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Research article

Biological evidence for limits to the duration of life

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Abstract

Projections of duration of life for humans based on mathematical models have led some researchers to claim that there is no lower limit to death rates or upper limit to life expectancy, and that a life expectancy of 100 will be achieved in the 21st century. To assess the biological plausibility of these claims, we examined temporal aspects of biological phenomena in three mammalian species. Our examination revealed that: (1) physiological declines associated with reproduction consistently occur at ages that are less than one-third of the median age at death, (2) physiological parameters associated with aging in humans lose eighty percent of their functional capacity by age 80, and (3) young versus old individuals can be distinguished by the pathologies detected at death. The biological evidence suggests that organisms operate under warranty periods that limit the duration of life of individuals and the life expectancy of populations. We use these findings to discuss the issue of limits to the duration of life and the validity of mathematical models used to forecast human longevity.

Introduction

When the Social Security program in the United States was created in 1935, the actuaries responsible for assessing the future solvency of the program were required to make forecasts of the number of beneficiaries that would draw annual benefits from the program. Consistent with accepted actuarial methodology, they devised a mathematical approach to extrapolate past trends in mortality and life expectancy into the future. The logic and methodology was simple. If life expectancy at birth increased by two years in the previous two decades, then the extrapolation model yielded a projected increase in life expectancy of two years in the subsequent two decades.

Throughout most of the 20th century the Social Security Administration (SSA) consistently underestimated the rise in life expectancy. The past invariably had slower rates of mortality improvement than the future. As a result, the upper limits to life expectancy projected by the SSA model were often exceeded within just a few years (Olshansky 1988). In addition, the SSA actuaries believed in a fixed biological limit to life, a now discredited view that at the time was supported by a widely accepted prediction that the rise in life expectancy would soon begin to abate (Bourgeois-Pichat 1978). In the latter part of the 20th century, the opposite problem occurred – the SSA overestimated the rise in life expectancy. This time the actuaries based their forecasts on a time period when declines in death rates at middle and older ages were the most rapid in recorded human history. Consequently, the observed increases were lower than the projected ones.

In recent years, the extrapolation model has been invoked to declare that history will repeat itself and human life expectancy will continue to rise far into the future. The latest reincarnations of the extrapolation model use longer time frames to compensate for fluctuating trends in life expectancy that occur

over the short-term (Lee et al. 1992). This long-term extrapolation model has been used to project that life expectancy at birth will continue to rise throughout the 21st century (Vaupel et al. 1986; Wilmoth 1998; Tuljapurkar et al. 2000). Recently, the historic rise in human life expectancy was described as one of the most remarkably regular events ever observed, and it was predicted that this trend would lead to a life expectancy at birth of 100 years by the year 2060 (Oeppen et al. 2002). The features shared by the extrapolation models used to forecast life expectancy are simplicity, proven reliability over the short-term, and a disregard of the biological evidence that contradicts their long-term applicability. Long-term forecasts of life expectancy and survival that are biologically realistic are essential to government agencies responsible for preserving the financial integrity of age-based entitlement programs like Social Security and Medicare.

The biodemography of aging

The morphological, physiological and biochemical attributes that exist within the current generation of any organism were fashioned by the blind eye of evolution from the biological materials that were available in preceding generations. Although this genetic legacy encompasses an extensive array of biological processes, those necessary for extreme longevity are not among them. As such, aging and death are inseparable partners to growth and development. The biological consequences of aging in the form of fatal and non-fatal aging-related diseases and disorders are revealed when individuals manage to live beyond their reproductive period. For humans and laboratory animals that are protected from environmental threats, remarkably predictable age patterns of morbidity and mortality (Olshansky et al. 1991; Carnes et al. 1996) suggest that the functional duration of bodies are constrained by what we will call '*biological warranty periods*'.[1]

Explanations for why death occurs and when the warranty period for living things expires can be found within the field of evolutionary biology (Williams 1957; Hamilton 1966). Although differing in the mechanisms involved, a common theme runs through the evolutionary theories of aging. It begins with the premise that the hostile environments of the natural world have always posed an insurmountable barrier to indefinite survival, making immortality unattainable even if organisms possessed a biology capable of eternal life (Carnes et al. 1993). No organism escapes death and the vast majority die prematurely from predation, starvation, and infectious diseases – causes of death that are largely extrinsic to the biology of aging (Carnes et al. 1997). Not only would the energy costs of maintaining the functional integrity of an organism for an indefinite time be prohibitively expensive (Kirkwood 1977), but a strategy that diverts physiological resources away from reproduction would be a recipe for certain failure in a world where extrinsic causes of death (Medawar 1952) make indefinite survival impossible (Weismann 1891). Faced with an implacably hostile world, life on earth discovered an effective strategy for coping with the inevitability of death. The solution was to make genes immortal rather than the bodies that carry them (Dawkins 1976).

We contend that the bodies of organisms are subject to biological warranty periods, and that the manifestations of aging are most clearly evident when the duration of life is extended beyond those warranty periods. Data on reproduction, physiological function over time, and the spectrum of pathology observed at death for three distinct mammalian species (mouse, dog and human) are used to explore the existence of biological warranty periods, and to identify their approximate expiration dates. Finally, limits on the duration of life of individuals and the life expectancy of populations, as well as the credibility of mathematical models that predict much higher life expectancies in the latter part of the 21st century will be discussed within the context of our biological findings.

Animal data

Duration of life experiments using a wide variety of laboratory mice (e.g., inbreds, hybrids, backcross generations) and the beagle dog were conducted over a 40-year period in the Biological and Medical Research Division at Argonne National Laboratory (ANL) in order to investigate the biological consequences of exposure to radiation (Grahn 1994; Grahn et al. 1995). Data on control animals from the extensive mortality and pathology databases compiled for these studies as well as reproductive data from the ANL breeding colony that produced them were used for all analyses in this paper involving laboratory animals. Additional pathology and mortality data for the beagle were provided by the Lovelace Respiratory Research Insti-

tute in Albuquerque, New Mexico – formerly known as the Inhalation Toxicology Research Institute.

Experimental protocol at ANL required that animals be allowed to die a natural death (i.e., medical interventions were not used to extend life). Pathology judgments were based on histological examinations performed by certified veterinary pathologists. When an animal died, a single cause of death was established (designated 'L'), pathologies judged to have contributed to death were identified (designated 'C'), and the remaining pathologies considered non-contributory (designated 'N') were also recorded. Mouse pathologies were assigned a unique four-letter pathology code, while the pathological assessment of dogs was based on codes from the Systematized Nomenclature of Medicine (SNOMED 1982) and the Systematized Nomenclature of Veterinary Medicine (SNOVET 1984). A translation between mouse and dog coding was created at ANL. When a cause of death could not be determined, the examining pathologist assigned cause of death unknown (CDU) to that animal.

The breeding colony of mice at ANL used single pair matings. The identity of every Dam and Sire for 22 strains (including inbreds, hybrids and backcross generations) were known and details of their reproductive history were recorded. Among these details were litter number (parity), gender and number of pups born, pup death prior to weaning, and the time interval (in days) between successive litters.

Human data

We used the most complete source of information on mortality in the United States – death certificates compiled by the National Center for Health Statistics (NCHS 1998). This file contains underlying and contributing causes of death for all recorded decedents in the United States in 1996. Each death record also contains information on age, sex, race, and up to 16 multiple causes of death, as well as basic demographic details of the decedents (e.g., marital status, usual occupation, education). The underlying cause is selected from an array of conditions reported in the medical certification section on the death certificate by the attending physician, and is defined as '(a) the disease or injury which initiated the train of events leading directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury'. These are then translated into standardized medical codes according to the 9th Revision of the International Classification of Diseases (ICD 1989). Because autopsies are rare (Johnson et al. 1998), the diagnoses reported on death certificates are not based on thorough pathological examination. We only considered deaths for individuals over age 20 because age-related diseases were the focus of our mortality analyses. We also applied a multiple cause pattern called the 'total mentions' approach which considers all conditions present on the death certificate, regardless of their relationship with other conditions listed (Hummer et al. 1998).

Human age-specific fertility rates were taken from reports produced by the National Center for Health Statistics (Ventura et al. 1998; NCHS 2002). In most cases, age of mother was computed from the mother's and infant's dates of birth as reported on the birth certificate. Information on age of father was also taken from birth certificates. Births with unknown paternal age were distributed in the same proportions as births with known paternal age within each five-year age classification of mother. Data representing a natural fertility population (the Hutterites) were taken from the published literature (Eaton 1953). Age-specific fertility rates for a high mortality/high fertility human population were generated as a composite fertility schedule based on survey data from the following three countries (equally weighted) – Mali (1987), Niger (1998), and Uganda (1988) (Demographic and Health Surveys 2002). These countries were chosen because all three had total fertility rates (TFR; total births per woman) in these years that exceeded 7.0. Single-year-of-age fertility rates for this population were then generated through a linear interpolation between the mid-year fertility estimates for the five-year age groups.

Methods

For the most frequently used mice in the ANL experiments (five strains: A/Jax, BALB/c, C57BL/6, C57L; and one hybrid: $B6CF_1$) the database for the breeding colony was used to calculate average values for litter size, pup mortality in the pre-weaning period, and the time interval between parities for every Dam (Grahn 1972). These reproductive summary statistics were plotted as a function of maternal age. For 22 mouse strains (including those previously mentioned), reproductive data from the breeding colony were used to estimate an effective end of reproduction (EER) for each Dam. EER was operationally defined as the

maternal age when a Dam's cumulative lifetime births reached 75% and pre-weaning pup mortality within a litter exceeded 35%. An average EER was then calculated for each of the 22 strains. For the control mice produced from these matings, a Gompertz distribution generalized for competing risks was used in order to estimate a median age at death (MAD) for causes of death judged from pathologic examination to have arisen from genetic and/or degenerative processes. These MAD values were then used as the dependent variable in a regression analysis with EER as the sole predictor variable.

For the investigation of age-dependent change in the types and frequency of pathology detected at death (subsequently referred to as pathology shifts), the pathology codes for the $B6CF_1$ mouse (the most frequently used mouse, and the one with the most detailed pathology data) and beagle dog were classified into a number of non-overlapping categories referred to as combined pathology groups. Two causes of death (cancer and diseases of the cardiovascular system) were chosen because these two disease categories also account for the vast majority of human deaths. Because of their importance, cancer and cardiovascular disease were further partitioned into their 'L', 'C' and 'N' subgroups (see Data description for definitions). For the $B6CF_1$ mouse, the remaining combined pathology groups were organized around organ systems: liver and biliary tract, lungs and pleura, reproductive organs and urinary tract. The greater pathology detail available for the beagle dog permitted additional groups to be established: digestive system, endocrine, hematopoietic, skeletal system and skin. Similarly, the death certificate data for humans permitted not only the inclusion of the pathology groups used for the beagle, but also categories for diseases of the eye and adnexa, mental disorders and diseases of the nervous system. Finally, codes not falling into any of the specific pathology groups were assigned to a miscellaneous group referred to as 'other'. Except for cancer and cardiovascular diseases, no distinction between L, C or N was made (i.e., no distinction was made between lethal, contributory or non-contributory pathologies). For every animal, the number of pathologies falling within each of the combined pathology groups was determined. In other words, the multiple pathology records that exist for an individual animal were collapsed into one record per animal containing counts for each of the pathology categories – subsequently referred to as counting bins.

Age at death plus the counting bins arising from the above pathology classifications were used as explanatory variables in logistic regression analyses (SAS 1995). In logistic regression, the response variable is dichotomous. For example, in these analyses the response variable was set to 0 or 1 in order to indicate group membership (e.g., cause of death known or unknown). The logistic model then uses the explanatory variables to predict the probability (p_i) that the response variable for a particular individual is either 0 or 1:

$$\text{logit}(p_i) = \log[p_i/(1 - p_i)] = \alpha + \sum \beta_i x_i \qquad (1)$$

where α is a constant (like an intercept in ordinary regression), β_i are logistic regression coefficients, x_i are the explanatory variables (i.e., age at death and the pathology counting bins), $p_i/(1 - p_i)$ is the odds ratio, and $\log[p_i/(1 - p_i)]$ is the log odds ratio or logit (Kleinbaum 1994). In other words, we used age at death and the frequency and identity of pathologies observed at death (i.e., the combined pathology counting bins) in the logistic model in order to predict a probability that a particular individual is a member of the population specified by the binary response variable. All available explanatory variables were included in the initial model, and a final model was achieved by the progressive elimination of non-significant predictors of group membership.

Two different logistic regression models were formulated. In one model the binary response was a contrast between individuals (performed for both laboratory animals and humans) that died at older and younger ages. Young or old was operationally defined as individuals that died in the first or fourth quartile of the death distribution respectively. In the other logistic model, the pathology data for the $B6CF_1$ mouse were used to compare mice that died of known causes of death to those where a cause of death could not be determined. The two logistic models differed slightly in the way that the pathology counting bins were used as predictor variables. All of the counting bins (including the L, C and N distinctions) were used in the young versus old contrast. The L, C or N designations were never used in the analysis of unknown causes of death because any pathology with an L or C designation would, by definition, be a perfect predictor of whether an animal did or did not have a known cause of death.

Proportional hazard models (Cox 1972) were also used to investigate the mortality dynamics of $B6CF_1$

mice dying from unknown causes. A proportional relationship between the hazard function for animals dying of a known cause, $\lambda_0(t)$, and animals dying from an unknown cause, $\lambda(t,I)$, was assumed:

$$\lambda(t, I) = \lambda_0(t)\exp[\beta * I] \quad (2)$$

where β is the regression coefficient, I is a binary indicator variable (I = 0 or 1) used to distinguish between animals dying from an identified cause (I = 0) and those where a cause of death could not be determined (I = 1), and $\exp[\beta * I]$ is the relative risk. This model parameterization generates a test formally identical to the Kaplan–Meier test traditionally used to evaluate the equality of cumulative survivorship curves. A more detailed inspection of mortality dynamics was achieved by partitioning the distribution of failure times (all deaths) into quartiles. The previously described hazard model was then applied within each quartile. Deaths falling outside the quartile being analyzed were considered censored observations (i.e., contributing to mouse days at risk, but not counted as events). This modeling approach is equivalent to taking the Kaplan–Meier homogeneity chi-square statistic for the entire age spectrum and dividing it into four additive pieces (Kalbfleisch et al. 1980) – one for each quartile. In other words, age patterns of mortality for known and unknown causes of death were compared conditional upon having survived to and died within a specified quartile of the cumulative survivorship distribution for all causes of death. Males and females were analyzed separately.

Results

Reproductive biology

Measures of reproductive performance are plotted (Figures 1–3) for the five mouse strains (A/Jax, BALB/c, C57BL/6, C57L) and hybrid (BCF_1) most frequently used in the ANL studies. Although variation in reproduction among mouse strains exists, the biological consequences of increasing maternal age are evident. Mean litter size decreases (Figure 1), pre-weaning pup mortality increases (Figure 2), and the time interval between parities lengthens (Figure 3). Further, these signs of physiological decline are consistently occurring at ages that are approximately 1/3 of the MAD for these mouse strains. The trend line (linear regression) in Figure 4 shows that MAD increased for mouse strains whose mothers

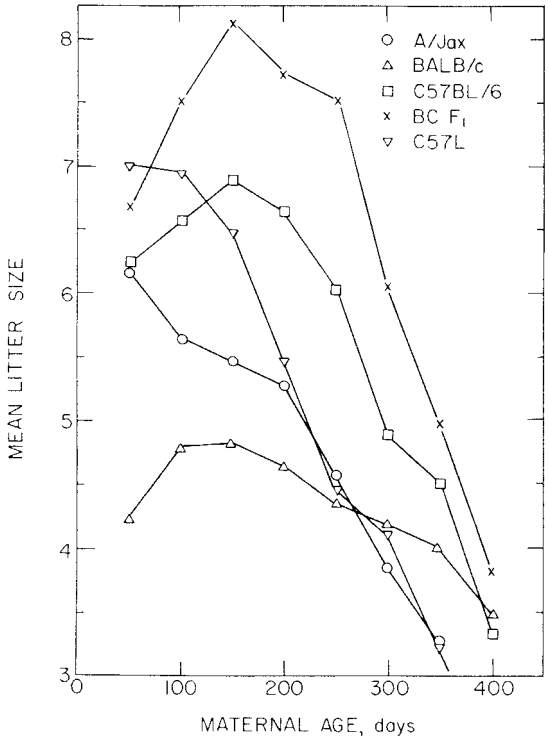

Figure 1. Mean litter size at birth plotted as a function of maternal age for four mouse strains (A/Jax, BALB/c, C57BL/6, C57L) and the hybrid (BCF_1) arising from a cross of the BALB/c and C57BL/6 strains (see Grahn (1972, 1994) for more details).

were capable of reproducing effectively at older ages (EER). This linkage between longevity and reproduction observed in mice is consistent with research findings for humans (Holliday 1996; Perls et al. 1997).

Figure 5 presents age-specific cumulative fertility for human females and males. The fertility data for females come from a developed country (United States), a natural fertility population (Hutterites), and a high mortality/high fertility population (a composite of women from Mali, Niger and Uganda). Cumulative fertility for males is depicted only for the male population of the United States in 1996. These data illustrate a consistent age pattern of reproduction that appears almost entirely uninfluenced by socioeconomic status, vast differences in mortality, and variation in the availability and use of contraception. In two of the three populations, children have been born to females as young as 10 years of age. Young births either do not occur or are not reported in the Hutterite population because marriage is not permitted until age 18. The figure demonstrates that approximately 75% of the cumulative reproductive output in these populations

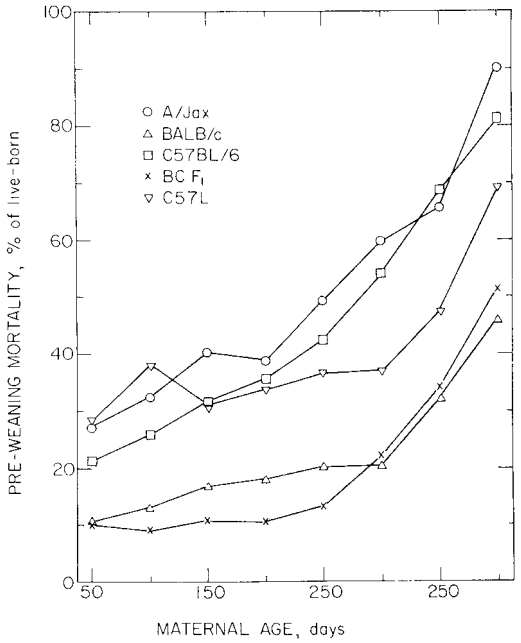

Figure 2. Mortality in pups prior to weaning (expressed as a percent of live births) plotted as a function of maternal age for four mouse strains (A/Jax, BALB/c, C57BL/6, C57L) and the hybrid (BCF_1) arising from a cross of the BALB/c and C57BL/6 strains (see Grahn (1972, 1994) for more details).

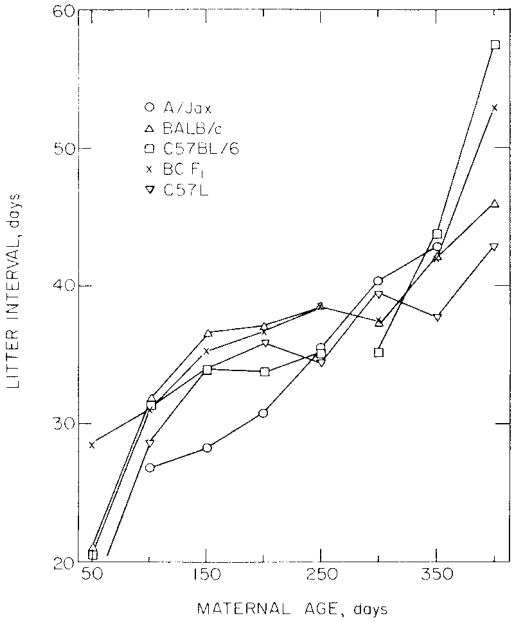

Figure 3. The interval width (in days) between successive parities plotted as a function of maternal age for four mouse strains (A/Jax, BALB/c, C57BL/6, C57L) and the hybrid (BCF_1) arising from a cross of the BALB/c and C57BL/6 strains (see Grahn (1972, 1994) for more details).

is accomplished by the age of 35 for both males and females.

The regression equation that was used to predict the median age of intrinsic death of offspring from their mother's age at the effective end of reproduction for 22 strains of mice is provided in the header of Table 1 and illustrated in Figure 4. This equation, estimated from data for mice, was then used to predict MAD values for humans. In order to be consistent with the definition used for mice, the EER values used to represent humans (ages ranging from 32 to 38) in the mouse model were selected from the cumulative fertility plots for humans (Figure 5) evaluated at 75%. Using these values, the mouse model predicted that the median age of intrinsic mortality for humans (males and females combined) should fall between the ages of 82 and 97 years (Table 1).

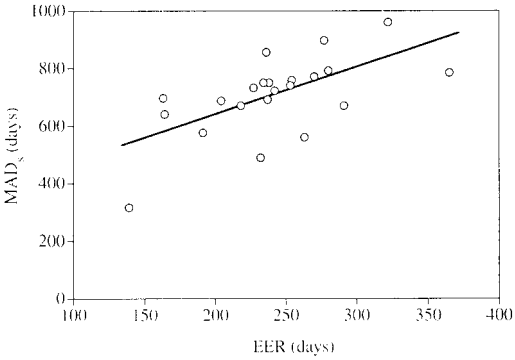

Figure 4. The linear regression and observed data points for the Gompertz estimated median age at death (MAD for intrinsic causes) for 22 mouse strains (i.e., inbreds, hybrids and backcross generations) plotted as a function of the age (EER, in days) when the females that gave birth to those animals were no longer capable of effective reproduction (i.e., cumulative births >75% and pre-weaning pup mortality >35%; see Grahn (1972) and Carnes et al. (1996) for more details).

Pathology

A comparison of pathology profiles between young and old $B6CF_1$ mice is summarized in Table 2. Young mice were defined as those dying within the first quartile of the failure distribution (before 844 days for females and 854 days for males) while old mice were defined as individuals surviving into the fourth quartile of the failure distribution (beyond 1,103 days for females and 1,123 days for males). Old animals of either sex died with a significantly elevated tumor burden as well as an increased number of patholo-

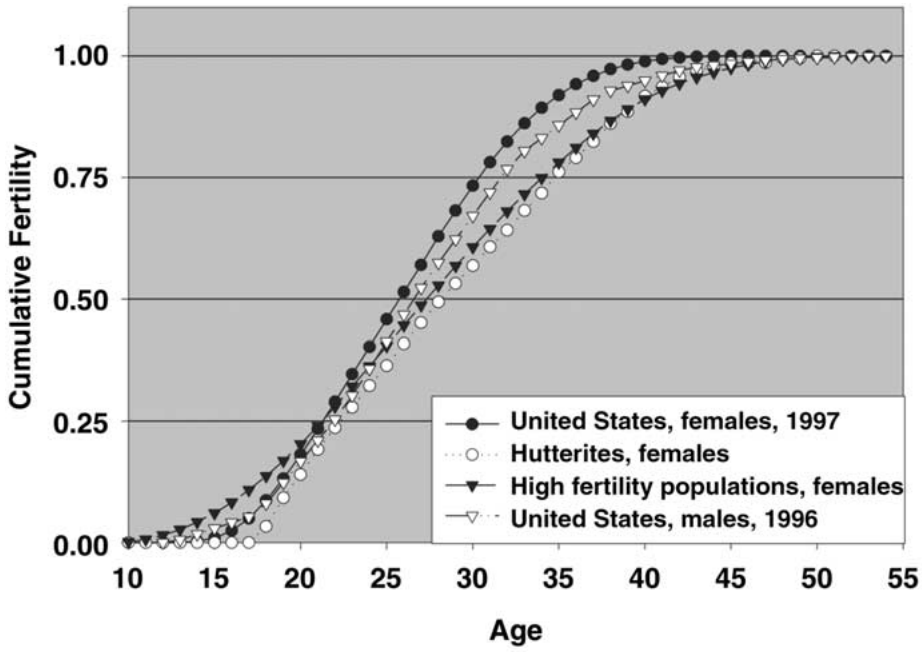

Figure 5. Age-specific fertility rates for US males (1996), and females for a low mortality/low fertility population (US, 1997), a natural fertility population (Hutterites) and a high mortality/high fertility population (a composite of Mali 1987; Niger 1998; Uganda 1988) plotted as a function of age (in years).

Table 1. Regression of median age at death for intrinsic causes of death (MAD) on effective end of reproduction (EER) estimated from mouse data and applied to hypothetical human data.

Human EER (years)	Human EER (days)	Human MAD (years)
32	11680	81.8
34	12410	86.9
36	13140	92.0
38	13870	97.0

MAD = 195 + 2.54 EER; $R^2 = 0.44$.

gies associated with the cardiovascular, lung and pleura, and reproductive organs. This interpretation changes little when the predictor variables for cancer and cardiovascular disease are split into their lethal (L), contributory (C) and nonlethal (N) subcategories. With the one exception of lethal tumors in males, all categories of cancer involvement were elevated in animals that died at old ages. This more detailed pathology diagnosis also reveals that the greater burden of cardiovascular disease in older animals of either sex is driven by conditions that contributed to death but were not the primary cause of death.

The results of an identical logistic regression analysis applied to the pathology data for beagle dogs are summarized in Table 3. In beagles, the first (before 4,093 days for females and 4,406 days for males) and fourth (5,385 days for females and 5,565 days for males) quartiles of the all-cause failure distribution were once again used as an operational definition of whether animals died at either young or old ages. Unlike the $B6CF_1$ mouse, only tumors judged to have neither killed nor contributed to death were elevated in dogs dying at older ages. Cardiovascular disease also had no discriminatory power in the dog analysis. The only pathology other than incidental tumors that was elevated in old dogs was diseases of the skeletal system. Endocrine, pulmonary and skin diseases were also significant predictors of when dogs died, but these pathologies were elevated in animals that died at young ages rather than at older ages.

The logistic regression results for human pathology are summarized in Table 4. In humans, death at younger ages was defined as occurring between 20 and 50 years of age, while death beyond age 80 was considered to have occurred at older

Table 2. Summary of odds ratios and their (*P*-values) generated from logistic regression analyses used to contrast deaths in the first (young) and fourth (old) quartile of the failure distribution for $B6CF_1$ mice. Odds ratios greater than one indicate elevated pathologies in old animals. *P*-values = (0.00) represent significance values less than (0.001). L = cause of death, C = contributing to death and N = observed at death. NA means variable not included in final model.

	Cancer			Cardio				
Sex	L	C	N	L	C	N	Pul	Repro
F		2.85 (0.00)			1.50 (0.01)		2.21 (0.00)	2.01 (0.00)
	4.03 (0.00)	2.72 (0.00)	2.59 (0.00)	NA	1.74 (0.00)	NA	2.20 (0.00)	2.07 (0.00)
M		2.29 (0.00)			2.28 (0.00)		2.45 (0.00)	5.86 (0.03)
	NA	2.55 (0.00)	2.52 (0.00)	NA	2.29 (0.00)	NA	2.36 (0.00)	NA

Cancer: diseases involving cancer.
Cardio: diseases of the cardiovascular system.
Pul: diseases of the respiratory system (lungs and pleura).
Repro: diseases of the reproductive organs.

Table 3. Summary of odds ratios and their (*P*-values) generated from logistic regression analyses used to contrast deaths in the first (young) and fourth (old) quartile of the failure distribution distribution for the beagle dog. Odds ratios greater than one indicate elevated pathologies in old animals. *P*-values = (0.00) represent significance values less than (0.001). L = cause of death, C = contributing to death and N = observed at death. NA means variable not included in final model.

	Cancer						
Sex	L	C	N	Endo	Pul	Skel	Skin
F	0.23 (0.01)	NA	1.37 (0.01)	NA	NA	2.58 (0.02)	0.36 (0.01)
M	NA	NA	2.22 (0.00)	0.65 (0.12)	0.42 (0.01)	2.07 (0.07)	NA
Both	0.33 (0.00)	NA	1.54 (0.00)	NA	0.62 (0.01)	2.21 (0.00)	0.51 (0.01)

Cancer: diseases involving cancer.
Endo: diseases of the endocrine system.
Pul: diseases of the respiratory system.
Skel: diseases of the musculoskeletal system and connective tissue.
Skin: diseases of the skin and subcutaneous tissue.

ages. The striking feature of the analyses of human pathology observed at death is the number of significant disease categories. Every disease category examined, other than the liver, exhibited pathology burdens in both males and females that were elevated in individuals dying at older ages. In addition, notable gender differences were observed for cardiovascular diseases, mental disorders, and diseases of the reproductive system.

Table 5 contains a summary of the proportional hazard model analyses used to make mortality contrasts between $B6CF_1$ mice dying of known causes versus those where a cause of death could not be determined. The *a priori* hypothesis was that animals dying at older ages have so many things going wrong with them (i.e., generalized organ failure) that it becomes extremely difficult to identify a specific cause of death. If true, then mice classified as having died of cause of death unknown (CDU) should tend to die at older ages than mice with an identifiable cause of death. Although the results of the mortality analyses were consistent with this hypothesis, the reality was more complicated. Mortality comparisons made within quartiles of the failure distribution revealed that mice diagnosed with CDU in the first quartile died earlier (i.e., relative risk greater than one) than non-CDU animals. However, once mice survive beyond the first quartile (approximately 850 days), the CDU animals died at significantly older ages than those dying of known causes (i.e., relative risk less than one).

The logistic regression results summarized in Table 6 provide additional support for the hypothesis that CDU animals have a more complex pathology profile than mice dying of known causes. Although mice with CDU listed as a cause of death had a higher overall burden of pathology at the time of death, the logistic regression analysis revealed that this elevated

Table 4. Summary of odds ratios and their (*P*-values) generated from logistic regression analyses of human data (intrinsic mortality) used to contrast the pathology burden at younger ages (20–50 years) to that observed at older ages (over 80 years). Odds ratios greater than one indicate elevated pathologies in older humans. *P*-values = (0.00) represent significance values less than (0.001).

Sex	Cancer	Cardio	Dig	Endo	Eye	Hema	Kidur
F	1.52 (0.00)	4.26 (0.00)	2.76 (0.00)	1.11 (0.00)	2.39 (0.00)	1.28 (0.00)	1.66 (0.00)
M	1.78 (0.00)	2.00 (0.00)	1.47 (0.00)	0.83 (0.00)	1.42 (0.01)	1.29 (0.00)	1.86 (0.00)
Sex	Lvr	Ment	Neur	Pul	Repro	Skel	Skin
F	0.19 (0.00)	9.52 (0.00)	2.39 (0.00)	2.85 (0.00)	0.82 (0.09)	1.48 (0.00)	3.14 (0.00)
M	0.22 (0.00)	2.16 (0.00)	1.53 (0.00)	3.40 (0.00)	12.23 (0.01)	1.69 (0.00)	2.11 (0.00)

Cancer: diseases involving cancer (ICD 140-239).
Cardio: diseases of the circulatory system (ICD 390-459).
Dig: diseases of the digestive system (ICD 520-579).
Endo: endocrine, nutritional, and metabolic diseases and immunity disorders (ICD 240-279).
Eye: disorders of the eye and adnexa (ICD 360-379).
Hema: diseases of blood and blood-forming organs (ICD 280-289).
Kidur: diseases of urinary tract (ICD 580-599).
Lvr: diseases of liver and biliary tract (ICD 571-575).
Ment: mental disorders (ICD 290-319).
Neur: diseases of the nervous system other than sense organs (ICD 320-359).
Pul: diseases of the respiratory system (ICD 460-519).
Repro: diseases of the reproductive organs (ICD 600-629).
Skel: diseases of the musculoskeletal system and connective tissue (710-739).
Skin: diseases of the skin and subcutaneous tissue (ICD 680-709).

burden could not be linked to any specific organ system – a finding consistent with generalized organ failure (i.e., multiple pathologies distributed across multiple organ systems).

Physiological parameters

The physiological changes that occur in humans with the passage of time have been documented in the scientific literature and known for decades (e.g., Falzone et al. 1956; Shock 1957; Norris et al. 1956). Some of these changes are described in a seminal article published in 1960 and still frequently cited (Strehler 1960) in which the percentage of reserve capacity remaining for various organ systems was estimated for humans between the ages of 20 and 90. Reserve capacity or vitality was described as a quantifiable age-dependent change in functioning between the maximum levels observed at birth and a lower limit of functioning that was defined by the lowest measured individual value, by organ system, for a population. Average values of reserve capacity by organ system were then calculated within selected age ranges. Eight separate parameters of reserve capacity (e.g., nerve conduction velocity, basal metabolic rate, maximal breathing capacity, standard cell water, standard renal plasma flow, vital capacity, standard glomerular filtration rate, and cardiac index) were observed to have declined steadily with chronological age to about 20% by age 80. Reserve capacity was at approximately 70–80% at age 20 for the same parameters.

Others researchers have also documented consistent patterns of change in physiological parameters associated with aging. For example, concentrations of free testosterone circulating in the serum of males were shown to decline at a consistent age-dependent rate after age 50, leading to a steady rise in hypogonadism that reaches 50% by age 80 (Harman et al. 2000). When a more sensitive measure of serum testosterone is used, the percentage of males experiencing hypogonadism by age 80 climbs to 94%. Using longitudinal data, it has been demonstrated that between the ages of 30 and 70, fat-free body mass for males declined by an average of 3 kg per decade (Forbes et al. 1970; Flynn et al. 1989; Flynn et al. 1992). Women were found to have lost fat-free body mass only after age 50, which coincides with the onset of menopause. Interestingly, the rate of loss of both muscle and body mass are amenable to modification through diet and exercise (Fiatarone et al.

Table 5. Summary of relative risks and their (*P*-values) generated from a proportional hazard model used to compare age patterns of mortality for $B6CF_1$ mice dying of known causes to those where a cause of death could not be determined (CDU). Relative risks less than one indicate that CDU animals have a lower age-specific risk of death (i.e., dying at older ages) within the specified time window than mice where a cause of death could be determined. *P*-values = (0.00) represent significance values less than (0.001).

	Relative risks (*P*-value) within quartiles of the failure distribution				
Sex	1st quartile	2nd quartile	3rd quartile	4th quartile	Quartiles 2–4
F	2.21 (0.00)	0.93 (0.75)	0.48 (0.01)	0.74 (0.11)	0.79 (0.01)
M	1.21 (0.26)	0.65 (0.04)	0.63 (0.02)	0.79 (0.15)	0.70 (0.00)

Table 6. Summary of odds ratios and their (*P*-values) generated from logistic regression analyses used to contrast deaths for $B6CF_1$ mice with known causes to those where a cause of death could not be determined (CDU). Odds ratios greater than one indicate elevated pathologies in CDU animals. *P*-values = (0.00) represent significance values less than (0.001). NA means variable not included in final model.

Sex	Cancer	Cardio	Kidur	Lvr	Pul	Repro	Total
F	0.11 (0.00)	0.40 (0.00)	0.34 (0.00)	0.19 (0.00)	0.29 (0.00)	0.40 (0.00)	3.29 (0.00)
M	0.11 (0.00)	0.39 (0.00)	0.19 (0.00)	0.18 (0.00)	0.33 (0.00)	NA	3.76 (0.00)

Cancer: diseases involving cancer.
Cardio: diseases of the circulatory system.
Kidur: diseases of urinary tract.
Lvr: diseases of liver and biliary tract.
Pul: diseases of the respiratory system.
Repro: diseases of the reproductive organs.
Total: total number of pathologies observed within an animal.

1990), but significant age-related declines still appear to be inevitable. Many other age-related changes in the physiological functioning of the human body have been documented, including the loss of maximum oxygen consumption (Astrand 1960), increase in systolic blood pressure (Lakatta 1979), loss of total body water that influences cardiac output (Goldman 1970), loss of lean body mass (Novak 1972), decline in the mineral content and density of bones (Garn 1975), and many others. Although many of these and other physiological parameters associated with aging have been shown to be amenable to partial modification through physical exercise (Bortz 1982), a large increase in life expectancy is not among the benefits derived from lifestyle modifications.

Discussion

It has been suggested that there is no demographic evidence from recent trends in mortality for the existence of limits on the life expectancy of humans, or that low mortality populations are approaching such limits if they do exist. It has been further suggested that there are no biological or demographic reasons why death rates for humans cannot decline to zero (Wilmoth 2001). If death rates for humans can decline to zero, then it follows that limits cannot exist for either the life span of individuals or the life expectancy of populations. In this study, we demonstrated that for mice, dogs and humans there are verifiable and consistent age-dependent changes in each species' reproductive biology, underlying physiology, and pathology burden that support the conclusion that the bodies of living things (including humans) are subject to biological warranty periods that limit the duration of their lives.

If most humans, on average, are biologically capable of living to 100 years or more as claimed (Vaupel 1997), then there should be little evidence of significant functional decline or pathologic anomaly among people living to the average survival times (75–80 years) that are already being attained today. The same logic should apply to other species as well. To examine this issue, the life courses of the mouse, dog and human were first partitioned into biologically meaningful age windows. Age-related changes in reproduction, physiological function and the pathology observed at death were then

examined in order to determine whether biological changes consistent with the effects of aging could be detected within these windows. The goal was to determine whether this biological evidence was more consistent with bodies capable of much longer survival than is currently observed, or with bodies that have approached or even surpassed (via medical interventions) the expiration date of their biological warranty periods.

The earliest age window examined was the reproductive period – a period of the life span dominated by a biology thought to play a major role in why and when aging occurs (Carnes et al. 1999). The data for female mice demonstrate that indicators of physiological decline in reproduction (e.g., smaller litter sizes, lower pup survival, longer intervals between litters) were detectable at ages that were only 1/3 of the median age at death for the mouse strains examined. The reproductive data for human females from a broad range of fertility and mortality backgrounds demonstrate that some girls as young as 9 years of age have given birth, and that by 35 years of age approximately 75% of the reproduction that will be accomplished by females, has been accomplished. Just like female mice, the reproductive age window for human females opens and closes at ages that are far younger than the life expectancy at birth currently achieved by women in low mortality countries (80 years). In addition, this age pattern of female fertility is remarkably similar for high mortality, low mortality and natural fertility populations (see Figure 5). These data suggest that like female mice (see Figures 1–3), the reproductive biology of human females is well defined and follows a stable and highly predictable time course. If evolutionary theories of aging are correct, the reproductive biology of a species is intimately related to the temporal manifestations of aging and the age distribution of death (Charlesworth 1994; Holliday 1996; Ellison 2001). The largely immutable reproductive biology observed for female mice and humans and the predictable age patterns of their respective mortality are consistent with bodies that are subject to biological warranty periods.

Unlike females, human males do not experience an abrupt cessation of reproductive capacity with age (Vermeulen 2000). Researchers have looked for andropause, the male equivalent of menopause, but have been unable to find it. Instead, there are: (1) documented cases of 90-year-old men becoming fathers, (2) data showing that 50% of 80-year-old men remain fertile, and (3) studies showing that infertility problems among couples rarely involve the male partner (Schill 2001). Nevertheless, males do experience age-related declines in reproductive capacity which include reductions in the number of Leydig (testosterone producing) cells, a parallel decrease in bio-active testosterone, diminished adrenal androgen secretion, morphological alterations (thickening and hernia-like protrusions) of the seminiferous tubules, increases in structural chromosomal abnormalities in spermatozoa, and lower libido (Plas et al. 2000). The greater risk of birth defects (especially heart-related disorders) associated with older fathers (Lian et al. 1986) – tentatively linked to transcriptional errors arising from the continuous cell division in spermatogenesis – has led the American Fertility Society to recommend an age cutoff of 50 years for semen donors (Bordson et al. 1991). Reproductive data like these suggest that while most males are biologically capable of reproducing longer than females, their age patterns of fertility exhibit a decline remarkably similar to that observed in females (Figure 5).

The fertility data presented in this paper are for 20th century humans. Since many women in modern times consciously delay their fertility, it is likely that the ages associated with specified levels of cumulative fertility for modern women are higher than those experienced by their ancestors. As such, the median age at death for humans from intrinsic causes estimated from the mouse model probably err on the high side (see Table 1). Intrinsic mortality was used as an endpoint in order to eliminate the contaminating influence of extrinsic causes of death (i.e., accidents, homicide, infectious and parasitic diseases, suicide) that vary so dramatically between populations (Shryock et al. 1975). If humans adhere to the same relationship between reproduction and longevity as mice, then the predicted median age of death from intrinsic causes would be less than 100 years (see Table 1). Furthermore, because deaths from extrinsic causes can never be completely eliminated, a more realistic estimate of life expectancy for humans as predicted from the mouse model would be in the range of 85–95 years. This result is incompatible with the prediction from extrapolation models that life expectancy for humans will reach or exceed 100 years in the 21st century.

Next, the age window under examination was expanded to include the post-reproductive period – a period of the life span that has typically been associated with a loss of functional integrity (Fries 1980). For a wide range of physiological parameters derived

from published studies of humans, approximately 80% of functional capacity is lost by age 80. Significantly, this is an age that, when viewed in terms of life expectancy, has been achieved by only a few populations (i.e., among females in some parts of the world). Because there is no aging or death program, the age-dependent rate of loss of some but not all of this lost functional capacity can be reduced through exercise, diet, and with medications. Nevertheless, the biological evidence is clear; the documented degradation of function (vital capacity) over time for numerous physiological parameters is consistent with bodies whose duration of functional existence is subject to biological warranty periods.

The data on the pathology burdens observed at death provide incontrovertible evidence that age takes a severe toll on the bodies of mice, dogs and humans. Laboratory animals surviving to the 4th quartile of the failure distribution (operationally defined as old age in this paper) experienced an increased burden of tumors that neither caused nor contributed to death, more pulmonary disease, and more frequent diseases of the skeleton. Using nothing more than this pathology profile, it was possible to statistically distinguish animals that died old from those that died young. Although death certificate data for humans are far less reliable than the pathology diagnoses available for laboratory animals, the pathology implications are no less conclusive. For humans dying over the age of 80, every organ system exhibits a greater burden of disease involvement (abnormal pathology) than was observed in people dying before age 50. As with the reproductive and physiology data, humans have an age-related pathology burden that is consistent with bodies that are subject to biological warranty periods that limit the duration of life.

Conclusions

The regularity of the rise in human life expectancy during the 20th century perceived by the advocates of mathematical extrapolation has led them to predict that a continuation of this trend into the future will produce a life expectancy of 100 years by the year 2060. Dramatic reductions in childhood death rates were responsible for most of the unprecedented life expectancy gains achieved during the 20th century. Duplicating these gains in low mortality populations is not possible because the lives of children can only be saved once.

The advocates of mathematical extrapolation also ignore the biomedical significance of the profound shift that has occurred in the causes of death. Historically, infectious and parasitic diseases (extrinsic mortality) caused the vast majority of deaths in humans. Heart disease, cancer, stroke and diabetes (intrinsic mortality) dominate the mortality schedule today. Biologically, there is no reason to expect that these two fundamentally different categories of death should or would adhere to the same mortality trend.

Contrary to the perception of those advocating extrapolation methods for projecting life expectancy, the time frame from the past that has been used to predict the future is anything but representative of the historical mortality experience of humans. The quantum leap in life expectancy achieved over the last 100 years is an unprecedented anomaly in a human history better characterized by fluctuating (Olshansky et al. 1996), stagnating, or slowly rising trends in life expectancy (McNeill 1976). Because the future course of mortality cannot possibly mimic such an episodic anomaly (characterized by declining early age mortality), this unusual time frame should not be used as the basis for predicting the future course of human life expectancy. The public policy implications of this recommendation are evident; it is essential that government agencies responsible for assessing the future solvency of their age-based programs incorporate biological reasoning into their long-term forecasts.

Death is a biological phenomenon of individuals, not a mathematical property of populations, and the biological evidence is undeniable. The pathology burden within individuals clearly exhibits an age dependence. Cancer and cardiovascular disease are symptoms of a complex underlying age-related pathogenesis that causes cells to lose functionality; a functionality that is necessary for the health and well-being of the individual. The molecular repair processes that maintain the functional integrity of cells also degrade over time. Managing the symptoms of age-related disease (geriatric medicine) is not the same as intervening in the underlying processes (biogerontology) that give rise to these manifestations (Hayflick 2000; Carnes et al. 2001). Although evolution does not and cannot produce genetic programs for aging or death, forces of deterioration that exist at virtually all levels of biological organization (e.g., molecules, cells, tissues, organs) lead to the undeniable conclusion that there is a limit (expiration date) to how long (warranty period) an individual can live. Since every

member of a population is operating under their own unique warranty period, then it is equally impossible to deny that limits also exist for the life expectancy of populations.

Although aging and death are not programmed, they are nevertheless a predictable byproduct of stable reproductive biologies that evolved under environments far less conducive to survival than those experienced today. Although it is likely that anticipated advances in biomedical technology and lifestyle modification will permit life expectancy to continue its slow rise over the short-term, a repetition of the large and rapid gains in life expectancy observed during the 20th century is extremely unlikely. Such gains would require an ability to slow the rate of aging (Miller 2002; de Gray et al. 2001) – a technological capability that does not exist today, and even if it did, would require implementation on a broad scale in order to have a measurable impact on the vital statistics of a population (Olshansky et al. 2001). As such, mathematical models that assume the future course of life expectancy over the long-term will continue the trend observed during the 20th century will inevitably fail because they ignore the underlying biology that influences duration of life. Further, the predictions of extreme longevity (life expectancy of 100 years or more) produced by these models are not supported by the biological evidence. Life expectancy is a statistic derived from a population of individuals whose biology is the product of an evolutionary history that established the tempo of growth, development and maturation needed to survive and reproduce. The image of a biological warranty period for the duration of life was used to capture a universal and undeniable biological reality – indefinite survival is not possible, and the duration of life would remain limited by biological constraints even if every cause of premature death could be eliminated.

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Note

1. Terms like longevity, duration of life and life span are generic measures of how long an individual exists. Although circumscribed survival is implied, these terms make no distinction between lives that are cut short by premature death and life span potentials that are achieved by individuals. Further, these terms convey no sense of why length of life has or should have limits. The image of 'biological warranty periods' was our attempt to remedy these shortcomings. A warranty period explicitly suggests a time frame within which failures are not anticipated. Using 'biological' as an adjective restricts the warranty to biological failures, and implies that failures of biological origin are likely to occur when survival extends beyond the warranty period. In this sense, a warranty period for duration of life is shorthand for the widely accepted view (Olshansky et al. 2002) that the accumulation of damage to the basic building blocks of life (DNA, proteins, carbohydrates and fats) eventually exceeds the maintenance and repair capacities of the body, which then renders the individual vulnerable to forces of morbidity and mortality. Unlike mechanical devices, biological warranty periods are an inadvertent byproduct of evolutionary neglect, and genetic programs for growth, development and reproduction.

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