ABSTRACT  Old noninbred fly mortality decreases according to the inverse linear law and reduces to a single suborder-specific age. Relative child mortality (the mortality at a given age related to the mortality at 10 years) from 1 mo to 11 years is the same with 8% mean accuracy for all humans, independent of race, country, sex, and birth year (from 1780 to 1995), in contrast to birth mortality, which in developed countries changed fiftyfold during the last century. The concept of invariants, which is very powerful in physics, is applied to mortality of species as remote as humans and flies. It provides quantitative estimates for the selection of hereditary Methuselahs, who live, e.g., over six-mean lifespans and who may be relatively young biologically. It also demonstrates that old fly and relative child mortality are determined genetically and that the former is related to genetic heterogeneity.

1. Mortality Invariants. The evidence that genes influence aging and longevity is abundant (1–4). It includes identification of longevity genes and lifespan extension mutants (3, 5–10), as well as artificial selection for postponed senescence. Yet, it is still uncertain to what extent mortality is genetic (11–14). Natural selection seems consistent with genetically programmed mortality because few wild animals live to senescence; it might be consistent with genetically determined mortality (1, 15–20), which is linked to some other vital character, such as, e.g., stress resistance (12). Large fly populations (13, 16, 17) demonstrated mortality leveling off and decreasing at older ages. To explain it, demographic heterogeneity models (18–20), density effects (21, 22), changes at the individual-level physiology (23), and extension (24) of the “disposable soma” model (25), a model of both the pleiotropy (trade-off) and mutation accumulation (26) in age-structured populations (27) was considered (28) according to the Hamilton–Charlesworth theory. Yet, it still remains a challenge (29, 17, 22), and numerical studies (ref. 30 and refs. therein) of a model of mutation accumulation yielded only mortality increase in old age. Fly mortality (13, 16) presents an even more explicit than the species-specific age, is body temperature of all active insects like aphids might be of special interest. If they yield universally decreasing old age mortality, then parthenogenetic eggs of their Methuselas might provide hereditary Methuselah clones. Populations of hereditary Methuselahs might determine explicit characters linked to longevity. Such characters may allow for an estimate of the lifespan of an individual and an easier selection of the populations with increasing mean lifespans.

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Mortality is used to quantify senescence in a population (1). If lower mortality implies younger biological age (for a given species), then the decreasing old age mortality implies that biologically older animals die out very rapidly, only biologically very young (and correspondingly rare) genotypes survive, and the average biological age of the surviving Methuselah subpopulation decreases with age. Thus, hereditary Methuselahs may be biologically relatively young (at least in some physiological aspects, which are to be specified).

Infant mortality is determined largely by environment. Indeed, improvements in social and medical conditions decreased it fiftyfold within the last century (32–36). However, life tables (32–36) prove that mortality always reaches a minimum at the age \( x_m = 10.5 \) years, which is a species-specific mortality invariant and is therefore genetic. The next section verifies with 272 life tables (32–36) that, although mortality changes fiftyfold in agreement with the prediction of phenomenological theory (39), the relative mortality (i.e., the mortality at a given age related to the mortality at 10 years) decreases with age.¶ Phenomenological theory predicts (31) that, depending on old population heterogeneity (see the next section for quantitative details), the inverse relative number of old survivors is linear or quadratic with age.

3. Universal Laws. Large noninbred fly populations were studied for male and female medflies (13, 16) in different conditions (1,203,646 in 167 cages, 27,181 in individual cells, and 21,204 in individual cups), and 121,894 male \( Drosophila \) in cages (stars). Twenty-six medflies in cages and 58 in individual cups lived beyond 120 days, to 171 and 241 days respectively (see Fig. 1B); cf. the ratio of the maximal and the mean (thick vertical lines) lifespans for humans and medflies. Mortality rate is calculated according to \( q_x = \ln(N_x/N_{x+1}) \), where \( N_x \) is the number of survivors to the age \( x \) (years for humans and days for flies). (B–D) Inverse relative number of survivors \( (N_{85}/N_x) \) to a given age \( x \) in days for medfly females ( ), males ( ), and all medflies ( ) in cups, cells, and cages respectively; for male \( Drosophila \) in cages ( ) and 5,751 (inbred ones in Fig. 1B only) in vials ( ) on semilogarithmic (B), linear (C), and quadratic (D) scales. For clarity, data beyond the age with reliable statistics in C and D, and before the linear region for medflies in cups in D, are dropped out. Solid lines are linear interpolations. Note that many data points overlap.

\[ N_{85}/N_x = (x - X)/(85 - X) \]
\[ \sqrt{N_{85}/N_x} = (x - X)/(85 - X). \]
The 7% accuracy in old age (with significantly higher fluctuations due to low statistics) is remarkable: before the universality of age, \( N_\text{x} \), and \( n_\text{x} \) changes thousandfold, from 0.00005 (male medflies in cages) to 0.05 (female medflies in cups). The validity interval of the interpolation is very long, significantly longer (compared with the mean lifespan) than the well-known Gompertz law (40, 31) (which corresponds to linear regions in Fig. 2A). According to Eq. 1, mortality rate \( q_x = -d\ln N_x/dx \) is correspondingly

\[
q_x = 1/(x - X) \quad \text{and} \quad q_x = 2/(x - X).
\]  

By Eq. 1 and refs. 13 and 16, five million medflies in cages and 150,000 in cups are expected to provide 50 survivors to 10-year lifespans, i.e., to 200 days in cages and to 300 days in cups. The validity of Eq. 1 with a species-specific \( X \) for insects like aphids is a litmus test for the possibility to use parthenogenetic clones to select hereditary Methuselahs.

Consider child mortality. Its statistics in modern, developed countries is rather low. For instance, 50,208 girls were born in 1995 Sweden. Fifty-one died the first day; 54 the next week; 24 the second, fourth, and ninth year, respectively. This yields relative number of deceased children. Phenomenological theory predicts (39) that it is a universal function of age with no fitting parameters. Specifically, if the number of survivors to \( x \) years is \( N_x \), and \( n_x = \ell n(N_x/N_0) \), then beyond a few weeks

\[
n_x/n_{10} = \ell n x/\ell n 10.
\]  

The function \( n_x/n_{10} \) is presented in Fig. 2A according to 1871–1994 German (35) and in Fig. 2B according to 1871–1994 German, 1891–1990 Japanese (36), and 1780–1995 Swedish male and female lifetables (32, 34). From 1 to 11 years the mean quadratic deviation from the average values is 5% in both figures. (Characteristically, the mean quadratic deviation at birth is 30 times larger and is presumably nongenetic.) The mean deviation of the average values from \( \ell n x/\ell n 10 \) is 2% in Fig. 2A and 5% in Fig. 2B. The 210 Swedish infant lifetables (32) (which present raw data daily until 1 mo and monthly until 1 year for every year from 1891 to 1995) yield \( \Delta N_x/\Delta N_{12} \) (x is in months) as shown in Fig. 2C. From 1 to 24 mo, the mean deviation from the averages and of the averages from \( \ell n x/\ell n 12 \) is 8%. Thus, from 1 mo to 11 years the relative number of deceased children is indeed a universal species specific (with 8% mean accuracy) function of age, independent of race, country, sex, and birth year, whereas the birth and the first week mortality is predominantly nongenetic (premature) and crucially depends on social and medical conditions.

Eq. 3 implies that child mortality \( q_x \) is inversely linear with age:

\[
q_x = 10q_{10}/x
\]  

(\( x \) is in years). This is similar to old fly mortality (2), but the factor \( q_{10} \) in Eq. 4 is not universal (see, e.g., Fig. 1A). However, relative mortality \( q_x/q_{10} \), by Eq. 4, is species-specific, \( = 10/x \) and is therefore genetically determined.

An important comment is in order. Although Eqs. 1 and 3 present (with 7% and 8% accuracy, respectively) empirical sur-

\[\begin{align*}
\text{Fig. 2.} \quad & \text{Relative number \( n_x \) of deceased male and female children between 1 and \( x \) years according to 1871–1994 German (A), 202 combined 1871–1994 German, 1891–1990 Japanese, and 1780–1995 Swedish lifetables (B) and between 1 and \( x \) mo according to 210 infant male and female 1891–1995 Swedish lifetables (C). In A and B, \( n_x = (\ell n(N_x/N_0))^{-1} \ell n(N_1/N_0); \) in C, \( n_x = (N_1 - N_0)/(N_1 - N_{12}); \) Solid lines are \( \ell n x/\ell n 10 \) in A and B and \( \ell n x/\ell n 12 \) in C. Each data point (a cross) corresponds to a lifetable.}
\end{align*}\]  

vival data, Eqs. 2 and 4 provide mortality rates according to their interpolations. If \( q_x \) is calculated according to \( q_x = \ell n(N_x/N_{x+1}) \), then the nonuniversality of \( q_{10}/q_x \) is significantly higher.

3. Phenomenological Theory and Human-Fly Universality.

The previous section empirically demonstrates a fly mortality invariant \( X \) (which is independent of conditions, sex, and the degree of population heterogeneity of a given suborder) and thus the predominantly genetic nature of old fly mortality, which, by Eq. 2, reduces to \( X \). Because an old individual does

\[\begin{align*}
\text{\textsuperscript{1\textsuperscript{1}}Theory (31, 38, 39) relates Eq. 1 to population heterogeneity (see section 3). And indeed, inbred male Drosophilas (14) die out much quicker than noninbred ones in the worst conditions (17) (cages), long before \( X \) and the onset of Eq. 1—see Fig. 1B. In Fig. 2 of ref. 15 genetically homogeneous mortality, apart from fluctuations, steadily increases. No inbred population provides statistically reliable mortality decrease in Fig. 2 of ref. 14 is provided by the last six survivors.)
\end{align*}\]  

\[\begin{align*}
\text{\textsuperscript{1\textsuperscript{1}}Usually (32, 34–36) \( n_x \) is close to the relative number of deceased children \( \Delta N_x/N_1 = (N_1 - N_0)/N_1 \), and \( n_x/n_{10} = \Delta N_x/\Delta N_{10} \) is their relative number with respect to \( \Delta N_{10} \).
\end{align*}\]  

\[\begin{align*}
\text{\textsuperscript{1\textsuperscript{1}}Thus, nongenetic diseases little hurt genetically robust Methuselahs. Mortality is predominantly genetic for old humans also (31). (But the lifespan is not. Much of its variation is nongenetic.) Then why do old flies and humans die? The nature of mortality with no specific external causes is an experimental challenge, but physics knows two such stochastic scenarios: radioactive decay (which occurs with no external or internal intervention) and freezing (under exceptionally near-perfect conditions, water may be supercooled to \(-40^\circ C\)). Similarly, old age deceases may not be the cause but just a manifestation of instability of a live state.
\end{align*}\]
not get younger with age, presumably the chances to die do not decrease either. So, genetic mortality decrease must be related to genetic heterogeneity of the fly population. To survive to very old age, individuals must have very low genetic mortality, significantly lower than the mortality of the population at large. Therefore, populations become more and more selected as they age, and subpopulations with low death rates constitute the majority of individuals in the oldest age classes. And, indeed, by Eq. 2 mortality of median survivors to 120 days is 10 times lower than mortality of the much larger number of survivors to 80 days. In fact, by Eq. 2, at 120 days it is the same as the mortality of the population in Fig. 1A at 10 days (with 90% of survivors). Thus, with respect to mortality, flies are genetically very heterogeneous, and old age mortality crucially depends on the heterogeneity of the initial population and on the subpopulations that survive to old age under given conditions.‡‡ At very old age, the number of survivors is so low that the population mortality becomes stochastic, strongly depending on individual mortalities, and is highly nonuniversal. Usually beyond a certain (nonuniversal) age, it rapidly increases, in agreement with phenomenological theory (31) (see Fig. 1B). However, the last survivors may accidently have anomalously low genetic mortality and yield long “survival plateaus” as shown in Fig. 1B, in which flies do not die (presumably, their genetic mortality is extremely low). Eighteen medflies in cages (0.003% of the initial population) survive to 4.3 mean lifespans \( \eta \). They all live another 0.9 \( \eta \). Two female medflies in cups survive to 5.5 \( \eta \) and live until 6.6 \( \eta \). Three medflies in cells (0.03% of the initial population) who survive to 4.4 \( \eta \), all three live another 3.5 \( \eta \) to 7.9 \( \eta \). (Such genetic “quasi-immortals” may be of special interest.) Smaller old age plateaus in Fig. 1B and C are multiple. Corresponding quasi-steps in Fig. 1D may manifest successive extinction of certain subpopulations.

The previous section demonstrated that, although the child mortality rate (especially at birth) crucially depends on conditions and strongly fluctuates, its decrease with age is predominantly species-specific and thus genetic. One may speculate that mortality decreases because genotypes with anomalously high mortality die out anomalously early and determine the law of mortality decrease (39) (i.e., relative child mortality is related to genetic heterogeneity). Remarkably, *Drosophila* mortality at early age also decreases to a minimum at the age \( \equiv X/10 \) and yields the same law (39) with the mean quadratic deviation of 16%. Mortality minimum in human louse (16) is reached in pupal stage. Possibly, in medflies and in some other insects mortality also decreases before an adult stage.

Universally for flies and humans, advanced age yields (31, 38, 39) plateaus in mortality curves. Because mortality strongly fluctuates, plateaus are more explicit as linear regions in the curves in Fig. 1B. (For other mortality regions and invariants, see refs. 31, 38, and 39.)

Similarities in mortality of species as remote as humans and flies suggest a general mortality pattern. This suggestion is verified with a general invariant, which unites metabolism and lifespan (41). All animals (from invertebrates to mammals) consume 20 oxygen molecules per body atom per lifespan. For many animals an experimental error may be by a factor of 3; some animals have anomalous (also by a factor of 3) oxygen consumption (41, 42). Yet, the relative accuracy of this invariance is remarkably high because 3 should be compared with 10\(^{10} \) (which represents the change in the number of body atoms). A general invariant suggests a general origin of genetically determined mortality, which did not change at any stage in evolution. Indeed, analysis of human and fly data presents (31) a general mortality law‡‡applicable to individual species. In contrast to the Gompertz–Stricker–Mildvan-type law (see it in refs. 31 and 40 and refs. therein), its mortality may vanish at any age for certain genotypes.‡‡

A few comments. Small terriers and large Irish wolf hounds, which belong to the same species of domestic dogs; workers and much larger queens of ants, social bees, and termites (43), have significantly different average lifespans. A universal allometric relation between the average lifespan and the body mass (refs. 41 and 44 and refs. therein) implies that this is not accidental. Possibly, some species have several mortality invariants (39), but a comprehensive study is called for.

The suggested phenomenological approach yields universal mortality laws and universal (across all animal species) oxygen consumption, demonstrates species- and suborder-specific mortality invariants, establishes predominantly genetic nature of old fly and relative child mortality, and provides quantitative estimates for the selection of hereditary Methuselah populations. Once verified, quantitative universal laws, which generalize empirical data, may serve as a basis for a theory of their biological origin. The latter was, e.g., suggested for allometric relations (44) (but a specific universal value of oxygen consumption remains to be explained). If a population of hereditary Methuselahs (which may be relatively young physiologically) is selected, it might elucidate the biology of mortality invariants and genetic mortality, which is beyond phenomenological approach.

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††Phenomenological theory (31) suggests a general mortality law. One of its parameters is a species-specific age \( X \). It is the maximal value of the mean lifespan with respect to all possible populations of and conditions for a given species. The other (the Gompertz slope \( B \)) depends on a genome, and the population heterogeneity (with respect to mortality) is quantitatively specified by its distribution function. The latter changes with conditions (and yields premature mortality, which may correlate with genetics). If in old age it is proportional (38, 39) to \( B \) (with an integer \( n \)) when \( B \to 0 \), then old age mortality rate \( q_x \) is “quantized” \( q_x = (n + 1)/(x - X) \). Typically \( n \neq 0 \) for \( n \neq 1 \), as in Eq. 2; different conditions may imply different surviving subpopulations, different values of \( n \), and somewhat different fly age, when Eq. 1 settles in \( (\equiv 74 \text{ days in cages and } \equiv 80 \text{ days in cups}) \). If \( n = 0 \) persists to arbitrarily old age, then the mean lifespan is proportional to \( n \), and when the initial population \( N_{0x} \to 0 \), then mortality exponentially increases with age: \( \tau_{nx} \propto (x - X) \). This is characteristic of humans. Note a misprint in ref. 31: line 3 above Eq. 4 should read \( b = 0 \) rather than \( b < 0 \).

‡‡The law (see it in refs. 31 and 40 and refs. therein) is applicable to individual species. In contrast to the Gompertz–Stricker–Mildvan-type law (see it in refs. 31 and 40 and refs. therein), its mortality may vanish at any age for certain genotypes.‡‡