations

We contend that the logic used to link natural selection and reproduction, and reproduction and senescence for individuals has a direct bearing on "when" senescent mortality should occur in a population. The timing of genetically determined processes such as growth and development is driven by a reproductive biology moulded by the necessity for early reproduction. If individual senescence is an inadvertent consequence of these developmental processes, then patterns of senescent mortality in a population should also be calibrated to some element(s) of a species' reproductive biology (34).

Although individuals within a population are responding to a common set of evolutionary pressures, genetic heterogeneity 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, a population is comprised 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.

Given stability in the genetic composition of a population, an age pattern of senescent mortality -- the **senescent mortality signature** -- should exist that remains invariant even under conditions where mortality pressures from extrinsic causes of death differ. Changes in the senescent mortality signature of a population would, however, be expected when forces of selection acting to maintain the genetic composition of a population are disrupted (e.g., environmental challenges) or methods

of intervention become available to modify -- either positively or negatively -- the expression of senescent disease processes.

The full array of potential senescent processes, their consequences, and the senescent mortality signature, are revealed only under the "unnatural" condition of survival beyond the age of sexual maturity by a significant proportion of a birth cohort. Organisms for which a senescent mortality signature can be identified have, without exception, involved species where individuals have been ushered beyond the age of sexual maturity either by controlling the extrinsic causes of death that kill early or by intervening in the expression of intrinsic diseases that kill later -- for example, the recent experience of humans, household pets, zoo and laboratory animals raised under controlled conditions.

Early reproduction reflects consistent biological responses to similar environmental challenges by organisms with a shared genetic heritage. Species are unable to escape the invariant action of natural selection that has imposed a link between a species' reproductive strategy and the disposal time of individuals. As such, the pervasive forces that mould reproductive strategies should lead to a common pattern of senescent mortality -- an **evolutionary imprint** -- when species are compared on a biologically comparable time scale.

A unique assemblage of data and over 50 years of theoretical developments in evolutionary biology allowed us to overcome many of the obstacles that hindered previous efforts to identify a law of mortality. Specifically, we have: 1) mortality data for a variety of species maintained in protected environments, 2) diagnoses of major pathologies observed at death, 3) methods of survival analysis that adjust for competing risks of death, 4) reproductive histories on the species for which we have mortality data, 5) established evolutionary theories for why senescence occurs, and 6) a

paradigm -- biodemography -- that by extending the implications of evolutionary theory to populations provides a conceptual framework that brings coherence to observed age patterns of senescent diseases and disorders.

Tests For A Law Of Mortality

The mortality data for laboratory control animals (mice and beagles) were derived from studies conducted in the Division of Biological and Medical Research (BIM) at Argonne National Laboratory (ANL) during the period 1953-1993 to study the biological effects of exposure to radiation (37,38,39,40). Data on the reproductive performance of mice were extracted from the records of a breeding colony maintained at ANL from 1953-1970 (37). The BIM animal facilities and husbandry practices were accredited by the American Association for the Accreditation of Laboratory Animal Care and were in compliance with the Animal Welfare Act.

Data for mice involve six widely used inbred strains (A/He, A/Jax, BALB/c, C3Hf/He, C57BL/6, and C57L), the F_1 and F_2 hybrids from strains C57BL/6 and BALB/c ($B6CF_1$ and F_2), the first backcross generation (BC_1) of the $B6CF_1$ to the BALB/c parent, the 11th backcross generation (BALB/c-C(N11)) that was subsequently full-sib mated, an additional nine inbred strains (C, K, Q, N, S, Z, E, BALB/Gw, BALB/Gw-B), and three genetic marker stocks (Ruby belt, P, MWA). This heterogeneous collection of mice will be referred to as strains for the remainder of this paper. Data on beagles came from control animals derived from an outbred closed breeding colony maintained at ANL.

Animals were provided food and water *ad libitum*, monitored daily for the duration of life, with diagnostic and therapeutic procedures carried out in compliance with established regulations for the

humane treatment of animals. Exact death dates were recorded for every animal. Detailed gross and/or histopathological information was limited for the majority of mice to 9 codes describing the most frequently observed neoplastic diseases, and 12 codes identifying the most prevalent acute or chronic infectious and degenerative diseases. Complete necropsies were carried out on the beagle. Specimens from all major organs were routinely fixed for histochemical and histologic classification. Based on an evaluation of all clinical, hematological, necropsy, and histopathological findings, a cause of death was assigned and coded for each dog (41).

With regard to mice and dogs, non-senescent causes of death were similar to those observed in humans -- including accidents, violence, acute and chronic infectious diseases of the pulmonary, gastrointestinal, and genitourinary systems, the liver, and the skin. Judgements were made regarding the intrinsic or extrinsic nature of degenerative conditions, principally pneumonia and amyloidosis, because of major genetically based differences among mouse strains in susceptibility to these lesions when they occurred later in life.

Grouped mortality data for humans (five year age groups from ages 5 to 84) were drawn from vital registration systems for the following countries and time periods: Australia (1964-68, 1969-73, 1974-78, 1979-83, 1984-88, 1989-93), Japan (1960, 1970, 1980, 1990), The Netherlands (1955-60, 1965-70, 1975-80, 1985-90), Sweden (1959-61, 1969-71, 1979-81, 1989-91), and the United States (1960, 1970, 1988). Central death rates (m_x's) and conditional probabilities of death (q 's) were calculated using standard actuarial methods (42). Senescent mortality rate doubling times (MRDT = $\ln(2)/\beta$, where β is the Gompertz rate parameter) were estimated for the population aged 10-84.

For interspecies comparisons, data from an epidemiological study on the health risks of occupational exposure to radium among women employed in the watch painting industry before

1930 were used in place of the grouped data described above (43). This population was selected because the time and cause of death for every individual was carefully reviewed, and recorded. The 301 women selected received either no exposure or their exposures were well below any known biological effects of radium. Sampling statistics, quality of pathology, and details about time of death for this group were comparable with the data used for laboratory animals.

Non-senescent mortality in humans was defined according to the 10th International Classification of Diseases as external causes of injury and poisoning (E800-E999), infectious and parasitic diseases (001-139), diseases of the respiratory system at ages 0-64 (460-519), lung cancer at ages 0-64 (460-519), chronic liver disease and cirrhosis (571), endocrine, nutritional, and metabolic diseases and immunity disorders (251-252, 256-259, 270-276, 277.1-277.9, 278.1-279), obesity (278), alcoholic psychoses (291), alcoholic dependence syndrome (303), drug dependence (304), meningitis (320-322), rheumatic fever and rheumatic heart disease (390-398), chronic hepatitis and biliary cirrhosis (571.4-571.6), and complications of pregnancy, childbirth, and the puerperium (630-676). Senescent mortality was defined as all other causes. Although minor changes in the ICD codes occurred across the time periods studied, the first four disease categories listed above were always available and accounted for over 88 percent of non-senescent mortality.

The standard form for the truncated version of the Gompertz hazard function (44), generalized to account for competing risks (45), was used to generate parameter estimates via the method of maximum likelihood (MLE) for the mouse strains and beagle. Accidental deaths, deaths resulting from infectious disease, and abnormal exits from the study (escapes, transfers) were treated as censored observations. With the exception of pneumonia, all other deaths (predominantly neoplastic) were interpreted as senescent deaths. Pneumonia was defined as senescent only if death

from this disease occurred after the median age at death for the other senescent events. MLE estimates of the Gompertz parameters were used to estimate the median age at death from senescent related causes (MAD_S), and mortality rate doubling times (MRDT).

Breeders from some strains of mice were permitted to closely achieve their maximum reproductive potential while females from other strains were retired when their reproductive performance diminished. This inequality made it impossible to determine the precise age when the females of a specified mouse strain were no longer capable of successful reproduction. An index, the "effective end of reproduction (EER)," was developed to compensate for this problem. EER combines information on reproductive productivity, pup mortality, and the population distribution of ages at final parity. Computation of EER begins with an identification of the age when either 75% of a female's total births is achieved or when the cumulative mortality of her pups exceeds 30%, whichever comes first. The average of these individual maternal ages for a strain was then averaged with the median age at last parity for the strain to produce EER.

Ordinary least squares (46) was used to establish a relationship between MAD_S calculated for control mice and EER values for breeders. Regression diagnostics (47) were used to determine whether estimated regression parameters were unduly influenced by specific strains of mice.

A proportional hazard model (48) was used to contrast temporal patterns of senescent mortality within 5 strains of mice (C3Hf, BALB/c, C57BL/6, and the F_1 and F_2 hybrids of BALB/c and C57BL/6) used in studies spanning several decades. Infectious disease processes caused considerable mortality in the early studies but became nearly nonexistent under the improved husbandry practices implemented in the later studies. Each strain was modelled separately. Nonsignificance of the model parameter identifying when an experiment was conducted implies that

early and late studies share a common senescent mortality schedule despite large differences in overall mortality attributed to infectious disease pressure.

It has been argued that the temporal distribution of senescent mortality has biological meaning. A summary measure of this mortality, MAD_S, also has biological relevance if the reasonable assumption is made that the mortality distribution is unimodal and not excessively skewed. An opportunity for interspecies comparisons arises if MAD_S is not only biologically relevant but also biologically comparable across species. Under this assumption, interspecies scaling was accomplished by multiplying the observed death times for a species by the ratio of the MAD_S for an arbitrarily selected species and the MAD_S for the species being scaled. This method of scaling time normalizes the MAD_S value for all species to that observed in the reference group -- the B6CF mouse.

Three alternative scaling approaches based on the ratio concept were also used. Failure times were scaled by the ratios of MRDT values (equivalent to the ratio of Gompertz rate parameters), EER values, and by the median death times for all causes of death. Using the scaled death times, hazard modelling was repeated to test for heterogeneity among the survival curves being compared.

Evidence for a Law of Mortality

A data summary is presented in Table 1. The estimated Gompertz parameters (α and β) were used to calculate MRDT and MAD_S for summarizing senescent mortality for each strain or species. Note, MAD_S values range from a low of 317 days for the Ruby belt to a high of 961 days for the $B6CF_1$ hybrid.

The relationship between MAD_S and EER for the mouse strains is presented in Figure 2. Significance (P=.002) of the regression (slope) coefficient for EER established that senescent related deaths occurred later in mouse strains where the effective end of reproduction also occurred at later ages. Regression diagnostics (47) revealed that the two hybrid strains ($B6CF_1$ and BC_1) influenced the estimated regression line but their exclusion altered neither the significance of the relationship between MAD_S and EER nor the variation in the data explained by the regression model (R^2=.45).

The hazard model analyses used to test for the existence of senescent mortality signatures are summarized in Table 2. Mice in the early studies died (from all causes) at significantly younger ages (risk > 1) than their counterparts in the later studies. However, with the exception of the C3Hf mouse, statistically significant differences in the risk of death from senescent mortality could not be detected between the two time periods. Even for this strain, where sample size was a problem, the significance of the difference in senescent mortality between the early and late studies was reduced 100 fold.

The analyses used to test the efficacy of scaling metrics for comparing senescent mortality across mouse strains are summarized in Table 3. When death times were not scaled, only one mouse strain was found to have a senescent mortality pattern similar to the reference ($B6CF_1$) strain. Results using the median age at death from total mortality as a scaling device are not presented because, as expected, this approach worked no better than not scaling time at all. Similarly, the senescent mortality signatures for the mouse strains could not be superimposed when either the ratio of EER values or the ratio of MRDTs was used to scale death times. However, 19 of 21 strains had senescent mortality patterns that could not be distinguished (at the 0.05 level of significance) from that observed for the $B6CF_1$ mouse when death times were scaled by the ratio of MAD_S values.

The comparison of senescent mortality patterns for the beagle and human relative to the $B6CF_1$ mouse using the MAD_S scaling approach is summarized in Table 4. When death times for beagles and humans were mapped onto the time scale for the $B6CF_1$ mouse, the senescent mortality patterns for the 3 species were statistically indistinguishable.

The Gompertz derived hazard functions for the mouse, beagle, and human (Figure 3) suggest that humans have an elevated risk of senescent death over time, particularly at older ages -- an interpretation that conflicts with the results presented for the proportional hazard analysis (Table 4). To test whether the elevated risk at older ages suggested by the Gompertz plots was significant, the time scale was partitioned into the period before and after MAD_S (961 days). Within each time partition, the proportional hazard model analysis was repeated with senescent events declared as censored if they did not occur within the time partition being analyzed. The risk of senescent death in humans relative to the $B6CF_1$ was lower in the early time period (risk = 0.8) and higher in the later time period (risk = 1.6) but did not attain statistical significance (P = 0.1) in either case.

In humans, reproductive maturation occurs in the second decade of life with a reproductive period that lasts approximately 35 years for females (Figure 1). This fact leads to identifiable properties of the senescent mortality signature, including an age-at-onset for senescent mortality, an initial senescent death rate, and a consistent pattern of increase in the senescent death rate (MRDT) following sexual maturity.

For each of the five countries and time periods considered, the minimum senescent death rate occurred consistently at the age of sexual maturity for both males and females -- between ages 10 and 15. The initial senescent death rate at these ages for both sexes combined ranged from .12 to .35 deaths per thousand in the 1960s, but converged to an average rate of .08 and .07 deaths per

thousand for males and females, respectively, by 1990 (Figure 4). Following sexual maturity the senescent MRDT for males and females across all population subgroups and time periods was in the range of 6.5 to 8.2 years (Figure 5). The average senescent MRDT declined during the 30 year time period from 7.4 to 7.0 years for males, and from 7.6 to 7.1 years for females.

Implications of a Law of Mortality

Our continuation of the search for a law of mortality could not have occurred without the conceptual framework provided by 170 years of research (51). Gompertz (1,2), Brownlee (14), Brody (15), and Greenwood (16) provided important actuarial insights, and the key role of pathology data was revealed when Pearl (18) admitted he was unable to disentangle *biological* causes of death from those attributable to *environmental* causes. Identifying the linkage between reproduction and senescence was a critical contribution made by evolutionary theorists (5-8,28,29). The relatively recent emergence of competing risk theory was necessary to perform the statistical tests of the biodemographic predictions (44,45,48,52). Finally, this research was made possible by access to the unique collection of data from the radiation studies conducted by Sacher (53-56) and Grahn (57-62) at Argonne National Laboratory.

The stochastic nature of extrinsic mortality across time and location makes total mortality an unreliable endpoint for analysis. Our *a priori* partitioning of total mortality into senescent and non-senescent components was an important element of the analysis strategy. Alternative approaches are encouraged by those who may not agree that our mortality partitions actually represent senescent and non-senescent deaths (63). The important point is that a mortality schedule for the animals

investigated was identified that remained invariant even when patterns of total mortality differed dramatically.

A strong relationship was established between an attribute of the reproductive period, EER, and a summary measure of senescent mortality, MAD_s. This result suggests that the age when reproduction ceases (menopause) should also be a predictor of senescent mortality. There is empirical support for this contention from epidemiological research (64). However, our approximation of age at menopause for mice, EER, did not work as a metric for scaling. It may be that senescence is associated with a complex of reproductive attributes (e.g., age of sexual maturity, length of the reproductive period, offspring per parity, parity interval).

The convergence of senescent mortality schedules for the mouse, dog, and human on a biologically comparable time scale implies that animal data are relevant for the prediction of human health risks -- a contentious issue in such fields as epidemiology, public health, toxicology, and radiation research. However, given that every species carries a unique genetic legacy, the convergence of senescent mortality signatures across species should not be interpreted to mean that the distribution and time of expression for the constituent elements (specific causes of death) of the signatures will also converge. This has important implications for animal-based research on risk assessment and the establishment of safety standards for humans.

Mortality signatures differed among the human subgroups presented in this paper when total mortality was partitioned into senescent and non-senescent components and observed over comparable time periods. Artificial differences in pathology diagnosis and coding over time and location could be responsible. It is also possible that real genetic differences exit among population subgroups -- a product of geographic isolation and adaptation to local environmental conditions.

Under the biodemographic paradigm, senescent mortality signatures are expected to remain invariant unless the genome itself is modified. Although senescent mortality may be calibrated to the reproductive biology of a species, the timing and expression of senescent diseases can only be locked into the genome in an *indirect* sense. By implication, the expression of senescent diseases and disorders and their health consequences should be inherently modifiable.

Observed secular declines in the initial senescent death rate and the senescent MRDT indicates that the expression of the signature for humans has, in fact, already been modified. Further modification of the signature's expression depends on the extent to which future technologies can: 1) continue to extend survival for individuals who would ordinarily die from genetic diseases before reaching reproductive maturity, 2) further postpone mortality associated with senescent diseases, or 3) delay expression and/or eliminate senescent diseases by direct manipulation of the genome. The recent identification of genes responsible for a variety of diseases and disorders will lead to further modifications to the expression of the senescent mortality signature. The extent to which length and quality of life will be affected by further modifications of the signature is already the subject of intense scientific interest with important relevance to public policy.

Scientists have speculated on the existence of an age barrier, or biologically based limit to life, that cannot be breached (65). Thus far, the evidence suggests that the age of the longest lived member and the median age at death increase in response to cohort size and modifications of the physical environment (66-68). This has led some to conclude that either there is no limit to life, or if one exists, it must be beyond the observed longevity horizon (66-68).

Evolutionary theories provide a consistent message on this issue -- there can be no biologically based barrier to survival that evolved under the **direct** influence of natural selection. However,

numerous biological processes have arisen as direct products of natural selection with some exhibiting sufficient temporal regularity to be called biological clocks. If selection calibrated the rates at which these clocks operate to attributes of the reproductive period, then the biological processes they govern (e.g., growth, development, DNA repair) could determine the time course of senescent mortality and, thereby, establish a senescent life expectancy for a species. By modifying the expression of senescent mortality, it is possible that some subgroups of the human population have life expectancies that exceed the biologically based limit imposed by the senescent mortality signature. Revealing the extent to which the expression of the senescent mortality signature has already been modified could be useful for evaluating the reasonableness of mortality schedules used for forecasting expenditures of government social programs (69).

Gains in life expectancy brought about by interventions in the **expression** of the senescent mortality signature is a critical health policy issue -- implying that humans may already be living on manufactured time -- healthy years of life for some and disabled years for others. New or infrequently observed senescent diseases at older ages may continue to have opportunities for expression -- with population health impacts yet to be understood (see prediction 8 in the Appendix) (71). Even if the signature itself is modified through direct manipulation of the genome, the long-term health and societal implications of such actions must be considered. The ultimate goal of efforts to extend life should be the preservation of healthy years of life and the avoidance of a prolongation of old age accompanied by significant disability (72).

In summary, senescence and death are the inevitable price paid for a strategy -- sexual reproduction -- that perpetuates life through an immortal germ line. In a hostile world filled with high risks from forces of mortality extrinsic to the biology of the organism, natural selection has

favored reproductive strategies where reproduction is restricted to early portions of the potential lifespan. The reproductive biology of organisms alive today is certainly a genetic legacy of the selective forces that shaped the basic biology of the species during its early evolutionary history. When non-senescent forces of mortality are reduced and survival into the post-reproductive period becomes a common event, a characteristic age distribution of senescent mortality is revealed for a species -- a distribution calibrated to attributes of its reproductive period.

The common pattern of senescent mortality observed across species represents an imprint of shared evolutionary forces -- a pattern normally hidden by the ever-present non-senescent causes of death that kill most organisms. The evolutionary imprint has only recently become visible among a limited number of species. The mathematical properties of the evolutionary imprint, therefore, define what may be the operating rules for a law of mortality.

APPENDIX

Predictions From The Biodemographic Paradigm

The biodemographic paradigm provides a framework for making predictions about the time course and age-specific intensity of senescent mortality in populations. Although the population consequences of survival beyond the age of sexual maturity is the focus of this paper, predictions for other time periods are included in a chronological order that follows the partitioning of the lifespan into biologically meaningful subdivisions (see Figure 1).

1. ***The incidence of embryonic loss should be at a maximum at fertilization.***

Reproduction requires a significant parental investment of biological resources. As such, parents that lose embryos as early as possible should have a reproductive advantage over parents whose embryonic loss occurs at later stages of development. The maximum penalty on reproductive fitness occurs when offspring die at the age when parental care ceases (29).

2. ***The beginning of the reproductive period should mark the age of lowest mortality and be characterized by an initial senescent death rate associated with inherited genetic diseases.***

Intrinsic mortality rates during the pre-reproductive period should drop from a maximum at fertilization to a minimum at sexual maturity -- representing a distinct law of mortality if the mortality rates are calibrated to the length of this portion of the lifespan. The expression of genes that compromise reproductive fitness should be shifted by selection to earlier ages where fitness costs are lower (7). Some intrinsic mortality is inevitable at the point of lowest mortality because of mutations and genetic mechanisms that shelter deleterious gene expression from the action of selection (73,74). As the effectiveness of selection declines once reproduction begins, senescent

mortality should increase from its lowest point at sexual maturity -- establishing an initial mortality rate (IMR) and providing a basis for subsequent mortality rate doubling times (MRDT).

3. ***Once the point of lowest mortality has been reached at sexual maturity, the law governing subsequent increases in senescent death rates -- the doubling time -- is determined by attributes of the reproductive period.***

Forces extrinsic to the biology of the organism determine the onset and length of the reproductive period. Once the reproductive period is established, the temporal nature of biological processes influenced by the timing of reproduction (e.g., growth and development) become locked into the genome. If senescence is an inadvertent consequence of these processes, then senescent mortality may follow a characteristic pattern that, by convention, has been described mathematically as the MRDT -- implying that the length of the reproductive period should be positively correlated with the magnitude of the senescent MRDT (75).

4. ***The reproductive period should be dominated by causes of death that are extrinsic to the basic biology of the organism.***

Residual amounts of intrinsic mortality during the reproductive period are inevitable because of mutations and genetic mechanisms that shelter deleterious gene expression from the action of selection. However, efficient molecular/cellular processes designed to maintain the biological integrity of the organism should operate during this period to minimize the risk of intrinsic mortality. What remains is a reproductive period dominated by the extrinsic forces of mortality that were responsible for reproductive strategies characterized by early reproduction.

5. ***The late reproductive and early post-reproductive periods should be characterized by the expression of inherited genetic diseases that were "pushed" by natural selection to this region of the lifespan.***

As selection weakens toward the end of the reproductive period, its ability to shift the expression of mutant alleles and inherited genetic diseases to older ages should diminish. The result should be a collection of genetic diseases (for example, amyotrophic lateral sclerosis, ataxia telangiectasia, Huntington's disease, LiFraumeni syndrome, multiple sclerosis, and others) that are expressed in the portion of the lifespan near the end (on either side) of the reproductive period. We refer to these diseases as "Medawarian diseases" -- named after the scientist who first described the post-reproductive period as a genetic dustbin (7).

6. ***Later in the post-reproductive period, there should be a transition from Medawarian diseases to senescent diseases and disorders that arise from either accumulated genetic damage or structural wear and tear.***

As individuals survive beyond the Medawarian disease period, the mortality schedule should become increasingly dominated by disease processes that require an accumulation of acquired damage to be expressed. Diseases and disorders in this category (e.g., vascular diseases, neoplasms, dementia, sensory impairments, arthritis, osteoporosis) could arise from 1) gene disregulation, 2) an accumulation of mutational damage, 3) structural wear and tear, and 4) declining effectiveness of repair processes. The mechanisms in this incomplete list are characterized by damage acquired during the course of living rather than arising from inherited defects present at fertilization.

7. ***Once the population is reduced to only the long-lived subgroups of the initial cohort, a transition to a new law of mortality should apply.***

A genetically heterogeneous population is characterized by individuals with a variety of mortality risks -- ranging from high mortality at younger ages to low mortality among the long-lived "Methuselahs." As such, long-lived and short-lived subgroups exist within the heterogeneous populations typically described by a single mortality distribution (50) -- each of which would be associated with a unique senescent mortality pattern. Quantitative descriptions of the Methuselahs (76) revealed by attrition would, therefore, be expected to differ from those used to describe the dying out pattern of the total population (77).

8. ***New or infrequently observed senescent-related diseases and disorders may be expressed when the genetic heterogeneity of the older population is increased.***

Under normal conditions, survivors into older ages are a rare and highly selected subgroup of the original cohort -- probably sharing genetic characteristics that contributed to their extreme longevity. In the 20th century where extrinsic mortality has been reduced and the risk of death from senescent diseases has been delayed, survival well beyond the reproductive period has become a common event. As such, the genetic heterogeneity of the older segment of the population should have increased (78). The appearance of new or increases in currently rare fatal diseases and non-fatal disorders may be an inadvertent consequence of the extended survival of individuals who would have previously died before these disease processes had the opportunity to be expressed.

9. ***In the absence of manipulation, senescent mortality signatures should be invariant across time. Variations in the senescent mortality signature of population subgroups may emerge as a result of adaptations to local environmental challenges.***

Species have a senescent mortality signature embedded within an overall pattern of total mortality. The usual expression of a senescent mortality signature may be altered by intervening in the disease processes that comprise the signature or by artificially manipulating reproduction (79,80). Industrial melanism in the Peppered Moth (81) and malaria resistance in humans carrying the sickle-cell gene are examples of changes that have occurred in the gene pool of subpopulations in response to local environmental challenges. Genetic drift and the import of new alleles through migration could also alter the signature of a subpopulation. It should also be possible for senescent mortality signatures among subpopulations to appear unchanged despite differences in the specific causes of death that comprise the signatures (82).

10. ***An evolutionary imprint should be revealed when senescent mortality signatures of sexually reproducing species are compared on a biologically comparable time scale.***

A general set of operating rules for the distribution of senescent mortality is implied if the disposal time of individuals in a population from intrinsic causes of death is a predictable consequence of biological responses made by organisms to a hostile environment. Further, if senescent deaths have a unimodal distribution and are not excessively skewed, then MAD_S is not only a biologically relevant summary measure of senescent mortality, but it may also be a biologically comparable time point across species. As such, senescent mortality signatures should overlap when death times for the species being compared are scaled by MAD_S. We refer to this "overlapping" of senescent mortality as an "evolutionary imprint" because natural selection has

imposed a link between the reproductive biology of a species and the disposal time of individuals in a population -- thus revealing what may be a law of senescent mortality following sexual maturity.

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FIGURE LEGENDS

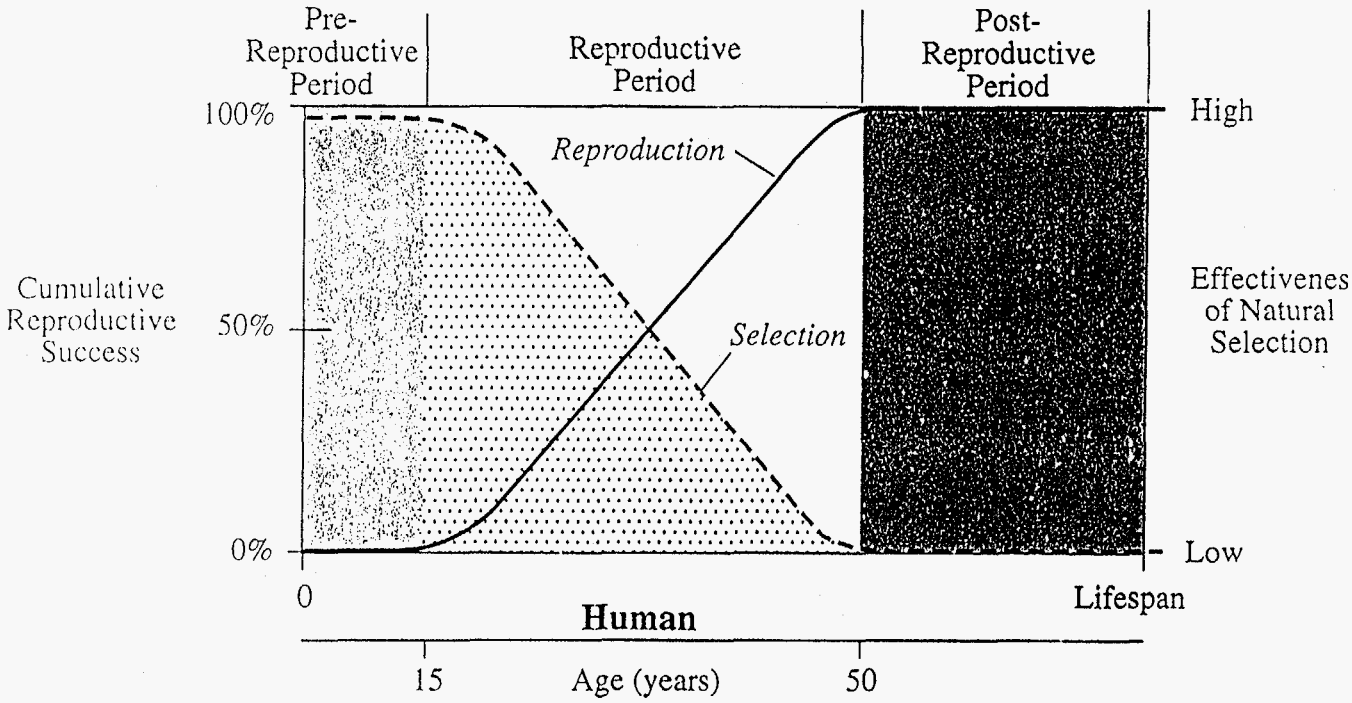
Figure 1. A partitioning of the potential lifespan of an organism into biologically meaningful time periods based on the decline in effectiveness of natural selection as the reproductive success of individuals is achieved.

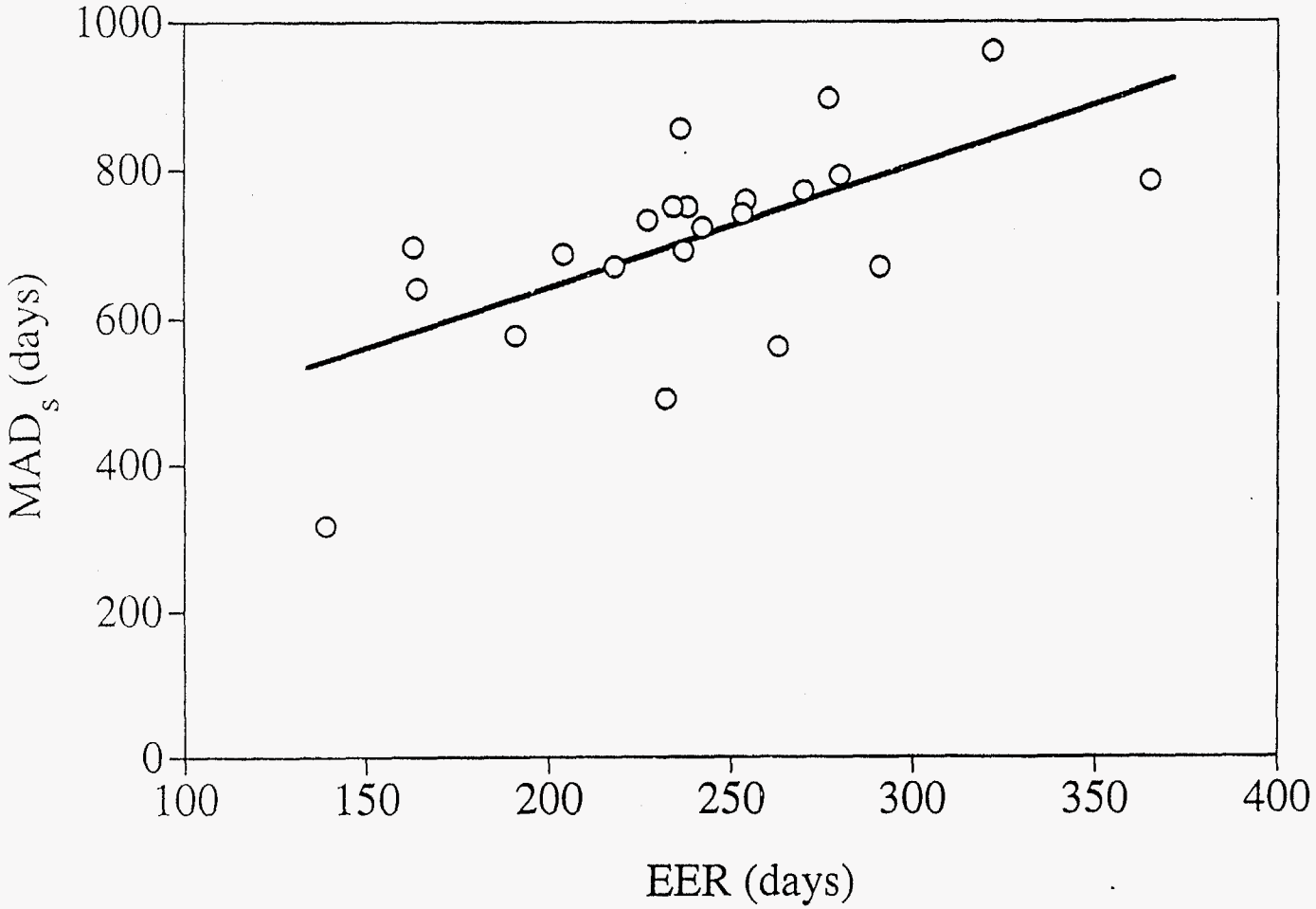
Figure 2. Regression relationship between the median age at death from senescent related causes (MAD_s) and the index referred to as the "effective end of reproduction" (EER).

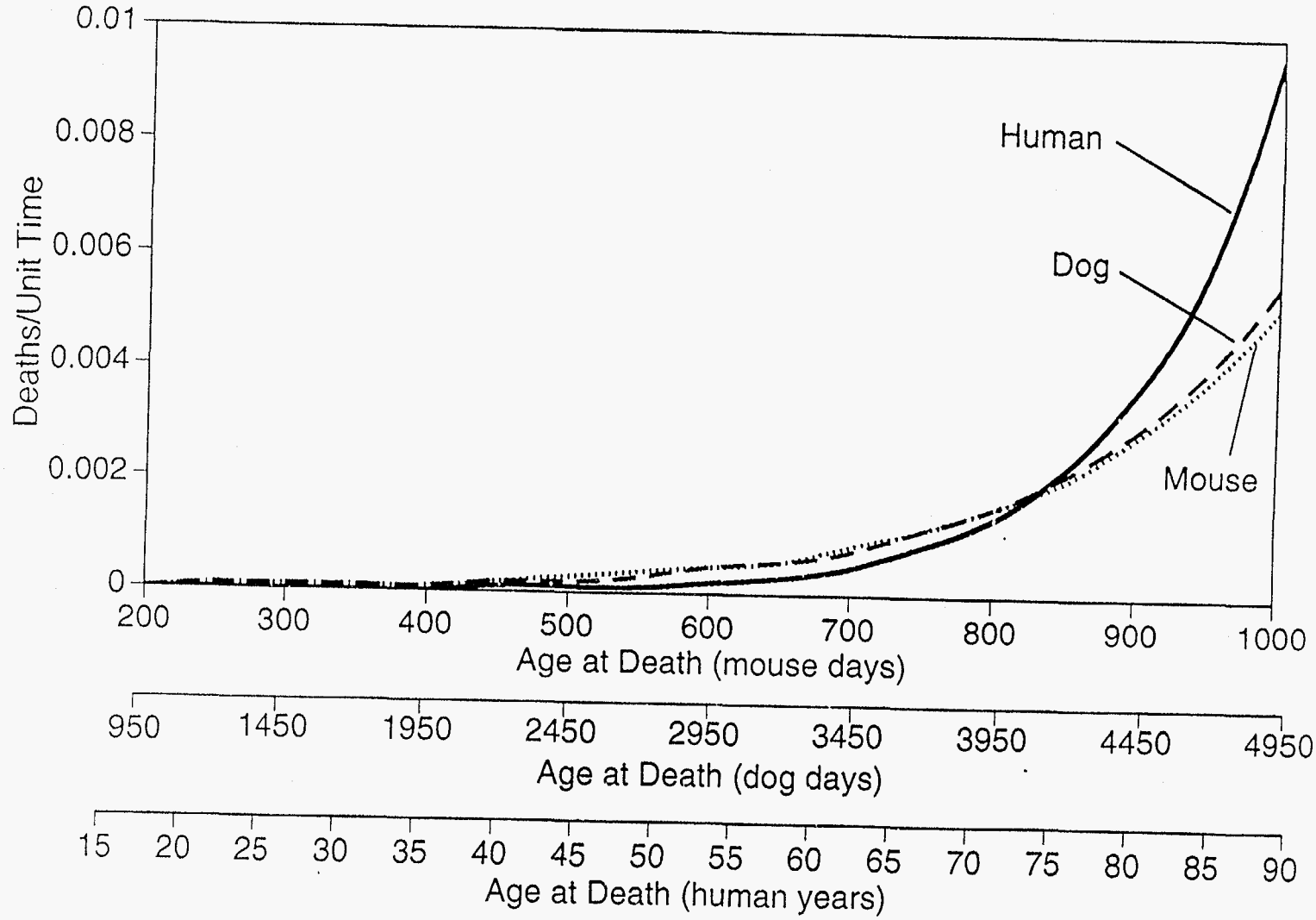
Figure 3. A comparison of Gompertz hazard functions for the mouse, dog, and human when plotted on the time scale for the $B6CF_1$ mouse. Additional abscissas are provided for the dog and human to emphasize the effect of scaling.

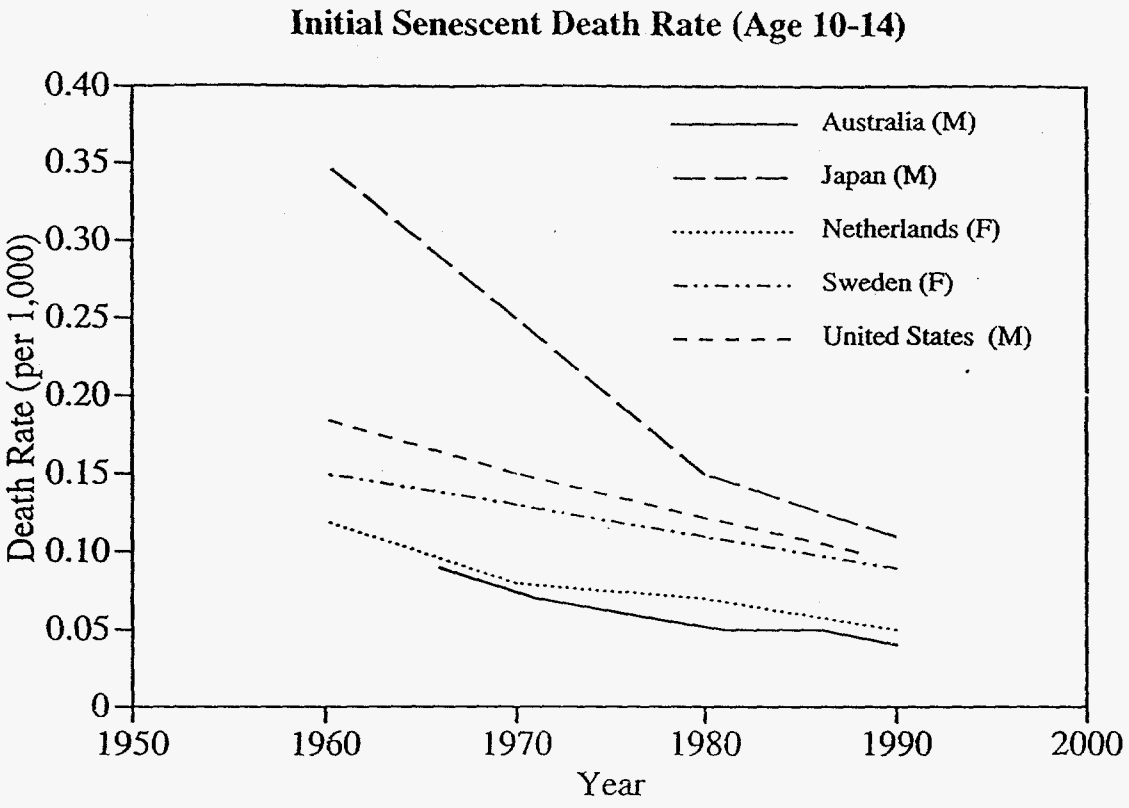
Figure 4. Initial senescent death rate for human males and females for selected time periods and countries using grouped data.

Figure 5. Mortality rate doubling time (MRDT) for human males and females for selected time periods and countries using grouped data.


Pre-
Reproductive
Period
Reproductive
Period
Post-
Reproductive
Period
100%
50%
0%
High
Low
Reproduction
Selection
Cumulative
Reproductive
Success
Effectivenes
of Natural
Selection
0
Lifespan
Human
15
Age (years)
50


1000
800
600
400
200
0
MAD$_s$ (days)
100
150
200
250
300
350
400
EER (days)


0.01
0.008
0.006
0.004
0.002
0
Deaths/Unit Time
Human
Dog
Mouse
200
300
400
500
600
700
800
900
1000
Age at Death (mouse days)
950
1450
1950
2450
2950
3450
3950
4450
4950
Age at Death (dog days)
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
Age at Death (human years)


Initial Senescent Death Rate (Age 10-14)
Death Rate (per 1,000)
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1950
1960
1970
1980
1990
2000
Year
Australia (M)
Japan (M)
Netherlands (F)
Sweden (F)
United States (M)

Mortality Rate Doubling Time

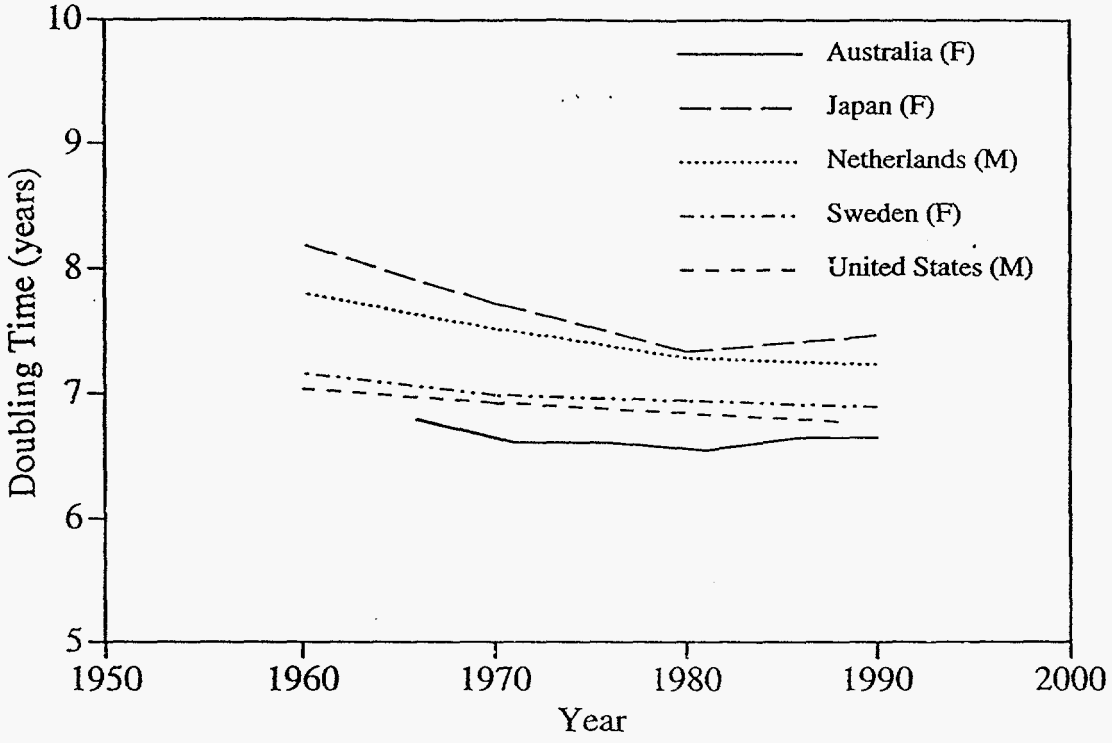


TABLE 1 Summary of Gompertz parameters ($\propto$,β), their standard error (S.E.), median age at death from senescent causes (MADs), the number of animals (N), number of senescent events, the effective end of reproduction (EER), and the number of female breeders for 22 strains of mice, the beagle, and humans.

Strain/ Species	$\propto$ (10^{-6})	S.E. (10^{-6})	β (10^{-3})	S.E. (10^{-4})	MADs (days)	N	Senescent Events	EER (Days)	Breeders
A/He	2.62	0.32	10.73	0.70	741	144	83	253	264
A/J	2.68	0.19	11.57	0.30	692	345	219	237	286
BALB/c	19.50	1.53	6.95	0.20	793	371	167	280	305
C3Hf/He	1.92	0.21	9.50	0.45	857	258	89	236	266
C57BL/6	4.04	0.35	8.06	0.26	898	358	138	277	325
C57L	43.83	2.97	6.40	0.15	723	387	223	242	216
$B6CF_1$	10.46	0.56	6.28	0.11	961	475	354	322	53
$CB6F_2$	15.53	1.80	6.33	0.38	893	180	79	—	—
BC_I	44.47	4.17	5.74	0.29	785	163	120	365	26
BALB/c-N11	11.12	3.46	8.22	2.95	759	25	18	254	59
C	18.74	2.55	10.29	0.99	578	88	64	191	44
K	217.44	26.82	3.71	0.35	688	78	68	204	60
Q	80.40	11.95	5.06	0.60	750	74	49	238	47
N	18.52	2.12	7.27	0.54	772	109	87	270	55
S	102.88	14.41	5.74	0.57	642	92	54	164	53
Z	70.97	9.42	5.45	0.57	733	75	62	227	43
E	14.27	2.47	7.95	1.05	750	75	40	234	49
Bab	8.59	1.12	9.99	0.83	670	107	70	291	40
BaB	25.39	4.35	8.04	1.19	671	57	42	218	38
Ruby belt	81.30	9.27	15.44	1.27	317	87	87	139	98
P	43.68	7.98	7.91	0.69	562	93	73	263	54
MWA	62.00	6.95	9.56	0.07	490	109	87	232	61
Beagle	2.79	0.26	1.22	0.06	4698	143	126	—	—
Human	7.84	0.71	106.4	3.75	85.95	301	136	—	—

Note: Gompertz parameters and MADs for humans (luminizers) estimated using time measured in years.

Table 2. Tests for the Existence of a Senescent Mortality Signature

*Model: $\lambda(t) = \lambda_0(t) \exp(\beta \cdot I)$

Mouse Strain	TOTAL MORTALITY				SENESCENT MORTALITY			
	β	Error	Risk	P-Value	β	Error	Risk	P-Value
BALB/c	0.24	0.13	1.27	0.07	-0.30	0.25	0.74	0.23
C3Hf	1.49	0.14	4.42	10^{-4}	0.75	0.31	2.11	0.01
C57BL/6	0.26	0.14	1.29	0.06	-0.40	0.31	0.67	0.19
$B6CF_1$	0.40	0.18	1.49	0.03	0.15	0.22	1.16	0.50
$B6CF_2$	0.61	0.16	1.84	10^{-4}	0.39	0.23	1.48	0.10

* $\lambda(t)$ = Hazard Function for Poor Caging Environment
$\lambda_0(t)$ = Hazard Function for Improved Caging Environment
I = 1 if Poor Environment, 0 if Improved Environment
$\exp(\beta)$ = Relative Risk

Table 3. Effectiveness of Scaling Methods for Comparing Senescent Mortality Patterns Evaluated by the Number of Mouse Strains with Superimposable Hazard Functions

*Model: $\lambda_j(t) = \lambda_o(t) \exp(\Sigma\beta_j I_j)$

Significance Value	H_o: $\beta_j = 0$			
	Time Unscaled	Method of Scaling Time		
		EER	$MRDT_s$	MAD_s
$P \leq 0.05$	20	14	18	2
$0.05 < P \leq 0.10$	0	1	0	2
$P > 0.10$	1	5	3	17

* $\lambda_j(t)$ = Hazard function for mouse strain 'j'
$\lambda_o(t)$ = Hazard function for $B6CF_1$ mouse
I_j = 1 if strain 'j', 0 otherwise
$\exp(\beta_j)$ = Relative risk for strain 'j'

Table 4. An Interspecies Comparison of Senescent Mortality Using Time Scaled to the $B6CF_1$ Mouse

***Model: $\lambda_j(t) = \lambda_o(t) \exp(\Sigma\beta_j I_j)$**

Species	β_j	S.E.	Risk	P-Value
Beagle	-0.064	0.104	0.94	0.54
Human	-0.106	0.106	0.90	0.32

* $\lambda_j(t)$ = Hazard function for species 'j'
$\lambda_o(t)$ = Hazard function for $B6CF_1$ mouse
I_j = 1 if species 'j', 0 otherwise
$\exp(\beta_j)$ = Relative risk for species 'j'