The Quest for a General Theory of Aging and Longevity

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Extensive studies of phenomena related to aging have produced many diverse findings, which require a general theoretical framework to be organized into a comprehensive body of knowledge. As demonstrated by the success of evolutionary theories of aging, quite general theoretical considerations can be very useful when applied to research on aging. In this theoretical study, we attempt to gain insight into aging by applying a general theory of systems failure known as reliability theory. Considerations of this theory lead to the following conclusions: (i) Redundancy is a concept of crucial importance for understanding aging, particularly the systemic nature of aging. Systems that are redundant in numbers of irreplaceable elements deteriorate (that is, age) over time, even if they are built of elements that do not themselves age. (ii) An apparent aging rate or expression of aging is higher for systems that have higher levels of redundancy. (iii) Redundancy exhaustion over the life course explains a number of observations about mortality, including mortality convergence at later life (when death rates are becoming relatively similar at advanced ages for different populations of the same species) as well as late-life mortality deceleration, leveling off, and mortality plateaus. (iv) Living organisms apparently contain a high load of initial damage from the early stages of development, and therefore their life span and aging patterns may be sensitive to early-life conditions that determine this initial damage load. Thus, the reliability theory provides a parsimonious explanation for many important aging-related phenomena and suggests a number of interesting testable predictions. We therefore suggest adding the reliability theory to the arsenal of methodological approaches applied to research on aging.

Introduction

Interest in understanding the process of aging is growing and has led to a need for a general theoretical framework that would allow researchers to explain many diverse observations related to this phenomenon. Such observations have become so abundant that a special four-volume encyclopedia, *The Encyclopedia of Aging* (1591 pages), is now required for even partial coverage of the accumulated facts (*1*). To transform these numerous and diverse observations into a comprehensive body of knowledge, a general theory of species aging and longevity is required.

The prevailing research strategy is to focus on the tiny details in the hope of understanding the proverbial nuts and bolts of the aging process. In accordance with this reductionist approach, the aging of organisms is often explained through the aging of organisms' components. However, this kind of reasoning of assuming aging in order to "explain" aging eventually leads to an interesting situation, because when moving in succession from the aging of organisms to the aging of organs, tissues, and cells, we eventually come to atoms, which are known not to age. Moreover, there is a possibility that some cells in an aging organism might demonstrate nonaging kinetics. For example, C. Finch (see "Listening to the Song of Senescence" at http://sageke.sciencemag.org/cgi/content/full/sageke;2003/5/nf3) noted that "an impressive range of cell functions in most organs remain unimpaired throughout the life span" [(*2*), p. 425], and these unimpaired functions might reflect the "no-aging" property known as "old as good as new" property in survival analysis [(*3*), p. 38].

Indeed, recent studies found that the rate of neuronal death does not increase with age in a broad spectrum of aging-related neurodegenerative conditions (*4*). These include 12 different models of photoreceptor degeneration, "excitotoxic" cell death in vitro, loss of cerebellar granule cells in a mouse model, and Parkinson's (http://sageke.sciencemag.org/cgi/content/full/sageke;2001/1/re1) and Huntington's diseases (*5*). In this range of diseases, five different neuronal types are affected. In each of these cases, the rate of cell death is best fit by an exponential decay law with constant risk of death independent of age (death by chance only), arguing against models of progressive cell deterioration and aging (*5*, *6*). An apparent lack of cell aging is also observed in the case of amyotrophic lateral sclerosis (*6*), retinitis pigmentosa (*7*, *5*, *6*, *8*) and idiopathic Parkinsonism (*9*-*11*).

Thus we come to the following fundamental question about the origin of aging: How can we explain the aging of a system built of nonaging elements? This question invites us to think about the possible systemic nature of aging and to wonder whether aging may be a property of the system as a whole. We would like to emphasize the importance of looking at the bigger picture of the aging phenomenon in addition to its tiny details, and we will suggest a possible answer to the posed question in this article.

An evolutionary perspective on aging and longevity (*12*) provides one way to stay focused on the bigger picture [see the most recent reviews in (*13*-*18*)]. From the standpoint of evolution, explanations of aging and the limited longevity of biological species are based on two major theories: the mutation accumulation theory (*19*) and the antagonistic pleiotropy theory (*20*) (see Williams Classic Paper at http://sageke.sciencemag.org/cgi/content/abstract/sageke;2001/1/cp13 and "Aging Research Grows Up" at http://sageke.sciencemag.org/cgi/content/full/sageke;2001/1/oa1). According to the mutation accumulation theory, aging is an inevitable result of the declining force of natural selection with age. For example, a mutant gene that kills young children will be strongly selected against (will not be passed to the next generation), whereas a lethal mutation that affects only people over the age of 80 will experience no selection pressure, because people with this mutation will have already passed it on to their offspring by that age. Over successive generations, late-acting deleterious mutations will accumu-

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late, leading to an increase in mortality rates late in life. The antagonistic pleiotropy theory further states that late-acting deleterious genes might even be favored by selection and be actively accumulated in populations if they have any beneficial effects early in life. Note that these two theories of aging are not mutually exclusive, and both evolutionary mechanisms might operate simultaneously. The main difference is that in the mutation accumulation theory, genes with negative effects during old age accumulate passively from one generation to the next, whereas in the antagonistic pleiotropy theory, these alleles are actively kept in the gene pool by selection (*15*). The relative contribution of each evolutionary mechanism to species aging has not yet been determined and remains an important issue.

A remaining question is whether the evolutionary perspective represents the ultimate general theoretical framework for explanations of aging. We know that evolutionary theories of aging are applicable only to systems that reproduce, because these theories are based on the idea of natural selection and the notion of the declining force of natural selection with age. However, aging is a very general phenomenon—it is also observed in many technical devices (such as cars), which do not reproduce and therefore are not subject to evolution through natural selection. Thus, a more general explanation(s) of aging might exist in addition to the mutation accumulation and antagonistic pleiotropy theories.

Before moving further, let us provide a working definition of aging. Most authors of gerontology textbooks define aging as a process that results in an age-related increase of death rate or failure rate (*2*, *12*). Correspondingly, systems whose death rates do not depend on age are considered nonaging (*3*). The quest for a general explanation of aging, applicable both to technical devices and biological systems, invites us to consider the general theory of systems failure known as reliability theory (*21-24*).

General Overview of the Reliability Theory Approach

Reliability theory is a body of ideas, mathematical models, and methods directed to predict, estimate, understand, and optimize the life span distribution of systems and their components (*23*, *24*). The reliability of the system (or component) refers to its ability to operate properly according to a specified standard (*25*). Reliability is described by the reliability function $S(x)$, which is the probability that a system (or component) will carry out its mission through time x (*26*) and which is closely related to the standard cumulative distribution function from probability theory (*27*) (Fig. 1, Eq. 1). The best illustration of the reliability function is a survival curve describing the proportion of those still alive by time x (the l_x column in life tables).

Equation 1: $$S(x) = P(X > x) = 1 - P(X \leq x) = 1 - F(x)$$

Equation 2: $$\lambda(x) = -\frac{dS(x)}{S(x)dx} = -\frac{d[\log_e S(x)]}{dx}$$

Fig. 1. The mathematics of reliability theory. The reliability function (also called the survival function) evaluated at time x is simply the probability P that the failure time X is greater than time x, designated as $P(X > x)$. Thus, the reliability function is represented by Eq. 1, where $F(x)$ is a standard cumulative distribution function from probability theory. The failure rate $\lambda(x)$, also called the hazard rate $h(x)$, is described by Eq. 2.

An important measure in reliability theory is the failure rate, also called the hazard rate, which is defined as the relative rate of reliability function decline (Fig. 1, Eq. 2). Failure rate is equivalent to the mortality force in demography and gerontology [traditionally designated as $\mu(x)$]. When the failure rate is constant (that is, does not increase with age), we have a nonaging system (component) that does not deteriorate (does not fail more often) with age (*3*). The reliability function of nonaging systems (components) is described by the exponential distribution (Fig. 2). This failure law describes the "life span" distribution of radioactive atoms and is also observed in many wild populations with high extrinsic mortality (*2*, *22*). The nonaging behavior of a system can be detected graphically when the logarithm of the survival function decreases with age in a linear fashion (Fig. 2).

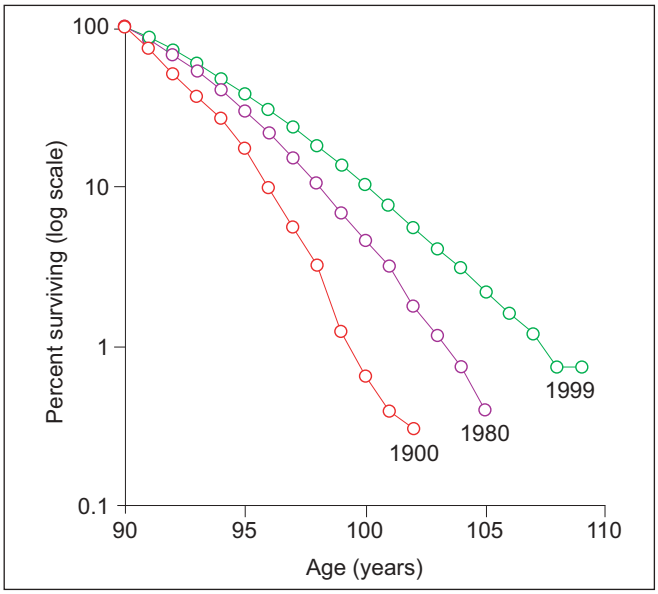
Interestingly, the survival patterns of humans at extreme old

Equation 3a: $$S(x) = S_0 \exp(-\lambda x)$$

Equation 3b: $$\ln S(x) = \ln S_0 - \lambda x$$

Fig. 2. Exponential distribution that describes the reliability of nonaging systems (Eq. 3a). In nonaging systems, the logarithm of the survival function linearly decreases with age (Eq. 3b).

ages (over 100 years old) are rather close to this linear dependence, suggesting that death rates, although very high, do not demonstrate further substantial deterioration with age (Fig. 3) (see "Dead Last" at http://sageke.sciencemag.org/cgi/content/abstract/sageke;2002/44/nw153). The same phenomenon of "almost nonaging" survival dynamics at extreme old ages is de-



SOURCE: CROSS-SECTIONAL (PERIOD) LIFE TABLES AT THE BERKELEY MORTALITY DATABASE

Fig. 3. Survival patterns after age 90. The percent surviving (in log scale) is plotted as a function of age of Swedish women for calendar years 1900, 1980, and 1999 (cross-sectional data). After age 100, the logarithm of the survival fraction is decreasing without much further acceleration (aging) in almost a linear fashion. There is also an increasing pace of survival improvement in history: It took less than 20 years (from year 1980 to year 1999) to repeat essentially the same survival improvement that initially took 80 years (from year 1900 to year 1980).

tected in many other organisms, including rodents (guinea pigs, rats, and mice) and invertebrates (nematodes, shrimps, bdelloid rotifers, fruit flies, and the degenerate medusae *Campanularia flexuosa*). This phenomenon has been well known since the 1970s (*28*) and even earlier (*29*, *30*) but still presents a theoretical challenge to gerontologists. Note that the concept of a fixed upper limit for individual life span makes no sense in light of these findings (*22*, *31*). The failure kinetics of manufactured products (such as steel samples, industrial relays, and motor heat insulators) also demonstrates the same "nonaging" pattern at the end of the products' "life spans" (*28*). This observation calls for a very general explanation of this apparently paradoxical "no aging at extreme ages" phenomenon, which will be suggested in this article.

If failure rate increases with age, we have an aging system (component) that deteriorates (fails more often) with age. There are many failure laws for aging systems, and the Gompertz law, with its exponential increase in failure rates with age (*32*), is just one of them [see review in (*22*)] (see Pletcher Perspective at http://sageke.sciencemag.org/cgi/content/full/sageke;2002/37/pe14). In reality, system failure rates may contain both nonaging and aging terms as, for example, in the case of the Gompertz-Makeham law of mortality (*2*, *22*, *33*, *34*), the mathematical description of which is given in Fig. 4.

If the Gompertz-Makeham law of mortality is valid, then loga-

Equation 4: $\mu(x) = A + R \times \exp(\alpha x)$, where parameters $A, R, \alpha > 0$

Fig. 4. The Gompertz-Makeham law of mortality. In Eq. 4, the first, age-independent term (Makeham parameter *A*) designates the constant, nonaging component of the failure rate (presumably due to extrinsic causes of death, such as accidents and acute infections), whereas the second, age-dependent term [the Gompertz function, $R \times \exp(\alpha x)$] designates the aging component, presumably a result of deaths from age-related degenerative diseases such as cancer and heart disease.

rithms of death rates minus the Makeham parameter increase with age in a linear fashion (Fig. 5). The log-linear increase in death rates (adjusted for the Makeham term) with age is indeed a very

Equation 5: $\log(\mu_x - A) = \log(R) + \alpha x$

Fig. 5. Testing the validity of the Gompertz-Makeham law of mortality (Eq. 5). A linear dependence is expected between the logarithm of mortality (minus the Makeham term) and age if the Gompertz-Makeham law is valid. Here the log(*R*) is an intercept coefficient and α is a slope coefficient in this linear relationship.

common phenomenon for many human populations at ages 35 to 70 years (Fig. 6). The slope of linear dependence characterizes an "apparent aging rate" (that is, how rapid the age deterioration in mortality is); if the slope is equal to zero, there is no apparent aging (death rates do not increase with age). At advanced ages (after age 70), old-age mortality deceleration takes place, so that death rates increase with age at a slower pace then expected from the Gompertz-Makeham law. This mortality deceleration eventually produces "late-life mortality leveling off" and "late-life mortality plateaus" at extreme old ages (*22*, *23*).

Another feature of mortality is described by the compensation law of mortality, which in its strong form refers to mortality convergence, when higher values for the slope coefficient α (in the log-transformed Gompertz function) are compensated for by lower values of the intercept coefficient *R* in different populations of a given species (Fig. 7). Sometimes this relationship is also called the Strehler-Mildvan correlation (*34*, *35*), although that particular correlation was largely an artifact of the opposite biases in the estimation of parameters caused by not

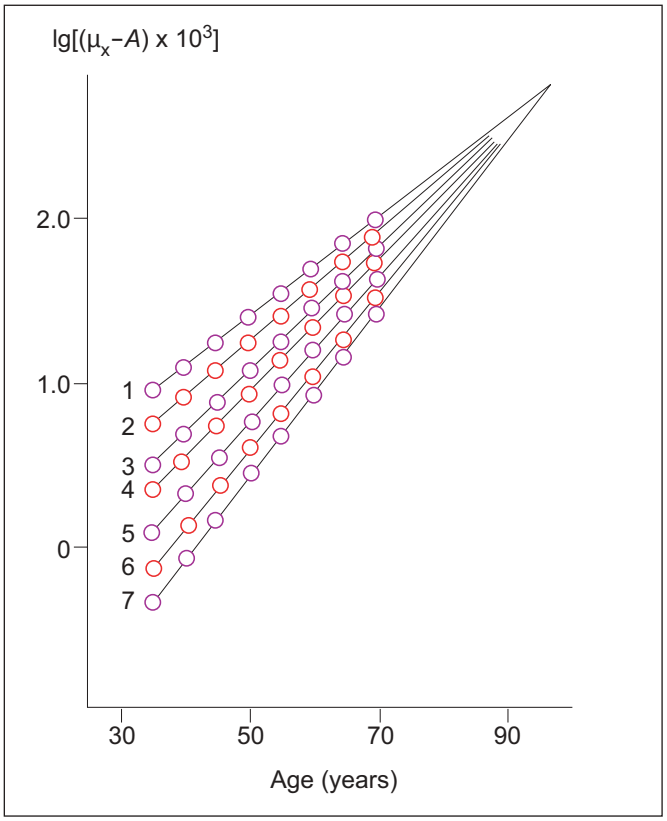


Fig. 6. Convergence of mortality rates in different populations at advanced ages (compensation law of mortality). Death rates (with removed Makeham parameter *A*, corresponding to the age-independent mortality component) are plotted in a log scale as a function of age in the following countries: (1) India, 1941-1950, males; (2) Turkey, 1950-1951, males; (3) Kenya, 1969, males; (4) Northern Ireland, 1950-1952, males; (5) England and Wales, 1930-1932, females; (6) Austria, 1959-1961, females; (7) Norway, 1956-1960, females. [Adapted from (*21*, *22*)]

Equation 6: $\ln(R) = \ln(M) - B\alpha$

Fig. 7. Compensation law of mortality. Eq. 6 shows the linear dependence between the logarithm of the intercept coefficient and the slope coefficient in the Gompertz function, where *B* and *M* are universal species-specific invariants.

taking into account the age-independent mortality component, the Makeham term *A* (*22*). Parameter *B* is the species-specific life span (95 years for humans), and parameter *M* is the species-specific mortality rate (0.5 per year for humans). These parameters are the coordinates for the convergence of all the mortality trajectories into one single point (within a given biological

species), when extrapolated by the Gompertz function (Fig. 6). In cases where the compensation law of mortality is not observed in its strong form, it may still be valid in its weak form; that is, the relative differences in the mortality rates of compared populations tend to decrease with age in many species. Explaining the compensation law of mortality is a great challenge for many theories of aging and longevity (*21*, *22*, *34*).

There are some exceptions to both the Gompertz law of mortality and the compensation law of mortality that have to be understood and explained. In some cases, the organisms die according to the Weibull (power) law (*36-39*). The validity of the Weibull law can be illustrated graphically, when the logarithm of the failure rate increases in a linear fashion as a function of the logarithm of age (Fig. 8). Some examples of such linear dependence are provided later in this article. The slope coefficient in the Weibull law characterizes an "apparent aging rate" (the rapidity of the age-related deterioration in mortality); if the slope is equal to zero, there is no apparent aging (death rates do not increase with age).

Equation 7: $\mu(x) = \lambda x^{\alpha}$ for $x \geq 0$, where $\lambda, \alpha > 0$

Equation 8: $\log[\mu(x)] = \log(\lambda) + \alpha Z$, where $Z = \log x$

Fig. 8. Weibull (power) law. This relationship is shown in Eq. 7. The validity of the Weibull law can be illustrated graphically, when the logarithm of the failure rate increases in a linear fashion as a function of the logarithm of age (Eq. 8). Here log(λ) is an intercept coefficient and α a slope coefficient in this linear relationship.

The Weibull law is more commonly applicable to technical devices (*24*, *26*, *40*), whereas the Gompertz law is more commonly used to describe biological systems (*2*, *22*, *34*). An exponential (Gompertzian) increase in death rates with age is observed in many biological species, including the fruit fly *Drosophila melanogaster* (*22*), nematodes (*41-43*), mosquitoes (*44*), the human louse *Pediculus humanus* (*22*), the flour beetle *Tribolium confusum* (*22*), mice (*45*, *46*), rats (*22*), dogs (*46*), horses (*34*), mountain sheep (*44*), baboons (*47*), and humans (*2*, *22*, *32-34*). Comparative meta-analysis of 129 life tables for fruit flies as well as 285 life tables for humans demonstrates that the Gompertz law of mortality provides a much better data fit for these species, as compared to the Weibull law (*22*). Possible explanations as to why organisms usually die according to the Gompertz law whereas technical devices typically fail according to the Weibull law are provided elsewhere (*22*, *23*) and will be briefly discussed later (see "The Idea of High Initial Damage Load" below).

The phenomena of mortality increase with age and the subsequent leveling off of mortality are predicted to be inevitable features of all reliability models that consider aging as a progressive accumulation of random damage (*22*, *23*). In simple words, if the destruction of an organism occurs not in one but in two or more sequential random stages, this is sufficient for the phenomenon of aging (mortality increase) to appear and then to vanish at older ages. Each stage of destruction corresponds to one of the organism's vitally important structures being damaged. In the simplest organisms with unique critical structures, this damage usually leads to death. Therefore, defects in such organisms do not accumulate, and the organisms themselves do not age—they just die when damaged. For example, the inactivation of microbial cells and spores exposed to a hostile environment (such as heat) follows approximately a nonaging mortality kinetics; their semi-logarithmic survival curves are almost linear (*48*). This observation of nonaging survival dynamics is extensively used in the calculation of the efficacy of sterilization processes in medicine and food preservation (*49-52*). A similar nonaging pattern of inactivation kinetics is often observed for viruses (*53*, *54*) and enzymes (*55*, *56*). In more complex systems with many vital structures and significant redundancy, every occurrence of damage does not lead to death (unless the environment is particularly hostile) because of this redundancy. Defects accumulate, therefore, giving rise to the phenomenon of aging (mortality increase). Thus, aging is a direct consequence (trade-off) of a system's redundancies, which ensure increased reliability and an increased life span for organisms. As defects accumulate, the redundancy in the number of elements finally disappears. As a result of this redundancy exhaustion, the organism degenerates into a system with no redundancy (that is, a system with elements connected in series, with the result being that any new defect leads to death). In such a state, no further accumulation of damage can be achieved, and the mortality rate levels off. The next section provides a mathematical illustration for these ideas.

Explanations of Aging Phenomena Using Reliability Theory: An Illustrative Example

Consider a system built of nonaging elements with a constant failure rate *k*. If these *n* elements are mutually substitutable, so that the failure of a system occurs only when all the elements fail (called parallel construction in the reliability theory context), the cumulative distribution function for system failure, the reliability function of a system, and the failure rate of a system depend on age *x* as shown in Fig. 9. This model can be considered as the simplest network (*23*) and there is general enthusiasm now about applying the networks approach [an approach focused on "the study of complex, interactive entities" (*57*)] to complex systems to understand their behavior and aging (*57-59*).

Fig. 9 shows that the failure rate of a system initially grows as a power function of age (the Weibull law). Then the tempo at which the failure rate grows declines, and the failure rate asymptotically approaches an upper limit equal to *k*. Here we should pay attention to three important points. First, a system constructed of nonaging elements is now behaving like an aging object; that is, aging is a direct consequence of the redundancy of the system (redundancy in the number of elements). Second, at very high ages the phenomenon of aging apparently disappears (failure rate levels off), as redundancy in the number of elements vanishes. The failure rate approaches an upper limit, which is totally independent of the initial number of elements but coincides with the rate of their loss (parameter *k*). Third, the systems with different initial levels of redundancy (parameter *n*) will have very different failure rates in early life, but these differences will eventually vanish as failure rates approach the upper limit determined by the rate of loss of the system's elements (parameter *k*). Thus, the compensation law of mortality (in its weak form) is an expected outcome of this illustrative model. These theoretical predictions are supported by experimental studies on *D. melanogaster*, which found no differences in late-life mortality between cohorts of flies having markedly different levels of early robustness (*60*). The point here is that the predic-

Equation 9: $$F(n,k,x) = P(X \le x) = \left(1 - e^{-kx}\right)^n$$

Equation 10: $$S(n,k,x) = 1 - F(n,k,x) = 1 - \left(1 - e^{-kx}\right)^n$$

Equation 11: $$\mu(n,k,x) = -\frac{dS(n,k,x)}{S(n,k,x)dx} = \frac{nke^{-kx}\left(1 - e^{-kx}\right)^{n-1}}{1 - \left(1 - e^{-kx}\right)^n}$$

Equation 11a: $\approx nk^n x^{n-1}$ when $x << 1/k$
(early-life period approximation, when $1 - e^{-kx} \approx kx$)

Equation 11b: $\approx k$ when $x >> 1/k$
(late-life period approximation, when $1 - e^{-kx} \approx 1$)

Fig. 9. Mathematical description of a model system built of nonaging elements. Cumulative distribution function for system failure $F(n,k,x)$ depends on age as shown in Eq. 9. This formula corresponds to the simplest case when the failure of elements is statistically independent. More complex models would require specific assumptions or prior knowledge about the exact type of the interdependence in element failure. One such model, known as the model of the avalanche-like destruction, is described elsewhere [pp. 246-251 in (*22*)]. The reliability function of a system, $S(n,k,x)$, can be represented as Eq. 10. Consequently, the failure rate of a system, $\mu(n,k,x)$, can be written as shown in Eq. 11. Eq. 11a provides an approximation when $x << 1/k$ (early-life period approximation, when $1 - e^{-kx} \approx kx$); Eq. 11b provides an approximation when $x >> 1/k$ (late-life period approximation, when $1 - e^{-kx} \approx 1$).

tions of the simple model of stochastic loss of nonaging elements with age are consistent with observations on *Drosophila* mortality (*61*). This suggests that perhaps the loss of components (cells) with age may be more important for *Drosophila* mortality than the age-related deterioration of remaining components. Otherwise, it is difficult to explain why mortality rates level off at advanced ages, if the remaining *Drosophila* cells continue to deteriorate. It seems plausible that the cells simply die when damaged, so that the quality of surviving (undamaged so far) cells does not deteriorate significantly with age.

These theoretical statements, based on general analytical considerations, are also illustrated with the following numerical example. Fig. 10 presents the results of computer simulation of mortality kinetics in systems with different levels of redundancy. Specifically, calculations of failure rates are performed according to the formula (Eq. 11) described in Fig. 9, for the initial numbers of elements n = 1, 2, 3, 4, and 5. The scales for mortality rates (vertical axis) and for age (horizontal axis) are presented in dimensionless units to ensure the generalizability of the results [meaning that in this situation, the graphs will be invariant regardless of the failure rates of the system's elements (parameter k)]. Also, the log scale is used to explore the system behavior over a wide range of ages (0.01 to 10 units) and failure rates (0.00000001 to 1.0 units).

The graph shown in Fig. 10 depicts mortality trajectories for five systems with different degrees of redundancy. System 1 has only one unique element (no redundancy), and it has the highest failure rate, which does not depend on age (no aging). System 2 has two elements connected in parallel (one extra element is redundant), and the failure rate initially increases with age (aging appears). The apparent rate of aging can be characterized by a slope coefficient that is equal to 1. Finally, the failure rate levels off at advanced ages. Systems 3, 4, and 5 have, respectively, three, four, and five elements connected in parallel (two, three, and four extra elements are redundant), and the failure rate initially increases with age at an apparent aging rate (slope coefficient) of 2, 3, and 4, respectively. Finally, the mortality trajectories of each system level off at advanced ages at exactly the same upper limit to the mortality rate.

This computational example illustrates the following statements: (i) Aging is a direct consequence of a system's redundancy, and the expression of aging is directly related to the degree of a system's redundancy. Specifically, an apparent relative aging rate is equal to the degree of redundancy in parallel systems. (ii) All mortality trajectories tend to converge with age, so that the compensation law of mortality is observed. (iii) All mortality trajectories level off at advanced ages, and a mortality plateau is observed. Thus, the major aging phenomena (aging itself, the compensation law of mortality, late-life mortality deceleration, and late-life mortality plateaus) are already observed in the simplest redundant systems. However, to explain the Gompertz law of mortality, an additional idea should be taken into account (see below).

The Idea of High Initial Damage Load

Reliability theory predicts that a failure rate of simple redundant systems increases with age according to the Weibull (power) law (Fig. 9, Eq. 11a; and Fig. 10). This theoretical prediction is consistent with empirical observations that the failure kinetics of technical devices follow the Weibull law (*22*, *23*, *40*). However, biological systems "prefer" to fail according to the Gompertz (exponential) law, which calls for explanations. An attempt to explain the exponential deterioration of biosystems in terms of reliability theory led to a paradoxical conjecture that biological systems start their adult life with a high load of initial damage (*22*, *23*). Although this idea might look like a counterintuitive assumption, it fits well with many empirical observations that reveal massive cell losses in early development. For example, the female human fetus at age 4 to 5 months possesses 6 to 7 million eggs (oocytes). By birth, this number drops to 1 to 2 million and then declines even further. At the start of puberty in normal girls, there are only 0.3 to 0.5 million eggs present—just 4 to 8% of the initial numbers (*62*, *63*).

Massive cell losses in early development result in a distribution of organisms with regard to the exact number of cells that remain in each individual within a population of a given species. If this distribution is close to either the binomial or the Poisson distribution, then a quasi-exponential (Gompertzian) pattern of mortality increase is expected, with subsequent mortality leveling off (*22*). Because the mathematical proof for this statement is already published elsewhere [see section 6.7, pp. 264-272, in (*22*)], we concentrate here on substantive discussion of the idea of high initial damage load (HIDL) in biological systems.

Biological systems are different from technical devices in

two respects. The first fundamental feature of biosystems is that, in contrast to technical (artificial) devices that are constructed out of previously manufactured and tested components, organisms form themselves from fertilization through maturity (ontogenesis) through a process of self-assembly out of de novo forming and externally untested elements (cells). The second property of organisms is the extraordinary degree of miniaturization of their components (the microscopic dimensions of cells, as well as the molecular dimensions of information carriers such as DNA and RNA), permitting the creation of a huge redundancy in the number of elements. Thus, we can expect that for living organisms, in contrast to many technical (manufactured) devices, the reliability of the system is achieved not by the high initial quality of all the elements but by their huge numbers (redundancy).

The fundamental difference in the manner in which the systems are formed has two important consequences. First, it leads to the macroscopic nature of technical devices in comparison with biosystems, because technical devices are assembled "top-down" with the participation of a macroscopic system (humans) and must be suitable for this macroscopic system to use. Second, because technical devices are assembled under the control of humans, the opportunities to pretest components (external quality control) are far greater than in the self-assembly of biosystems. The latter inevitably leads to organisms being "littered" with a large number of defective elements. As a result, the reliability of technical devices is ensured by the high quality of elements (fault avoidance), with a strict limit on their numbers because of size and cost limitations; whereas the reliability of biosystems is ensured by an exceptionally high degree of redundancy to overcome the poor quality of some elements (fault tolerance).

The idea that living organisms start their lives with a large number of defects has deep historical roots. Biological justification for this idea was discussed by Dobzhansky (*64*). He noted that, from the biological perspective, Hamlet's "thousand natural shocks that flesh is heir to" was an underestimate and that in reality "the shocks are innumerable" (*64*, p. 126). Recent studies found that the troubles in human life start from the very beginning: The cell cycle checkpoints (which ensure that cells will not divide until DNA damage is repaired and chromosomal segregation is complete) do not operate properly at the early, cleavage stage of the human embryo (*65*). This produces mosaicism of the preimplantation embryo, where some embryonic cells are genetically abnormal (*66*) with potentially devastating consequences in later life. Most of the damage caused by copy errors during DNA replication also occurs in early life, because most cell divisions happen in early development. As a result, many apparently normal tissues of young organisms have a very high mutation load, including a large number of oncogenic mutations and frequent clones of mutated somatic cells (*67-69*).

Loss of telomeres is another process that begins before birth. This process eventually leads to such outcomes as genomic instability, cell death (apoptosis), cell senescence, and perhaps to aging (*70*) (see "More Than a Sum of Our Cells" at http://sageke.sciencemag.org/cgi/content/full/sageke;2001/1/oa4 and Heist Perspective at http://sageke.sciencemag.org/cgi/content/full/sageke;2003/19/pe11). Telomere loss is directly linked to DNA replication during cell division, which occurs with high frequency at early stages of growth and development (*70-73*).

Another potential source of extensive initial damage is the birth process itself. During birth, the future child is deprived of oxygen by compression of the umbilical cord (*74*) and suffers

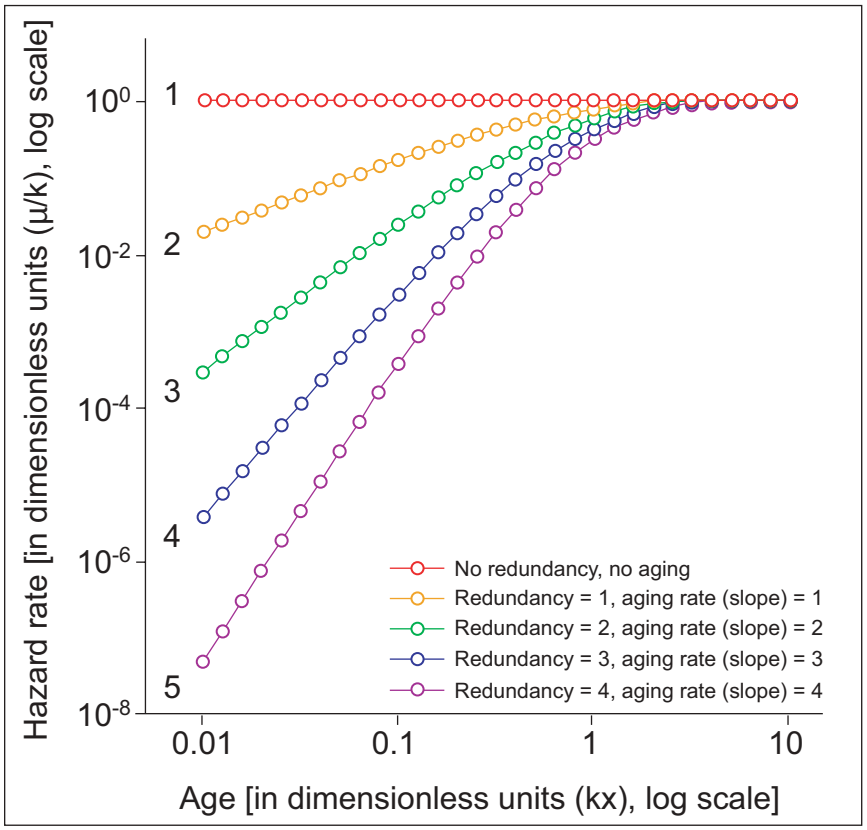


Fig. 10. Failure kinetics of systems with different levels of redundancy. The dependence of the logarithm of mortality force (failure rate) on the logarithm of age in five systems with different levels of redundancy (computer simulation experiment) is shown. Both the failure rate and the age are presented in dimensionless units (μ/k for hazard (mortality) rates and kx for age) to ensure the generalizability of the results (the invariance of graphs on failure rate of the elements in the system, parameter k). Dependence 1 is for the system containing only one unique element (no redundancy). Dependence 2 is for the system containing two elements connected in parallel (degree of redundancy = 1). Dependencies 3, 4, and 5 are for systems containing, respectively, three, four, and five elements connected in parallel (with increasing levels of redundancy). Even in this simplest case, the following aging-related phenomena are observed: (i) the emergence of aging as the system becomes redundant, (ii) the increase in apparent aging rate with increasing levels of system redundancy, (iii) the compensation law of mortality (mortality convergence), and (iv) late-life mortality deceleration and leveling off to a mortality plateau.

severe hypoxia [often with ischemia (inadequate blood flow) and asphyxia (respiratory distress syndrome leading to oxygen deficiency)]. Then, just after birth, a newborn child is exposed to oxidative stress because of acute reoxygenation while starting to breathe. It is known that acute reoxygenation after hypoxia may produce extensive oxidative damage through the same mechanisms that produce ischemia-reperfusion injury (an inflammatory response that occurs after the restoration of blood flow) and the related phenomenon, asphyxia-reventilation injury (*75*). Asphyxia is a common occurrence in the perinatal period, and asphyxial brain injury is the most common neurologic abnormality in the neonatal period (*76*) that may manifest in neurologic disorders in later life. The brain damage that occurs after asphyxia may cause long-term neurological consequences in full-term infants (*77*) and lead to cerebral palsy, epilepsy, and mental retardation (*78*, *79*). Perhaps the rare geniuses are simply those lucky persons whose early-life brain damage was less extensive than the "normal" level. Thus, using Hamlet's metaphor, we may conclude that humans "suffer the slings and arrows of outrageous fortune" and have "a sea of troubles" from the very beginning of their lives.

It follows from this concept of HIDL that even small progress in optimizing the processes of ontogenesis and increasing the numbers of initially functional elements can potentially result in a remarkable fall in mortality and a significant improvement in life span. This optimistic prediction is supported by experimental evidence (in laboratory mice) of increased offspring life span if future parents were fed antioxidants, which presumably resulted in protection of parental germ cells against oxidative damage (*80*) (see "The Two Faces of Oxygen" at http://sageke.sciencemag.org/cgi/content/full/sageke;2001/1/oa5 for further discussion of oxidative damage). Increased life span is also observed among the progeny of parents with a low resting respiration rate [proxy for the rate of oxidative damage to the DNA of germ cells (*22*)]. The concept of HIDL also predicts that early-life events might affect survival in later adult life through the level of initial damage. This prediction proved to be correct for such early-life indicators as parental age at a person's conception (*81-85*) and the month of a person's birth (*84-87*). Accumulation of germline mutations in aging parents could be one possible explanation for observed parental age effects, whereas the season-of-birth effects may be related to seasonal variation in nutritional status and disease exposure during critical periods of early development. There is mounting evidence in support of the idea of fetal origins of adult degenerative diseases (*88-91*), and early-life programming of aging and longevity (*22*, *84*, *85*, *92*).

Women may be particularly sensitive to early-life exposures, because they are mosaics of two different cell types (one with an active paternal X chromosome and another one with an active maternal X chromosome). The exact pattern of this mosaic is determined early in life. If early-life conditions affect the proportion (or distribution pattern) of cells with a given X chromosome, such conditions might have long-lasting effects in later life. Indeed, this conjecture of stronger female response to early-life exposures is confirmed for such early-life predictors of adult life span as paternal age at a person's conception (*81-85*) and the month of a person's birth (*84*, *85*).

Another testable prediction of the HIDL hypothesis is a prediction of an unusual nonlinear pattern of life span inheritance. Traditionally, it is assumed that the dependence of progeny life span on parental life span should follow a linear relationship, which is common to all other quantitative traits in classic quantitative genetics (*93*, *94*). In other words, for each additional year of parental life span, the children are expected to have some fixed gain in their average life span too, as a result of polygenic inheritance of quantitative traits (*93*). However the HIDL hypothesis leads to a very different prediction of a nonlinear (accelerated) "concave-up" pattern of life span inheritance. There should be virtually no life span heritability (a negligible response of progeny life span to the changes in parental life span) when parental life span is below a certain age, and a much higher heritability (an increased response to parental life span) when parents live longer lives. This prediction follows from the hypothesis of HIDL among short-lived parents, whose bodies are damaged during early developmental processes, although their germ cell DNA might be perfectly normal. (If the germ cell DNA were damaged too, these short-lived parents would probably produce offspring who also live short lives. This category will therefore be unlikely to distort the linear dependence of offspring life span on parental life span by a large amount.) Therefore, the progeny of some short-lived parents may have quite normal life spans, well beyond genetic expectations. This result would thus obstruct the classic linear offspring-on-parent dependence for life span. Only at some high parental life span, when most of the germ-normal/somatically damaged parents are eliminated because of their shorter length of life, will the classic linear pattern of life span inheritance eventually reveal itself in its full capacity. This prediction of the HIDL hypothesis was tested and confirmed in humans: Familial transmission of life span from parents to children proved to follow a nonlinear (accelerating) pattern, with steeper slopes for the life span of offspring born to longer-lived parents, as predicted (*92*, *94-96*).

Concluding Remarks

Considerations of reliability theory lead to the following conclusions:

(i) Redundancy is a key notion for understanding aging and the systemic nature of aging in particular. Systems that are redundant in numbers of irreplaceable elements do deteriorate (that is, age) over time, even if they are built of nonaging elements. The positive effect of systems' redundancy is damage tolerance, which decreases mortality and increases life span. However, damage tolerance makes it possible for damage to be tolerated and accumulated over time, thus producing the aging phenomenon.

(ii) An apparent aging rate or expression of aging (measured as age differences in failure rates, including death rates) is higher for systems with higher redundancy levels (all other things being equal). This is an important issue, because it helps to put a correct perspective on the fascinating cases of negligible senescence (no apparent aging) observed in the wild (although aging is sometimes observed in the wild; see Spencer Perspective at http://sageke.sciencemag.org/cgi/content/full/sageke;2002/47/pe19) and at extreme old ages. Specifically, reliability theory explains that some cases of negligible senescence may have a trivial mechanism (lack of redundancies in the system being exposed to a challenging environment) and, therefore, will not help to uncover "the secrets of negligible senescence." The study of organisms that display negligible senescence makes sense, however, when the death rates are also demonstrated to be negligible. Some interesting examples of

organisms that undergo negligible senescence (which deserve more detailed studies in the future) include inverterbrates such as *Aelosoma tenebrarum* and *Pristina aequiseta* (small oligochaetes living in fresh water) (*97*) and hydra (*Hydra vulgaris*) (*98*).

Reliability theory also suggests that we reevaluate the old belief that aging is somehow related to limited economic or evolutionary investments in systems' longevity. The theory provides a completely opposite perspective on this issue—that aging is a direct consequence of investments into systems reliability and durability through enhanced redundancy. This is an important statement, because it helps to explain why the expression of aging (age-associated differences in failure rates) might be more profound in more complicated redundant systems, designed for higher durability.

(iii) During the life course, organisms lose their cells (*62*, *99*) and reserve capacity (*100*, *101*), and this redundancy depletion explains the observed compensation law of mortality (mortality convergence at older ages) as well as the observed late-life mortality deceleration, leveling off, and mortality plateaus.

(iv) Living organisms seem to be formed with a high load of initial damage, and therefore their life span and aging patterns may be sensitive to early-life conditions that determine this initial damage load during early development. The idea of early-life programming of aging and longevity might have important practical implications for developing early-life interventions that promote health and longevity.

The theory also suggests that research on aging should not be limited to the studies of qualitative changes (such as age-related changes in gene expression), because changes in quantity in (numbers of cells and other functional elements) could be an important driving force of the aging process. In other words, aging might be largely driven by a process of redundancy loss.

Reliability theory predicts that a system may deteriorate with age even if it is built from nonaging elements with constant failure rates. The key issue here is the system's redundancy for irreplaceable elements, which is responsible for the aging phenomenon. In other words, each particular step of system destruction or deterioration may seem to be random (no aging, just occasional failure by chance), but if a system failure requires a sequence of several such steps (not just a single step of destruction), then the system as a whole may have an aging behavior. Why is this conclusion important? Because the significance of beneficial health-promoting interventions is often undermined by claims that these interventions are not proven to delay the process of aging itself, but instead that they simply delay or cover up some particular manifestations of aging.

In contrast to these pessimistic views, reliability theory says that there might be no specific underlying elementary aging process; instead, aging might be largely a property of a redundant system as a whole, because it has a network of destruction pathways, each being associated with particular manifestations of aging (types of failure). Therefore, we should not be discouraged by only partial success of each particular intervention, but instead we can appreciate that we might have many opportunities to oppose aging in numerous different ways.

Thus, the efforts to understand the routes and early stages of age-related degenerative diseases should not be discarded as irrelevant to understanding true biological aging. On the contrary, attempts to build an intellectual firewall between biogerontological research and clinical medicine are counterproductive. After all, the main reason why people are really concerned about aging is because it is related to health deterioration and increased morbidity. The most important age-related changes, with respect to quality of life, are those that make older people sick and frail (*101*).

Reliability theory suggests general answers to both the "why" and the "how" questions about aging. It explains why aging occurs by identifying the key determinant of aging behavior: system redundancy in numbers of irreplaceable elements. Reliability theory also explains how aging occurs, by focusing on the process of redundancy loss over time as the major mechanism of aging. It is perfectly compatible with evolutionary theories of aging, and it helps to identify key components, which might be important for the evolution of species reliability and durability (longevity): initial redundancy levels, rate of redundancy loss, and repair potential. Moreover, reliability theory helps evolutionary theories explain how the age of onset of deleterious mutations could be postponed during evolution, which could be easily achieved by a simple increase in initial redundancy levels. From the reliability perspective, the increase in initial redundancy levels is the simplest way to improve survival at particularly early reproductive ages (with gains fading at older ages). This matches exactly with the higher fitness priority of early reproductive ages emphasized by evolutionary theories. Evolutionary and reliability ideas also help in understanding why organisms seem to "choose" a simple but short-term solution of the survival problem through enhancing the systems' redundancy, instead of a more permanent but complicated solution based on rigorous repair (with the potential of achieving negligible senescence). Thus there are promising opportunities for merging the reliability and evolutionary theories of aging.

Aging is a complex phenomenon (*100*), and a holistic approach using reliability theory may help to analyze, understand, and perhaps control it. We suggest, therefore, that reliability theory should be added to the arsenal of methodological approaches applied in research on aging. Additional and continuously updated information related to the topic of this article can be found at our scientific and educational Web site on human longevity studies (http://www.src.uchicago.edu/~gavr1/), named "Unraveling the Secrets of Human Longevity."

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