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ABSTRACT: Many researchers working in the area of aging and longevity base their conclusions on the behavior of empirical age trajectories of mortality rates. In such analyses, changes in the slope of the logarithm of the mortality curve are often associated with changes in the rate of individual aging. We show that such interpretation may be incorrect: the changes in the slope of this curve do not necessarily correspond to the changes in the rate of individual aging. We use three models of mortality and aging to illustrate this statement. The first one is based on the idea of frailty. We show that changes in frailty distribution alone may be responsible for changes in the slope. The second model exploits the idea of saving lives. It evaluates changes in mortality rate after elimination of lethal stressful events. The third model uses the idea of Streibler and Mildvan (1960). It shows that changes in the rate of individual aging may take place without changes in the slope of the logarithm of the mortality curve.

INTRODUCTION

How fast do organisms age? Which factors make the most important contributions to the aging rate? How can the rate of aging be measured and modulated? These questions are often addressed in experimental studies of aging and longevity (Finch et al., 1990; Finch, 1990; Driver, 2001). Aging of a living organism is characterized by the decline of its physiological and biological capacities with age accompanied by an increase in the chances of death. The rate of such a decline is called the biological aging rate. The search for biological and physiological indicators of aging is the subject of many studies in modern gerontology (Ingram, 1988). In demography, the aging process is associated with an increase in the mortality curve (the force of mortality) with age. We will associate the rate of such an increase with the rate of demo-

graphic aging, to distinguish it from the biological rate of aging. Since both rates characterize different aspects of the aging process, it would be interesting to find out how these rates are related to each other. To what extent can the rate of demographic aging characterize the biological rate of aging?

In many population studies of aging and longevity a simplified approach to evaluation of the biological aging rate is used. In this approach the slope of the logarithm of the empirical mortality curve often approximated by the Gompertz curve ($\mu(x) = ae^{bx}$) is used as a measure of such a rate. (In such an approximation this slope coincides with the demographic aging rate equal to parameter b .) Such an interpretation, although simple and straightforward, is not always satisfactory. Sometimes it is misleading. For example, the improvement in survival in developed countries in the first half of

the past century was characterized by rectangularization of the survival curve. Such a trend corresponds to an increase in the slope of the respective logarithm of the mortality rate. Does it mean that the rate of individual aging increased as well? If not, then how can the changes in the slope of the logarithm of the mortality curve be interpreted?

Similar problems arise in the analysis of survival data from experimental studies of aging and longevity with laboratory animals. Often in such experiments, an increase or decline in the slope of the logarithm of the mortality curve is interpreted as a respective change in the rate of individual aging. It turns out, however, that changes in the slope of the logarithm of the mortality rate may take place without changes in the rate of physiological and biological decline for individuals.

In this paper we discuss three possible mechanisms of shaping the age pattern of the mortality rate. These mechanisms are described in three models of aging and mortality based on three different ideas. The first one relates characteristics of population heterogeneity to the survival chances of individuals at different ages. The second evaluates the contribution of progress in saving individuals' lives to mortality and longevity. The third one shows how improvements in the standards of living may change the slope of the force of mortality.

CHANGES IN HETEROGENEITY DISTRIBUTION MODULATE THE SLOPE OF THE MORTALITY RATE

The fact that hidden heterogeneity may modify the mortality curve was discussed in actuarial sciences more than 150 years ago (Higham, 1851). However, the intensive studies of this phenomenon

began when convenient heterogeneity distributions, appropriate for analytical studies of the effects of heterogeneity, were found. The model with gamma-distributed heterogeneity was introduced in demography by Beard (1959). Beard (1971) published a detailed review of heterogeneity studies in demography. Vaupel et al. (1979) coined the term "frailty" in heterogeneity analysis and used the gamma-frailty model in an explanation of the deceleration of the mortality rate at advanced ages. Vaupel and Yashin (1985) described different effects of heterogeneity in mortality. Thatcher (1999) reviewed many other applications of the heterogeneity model in demographic studies. Here we recall one effect of heterogeneity in frailty relevant to the subject of our paper.

Suppose that individuals in a population differ from each other in the value of "frailty" (parameter Z) characterizing their susceptibility to death, such that the hazard conditional on Z is:

$$\mu(x, Z) = Z\mu_0(x) \quad [1]$$

Here $\mu_0(x)$ is the baseline hazard. Since frailties differ among individuals, such a population is subject to demographic selection following the rule "frail die first." This selection contributes to the shape of observed mortality $\bar{\mu}(x)$. If frailty Z is gamma-distributed with $EZ = 1$ and $\text{var}(Z) = \sigma^2$, then the total mortality rate is (Vaupel et al., 1979):

$$\bar{\mu}(x) = \frac{\mu_0(x)}{1 + \sigma^2 H(x)} \quad [2]$$

Here $H(x) = \int \mu_0(u) du$. One can see from [2] that the higher the value of σ^2 , the more the slope of $\bar{\mu}(x)$ deviates from that of $\mu_0(x)$. The deviation increases with age. Thus, changes in heterogeneity distribution may produce different changes in the slope of observed mortality. Figures 1

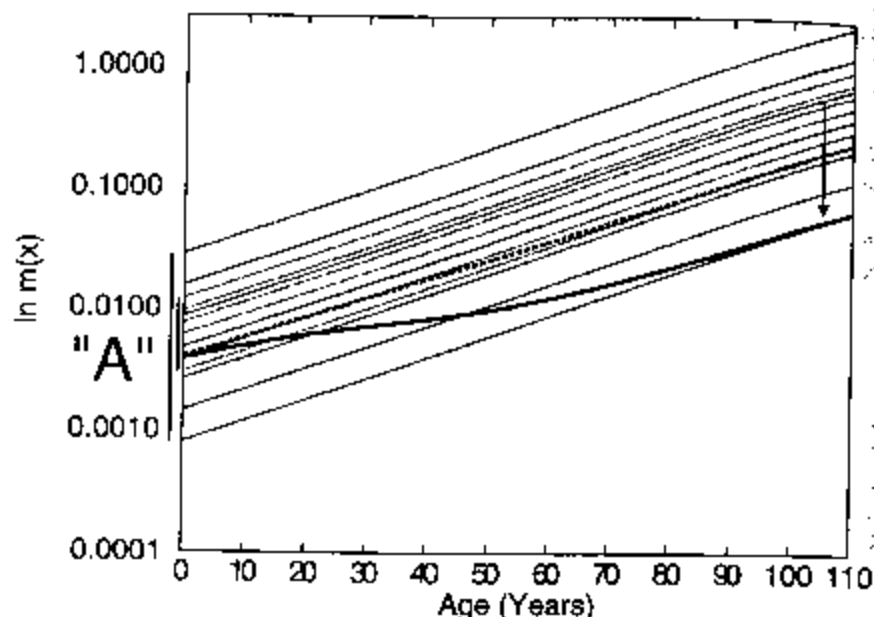


FIG. 1.—Possible pattern of mortality improvement in a heterogeneous population. The slope of the resulting mortality rate declines when the variance of heterogeneity distribution increases. The logarithms of the mortality rates in populations with small (dashed lines for sub-populations and thick red line for the mixture) and with larger variance of heterogeneity distribution (thin lines for sub-populations and thick line for the mixture). When the variance increases gradually, the effect of clockwise rotation around point "A" is observed.

and 2 illustrate the situation in the case of a discrete mixture of hypothetical homogeneous populations with proportional hazard rates and Gompertz baseline hazard.

One can see from these figures that the slope of the logarithm of the mortality curve $\mu(x)$ may change because of changes in the parameters of heterogeneity distribution. The baseline hazard, however, in these transformations remains unchanged. In frailty models the slope of the logarithm of the baseline hazard rate is often associated with the rate of individual or biological aging (Vaupel et al., 1979). If such an association is correct, the slope of observed mortality can be changed without

changes in the rate of biological aging. Thus, changes in population composition may mask the effects of modulation in the rate of the individual aging process in experimental studies of aging and longevity. To separate these effects, methods of statistical modeling capable of taking into account all mechanisms shaping the observed mortality rate are needed.

SAVING INDIVIDUALS' LIVES STEEPENS THE MORTALITY CURVE

Vaupel and Yashin (1987) show that an increase in the frequency of saving individuals' lives may have substantial contribution to the process of mortality

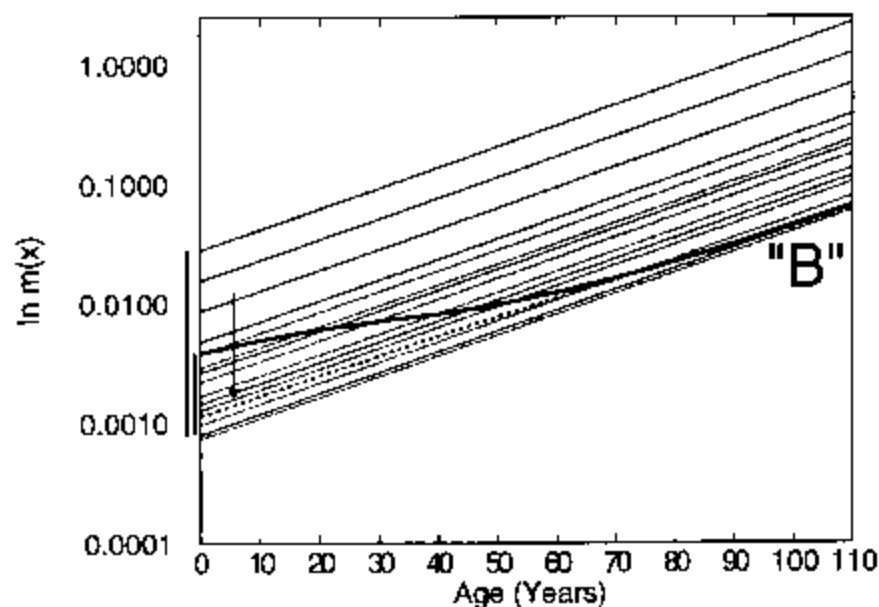


FIG. 2.—Possible pattern of survival improvement in a heterogeneous population. The slope of the resulting mortality rate increases when the variance of heterogeneity distribution declines. The logarithms of the mortality rates in hypothetical heterogeneous populations with large variance (thin lines for sub-populations and thick line for the mixture), and with smaller variance of heterogeneity distribution (dashed lines for sub-populations and thick line for the mixture). When both the mean and the variance of frailty distribution decline gradually, the effect of rotation around point "B" is observed.

reduction in humans. This process may be direct (e.g., through medical intervention) or indirect (e.g., through an increase of internal capacity of DNA repair, activation of heat shock proteins, an antioxidant defense, etc.; Yashin et al., 2000). Let us consider how the number of times an individual's life has been saved may influence the slope of the logarithm of the mortality curve. Assume that in some population with mortality rate $\mu(x)$ the life of each individual can be saved once, and that after such "resuscitation" the chances of survival for individuals saved at age x remain unchanged, i.e., they are characterized by the same mortality rate $\mu(x)$ (Fig. 3). Straightforward calculations show that the new mortality rate for

individuals whose lives have been saved once becomes (Vaupel and Yashin, 1987):

$$\mu^{(1)}(x) = \frac{\mu(x)H(x)}{1 + H(x)}$$

One can see that mortality $\mu^{(1)}(x)$ is lower than $\mu(x)$. The mortality rate for those whose lives have been saved n times is:

$$\mu^{(n)}(x) = \mu(x) \frac{H^n(x)}{n! \sum_{i=0}^n \frac{H^i(x)}{i!}}$$

Figures 4 and 5 illustrate changes in the logarithm of the mortality curve for those whose lives have been saved several times.

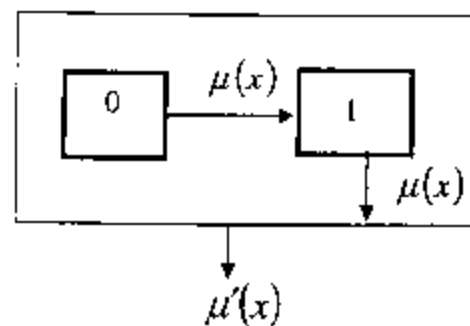


FIG. 3.—Transition Diagram for Those Whose Lives Were Saved Once

One can see from these figures that an increase in the number of times an individual's life has been saved produces an increase in the slope of the logarithm of the mortality curve. This effect can also be calculated analytically. Biologically it means that saving individual lives by the mechanism described above produces a non-uniform age effect on observed mortality. This is because the procedure of saving lives tends to shift early death times to the right, toward older ages. As a result, chances of death decline faster for the younger individuals than for the older ones. It seems to be clear that the process of saving lives cannot be interpreted as the process that accelerates the biological aging rate. Thus, saving individuals' lives due to improvements in medical and living conditions can produce the effect of an increase in the rate of demographic aging also without any additional assumptions concerning the rate of biological aging.

IMPROVEMENTS IN THE STANDARDS OF LIVING INCREASE THE DEMOGRAPHIC AGING RATE

The influence of changes in living standards on trends in mortality rates can

be studied in the framework of the Strehler and Mildvan (1960) (SM) model. This model relates the exponential increase in human mortality between the ages of 35 and 85 (the Gompertz law $\mu(x) = ae^{bx}$) with the linear decline of a vitality index $V(x)$ describing age-related decline in individual homeostatic capacities $V(x) = V_0(1 - Bx)$ and parameters (the frequency K and the average magnitude ϵD) of environmental stresses. As a result, the intercept $\ln a$ and the slope b of the logarithm of the Gompertz mortality curve become represented in terms of parameters characterizing physiological aging and environmental stress. An important theoretical finding of Strehler and Mildvan was that $\ln a$ and b are negatively correlated. This result means that the evolution of the Gompertz part of the mortality curve must follow a certain regularity pattern. Strehler and Mildvan's analysis of demographic data confirmed this theoretical finding. Gavrilov and Gavrilova (1991) have shown that improper specification of the mortality model (e.g., neglecting the Makeham term when its presence is necessary) may produce a spurious correlation between Gompertz's parameters. They excluded possible influence of the Makeham

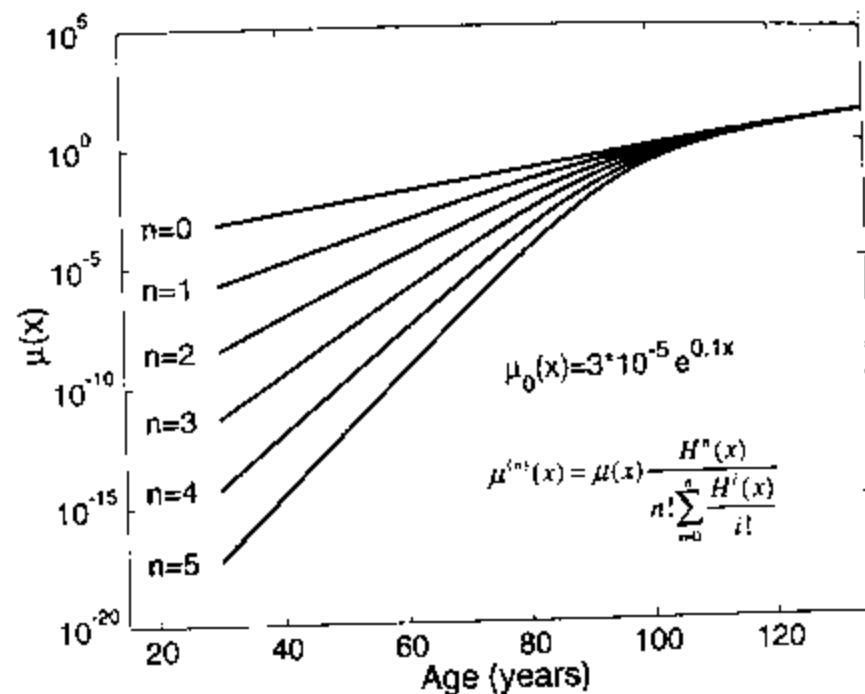


FIG. 4.—The Logarithms of the Mortality Rates for Those Whose Lives Have Been Saved n Times for $n = 0, 1, 2, 3, 4, 5$ Times

term in their analysis of data. However, that strong negative correlation between Gompertz's parameters remained. The SM model has been successfully used in the analysis of trends in mortality by cause (Riggs, 1994; Imaizumi, 1996). It was also useful in the analysis of the decline of the mortality rate in developed countries (Riggs, 1992; Riggs et al., 1998; Yashin et al., 2001, 2002). It has been applied to the analysis of data from stress experiments with nematode worms *Caenorhabditis elegans* (Michalski et al., 2000). In this model the rate of increase of the logarithm of the mortality rate (parameter b) may be represented as follows (see the Appendix):

$$b = \frac{V_0 B}{\epsilon D}$$

Here parameter B characterizes the rate of decline of vitality index $V(x)$ (rate of biological aging), V_0 is the initial value of this index, and ϵD is the average value of energy demands necessary to defend the individual organism from consequences of stresses. Do changes in the parameter b of the Gompertz curve correspond to changes in the rate of biological aging? One can see from the equation above that such is not necessarily the case: an increase in the parameter b can be produced without any change in the rate of individual aging (characterized by

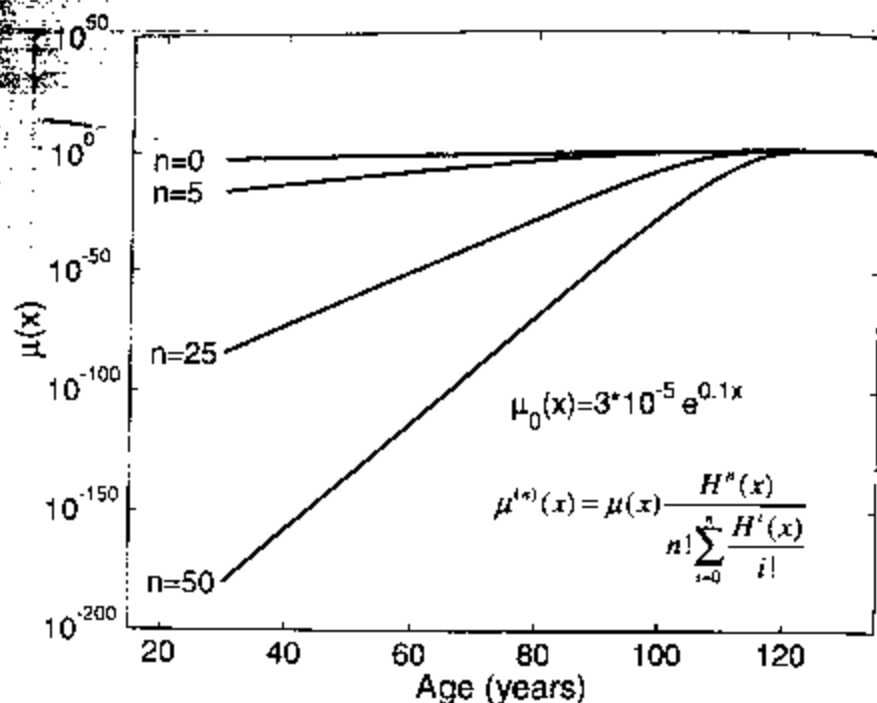


FIG. 5.—The Logarithms of the Mortality Rates for Those Whose Lives Have Been Saved n Times for $n = 0, 5, 25, 50$ Times

parameters V_0 and B). The structure of the SM model allows us to make a clear biological interpretation of this phenomenon. Indeed, since the ability to withstand stresses (vital capacity index $V(x)$) declines with age, any reduction in the magnitude of stresses produces much more benefit to younger individuals than to older ones. This is because such reduction is not so important at older ages: even a small stress is enough to kill a person having a small level of vital capacity. Such a reduction can be reached by a decrease of the average energy demands eD , necessary for an organism to cope with and to recover from stresses. Such a pattern of changes in the mortality rate took place in

developed countries in the first half of the last century. The decline in eD was likely to be reached by total or partial vaccination of individuals, increased consumption of vitamins, quicker medical emergency service, etc. The statistical analysis of mortality data, using the Strehler and Mildvan (1960) model, shows that parameters V_0 and B in such trends remain unchanged (Yashin et al., 2001).

SURVIVAL CAN BE IMPROVED WITHOUT CHANGES IN THE SLOPE OF THE LOGARITHM OF THE MORTALITY RATE

Analysis of time series mortality data shows that the "rectangularization" pattern

of survival improvement observed in the first part of the century in developed countries was later replaced by the "parallel shift of the survival curve to the right" pattern (Yashin et al., 2001) (Fig. 6). This corresponds to an almost parallel shift of the mortality rate to the right. In such a trend almost no changes in the slope of the logarithm of the mortality rate are observed. Does this mean that the change in this trend was not accompanied by changes in the rate of biological aging? Not necessarily. As is shown by Yashin et al. (2001a; 2002), the explanation of the change in the trends involves changes in the parameter B which characterizes the biological aging rate. Note that such change cannot be described in the traditional framework of the Strehler and Mildvan (1960) model where parameters of individual aging V_0 and B are fixed.

The extension of this model requires an additional assumption about dependence between parameter K , characterizing the intensity of environmental stresses reaching the organism, and parameter B , which seems to change simultaneously. Such an assumption involves an additional model of "survival trade-off" where the organism may organize a defense against stresses balancing between two different strategies. One strategy is to make the organism more robust. This strategy reduces the intensity and the magnitude of the stress process reaching an organism. However, since its resources are limited these efforts reduce the organism's adaptive capacity, which leads to an increase in the rate of physiological decline B . Another strategy is to increase adaptive capacity (e.g., the rate of DNA and protein repair) at the expense of a reduction in robustness. In this case the value of parameter B declines but the intensity of stresses K increases. This change has been ob-

served in cohort analysis of female data in Sweden (Yashin et al., 2002).

We performed statistical analysis of demographic data about mortality in thirteen developed countries. The results of our analysis confirm the possibility of the presence of a trade-off mechanism capable of modulating the individual aging rate in a human organism in response to changes in the intensity and magnitude of environmental stresses. It may be assumed that this mechanism is also involved in regulation of a balance between protection against internal and external stresses (Yashin et al., 2002).

DISCUSSION

The evolutionary approaches to studying aging and longevity assume the presence of an adaptation mechanism in individual organisms capable of modifying age patterns of life history traits. Such an adaptation may require many generations to adjust population life history traits to certain environmental conditions.

At the same time any organism has an ability to adapt to such conditions during its life course, modulating its reproductive output and changing the rate of its physiological and biological decline in accordance with internal mechanisms the functioning of which is still not well understood.

Why does such a decline in physiological and biological capacities occur in organisms of many species we know? Why is senescence not developing in organisms of some other species (Finch, 1990)? Is individual aging a price for adaptation to unfavorable environmental conditions? Note that although the evolutionary models of aging and longevity are important for better understanding the essence of these phenomena, studies of the

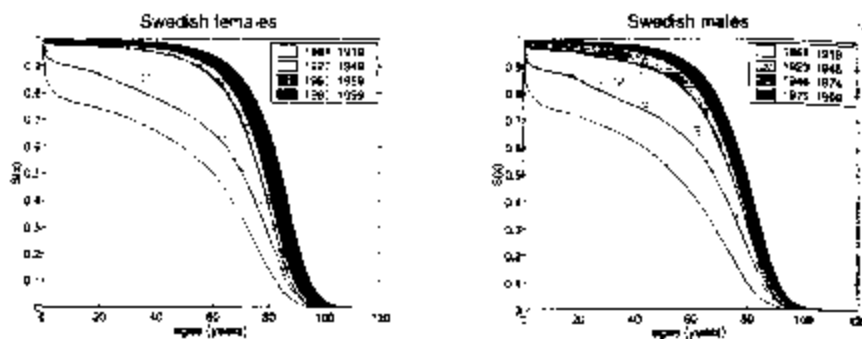


FIG. 6.—Period Patterns of Survival Improvement for Males and Females in Sweden (1861-1999)

adaptation process during the individual life course have direct practical interest. For humans, they open an opportunity to make the aging process less unpleasant, increase active life span, and reduce changes of premature death for individuals living today. It would not be an exaggeration to say that most people today would like to live a long and healthy life.

To clarify the process of individual adaptation and its role in aging is the goal of many population studies of aging and longevity. For humans, information about changes in life history traits (such as fertility and mortality) presented in most demographic data embraces a relatively short (from the evolutionary perspective) period of time in the demographic history of a population. Therefore, observed changes in such trends are likely to be due to individual rather than evolutionary adaptation (which involves many generations of individuals). In this case one has an opportunity to learn about mechanisms of individual aging by analyzing age trajectories and time trends in the population mortality rate. For this purpose, we need models that describe the process of individuals' physiological and

biological decline with age, elucidate the role of defense and adaptation mechanisms in coping with different kinds of stresses in this decline, and relate all these processes to an individual's survival chances.

Some experimental biologists and demographers involved in the population studies of aging and longevity tend to simplify the situation and interpret the slope of the logarithm of the mortality curve with the rate of individual aging. For example, parameter b in the Gompertz model of mortality rate $\mu(x) = ae^{bx}$ is often considered a valid measure of the individual aging rate. This practice must be avoided since it does not stimulate further thinking about the essence of the aging process and substitutes the notion of individual aging with the notion of demographic aging. The latter has to be decomposed into the individual aging per se and changes not related to such an aging. The analysis of three different mortality models performed above shows that changes in demographic aging may be observed without changes in the individual aging rate. This observation indicates the need to evaluate forces capable of

influencing the slope of the observed mortality rate. We show that these forces may be related to changes in population heterogeneity distribution, progress in saving individual lives, and improvement in the standards of living. More studies are needed to identify other factors and mechanisms that relate biological and demographic indices of aging.

ACKNOWLEDGMENTS

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APPENDIX

THE STREHLER AND MILDVAN (SM) MODEL

Let $(T_1, Y_1), (T_2, Y_2), \dots, (T_n, Y_n), \dots$ be the sequence of pairs of random variables characterizing the times of occurrence of stress events and the energy demands for an organism needed to recover from this stress, respectively. Let $K(x)$ be the intensity of the counting process $T_1, T_2, \dots, T_n, \dots$ describing arrival times of stress events. We assume that for each $i = 1, 2, \dots$, the variable Y_i is exponentially distributed.

$$P(Y_i > y) = e^{-y/D} \quad [3]$$

Let $V(x)$ be the maximum capacity of the energy supply for an organism at age x . Strehler and Mildvan provide physiological evidence that the changes of this capacity with age may be approximated by linear function:

$$V(x) = V_0(1 - Bx) \quad [4]$$

Here V_0 is the initial value of this capacity, and B is the parameter characterizing the rate of its decline with age (see Fig. 7).

MORTALITY RATE IN THE SM MODEL

The SM model assumes that for an individual who has survived to age x , the death occurs at the age interval $[x, x + \Delta x]$ if:

1) A stress event happens at the age interval $[x, x + \Delta x]$. This means that for some $i = 1, 2, \dots$, the following inequality takes place: $[x \leq T_i < x + \Delta x]$. This happens with probability $K(x)\Delta x$.

2) The magnitude of energy demand Y_i exceeds $V(x)$. The probability of this event is

$$P(Y_i > V(x)) = e^{-\frac{V(x)}{D}} \quad [5]$$

Hence

$$\mu(x)\Delta x = K(x)e^{-\frac{V(x)}{D}}\Delta x \quad [6]$$

Here $\mu(x)$ is the mortality rate at age x . When $K(x) = K$, we get

$$\mu(x) = Ke^{-\frac{V(x)}{D}} \quad [7]$$

THE SM CORRELATION

Taking into account that $V(x) = V_0(1 - Bx)$, we get

$$\mu(x) = Ke^{-\frac{V_0(1-Bx)}{D}} = Ke^{-\frac{V_0}{D}} e^{\frac{V_0 B}{D}x} \quad [8]$$

or

$$\mu(x) = ae^{bx} \quad [10]$$

where

$$a = Ke^{-\frac{V_0}{D}} \quad [11]$$

and

$$b = \frac{V_0 B}{eD} \quad [12]$$

From here we get the SM correlation (linear relationship between $\ln a$ and b):

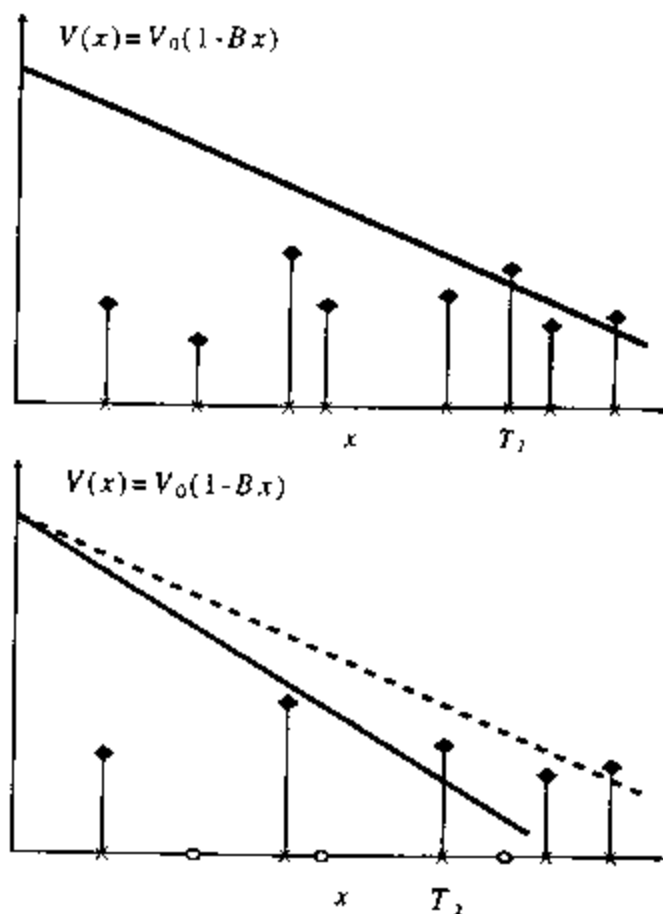


FIG. 7.—a) The vital capacity index $V(x)$ (solid line) and the process of stress events. The vertical lines with diamonds at the top show the magnitudes of the specific stress events (energy demands) (upper panel). The age of death (T_1) is the age at first intersection of vital capacity index $V(x)$ and the value of the respective energy demand.

b) An increase in the slope of the vital capacity index (an increase in B , solid line), as a result of "thinning" of the process of stress events (a decline in K) (lower panel). Circles at the x -axis show eliminated stress events. The dashed line shows the trajectory of $V(x)$ before thinning. The age of death (T_2) is the age at first intersection of vital capacity index $V(x)$ and the value of the respective energy demand.

$$\ln a = \ln K - \frac{1}{B} b \quad (13)$$

Here K is the intensity of environmental stresses reaching the organism, and B characterizes the rate of decline of its physiological capacities with age. Formula [13] is known as the Sreher and Mildvan

(SM) correlation between Gompertz parameters $\ln a$ and b . Such correlation has been confirmed in a number of empirical demographic studies. For several decades such correlation was believed to be a kind of universal demographic law valid for both period and cohort mortality data.

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