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A Critique of Theories of Mortality

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INTRODUCTION

WITHIN THE PAST FEW YEARS, a number of theories have been proposed to account for the mathematical functions describing mortality curves (8, 12, 20, 24, 25, 26, 27, 29). This increased interest was indirectly stimulated by the observed life shortening effects of high energy radiation (1, 2, 4) and by the growing interest in the biology of the aging process. As a result, there exist, at present, at least four independent classes of theories of mortality kinetics. In the course of establishing criteria for our own quantitative theory of mortality and aging (25, 26), we have made an intensive investigation and analysis of the various theories of mortality. In view of the fact that existing data permit a tentative choice to be made, we are undertaking, in this paper, a critical analysis of both the bases and consequences of the various theories. The considerations treated herein have consequences relevant to theories of aging and to the field of radiation biology.

The two elementary procedures utilized in testing the validity of theories reviewed in this critique are:

1. Does the theory require assumptions which are qualitatively or quantitatively inconsistent with observation?

2. Does the theory make predictions which are qualitatively or quantitatively inconsistent with observation or natural law?

A third, but less crucial, criterion is the parsimony of the theory.

Four general groups of theories of mortality have been analyzed. These are: 1) the Brody-Failla theory (3, 8); 2) the Simms-Jones theory (24, 12); 3) the Sacher theory (20), and 4) the Strehler-Mildvan theory (25, 26).

The first and second theories are apparently inconsistent with criterion 2. The third theory does not meet criterion 1. The last theory makes predictions which are qualitatively and quantitatively consistent with observation and thus does not suffer from the above difficulties. However, it, like the others, is not designed to take account of the observed departure of natural populations from the Gompertz equation at great ages. Whether this signifies a basic error in the assumptions of the theory, or inadequacies of the data, cannot now be decided.

DEFINITION OF MORTALITY RATE AND OTHER ACTUARIAL TERMS

The mortality rate (R_m) is defined as the instantaneous rate of loss by death of members of a population divided by the instantaneous size of the population. Mathematically, this is expressed by the derivative term $-(1/n)(dn/dt)$. Mortality rate may also be considered to be the instantaneous probability of dying for a member of the population n.[1]

OBSERVATIONS

There are six observations that any mathematical theory of mortality must incorporate into its postulatory structure, explain, or at least not violate. These are:

1. *Gompertz Function* (7, 10, 28) (Fig. 1). For a number of species of animals, there is an approximately exponential increase in the mortality rate with age (particularly after reproductive maturity is reached). This relationship, first pointed out by Benjamin Gompertz in 1825, may be expressed mathematically as follows:

$$R_m = -\frac{1}{n}\frac{dn}{dt} = R_0 e^{\alpha t} \tag{1}$$

where n = number of individuals at time t and α and R_0 are constants, the latter being the hypothetical extrapolated mortality rate at $t = 0$.

Many mortality rate curves which depart from simple Gompertzian kinetics at early ages can be fitted by including an additive constant, A (11), in the mortality rate expression; thus

$$R_m = R_0 e^{\alpha t} + A \tag{2}$$

[1] For practical purposes two simplifications are usually made. Firstly, rates are not measured continuously, but at convenient time intervals. Secondly, n is usually taken as the number living at the beginning or at the mid-point of the time interval. These simplifications do not greatly affect the shape of mortality curves except where the number dying per unit time is an appreciable fraction of n.

The age specific death rate is only one of the ways in which mortality statistics can be expressed. Crude data relating the deaths occurring in a population to the age of individuals are also plotted as numbers of deaths per age and as survivorship curves. In the first case, the number dying per unit time is directly plotted as a function of age. The survivorship curve, on the other hand, consists of a plot of the percent or number remaining alive versus time. The mortality rate curve can be obtained from the latter, by dividing the slope of the survivorship curve by its altitude at every point.

Mathematically, there is an advantage in the use of mortality rates to describe population mortality behavior, particularly if such populations behave in a Gompertzian manner. The Gompertz equation is a simple exponential function which is determined by only two constants. The survivorship curve, although a more direct expression of the experimental data, is a more complicated function of time or age. This may be seen by integrating the Gompertz equation $-dn/ndt = R_0 e^{\alpha t}$ (after separating the variables) between the limits $t = 0$ and t thus: $N/N_0 = \exp(R_0/\alpha)(1 - e^{\alpha t})$. Thus, the surviving fraction of a Gompertzian population is a "double exponential" function of age.

The number dying per unit time is also a complicated function of age as seen by differentiating the above equation with respect to time.

$$\frac{dn}{dt} = -N_0 R_0 e^{R_0/\alpha} \exp\left(\alpha t - \frac{R_0}{\alpha} e^{\alpha t}\right)$$

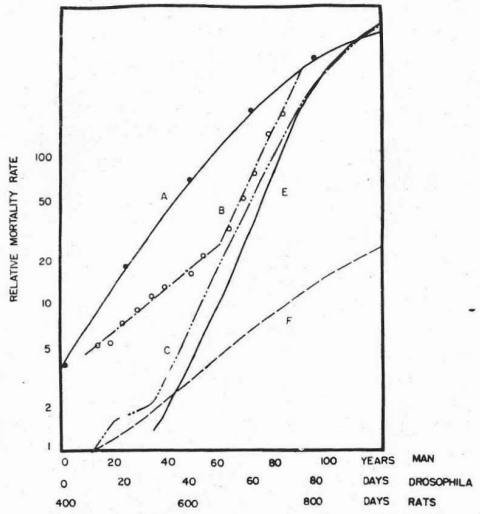

FIG. 1. Mortality rate versus age for various species of animals (7, 28).

A. Male rats
B. Human male (Egypt, 1947)
C. Human male (U. S., White—North Central Division, 1949–51)
E. Human female (U. S., White—North Central Division, 1949–51)
F. Drosophila melanogaster

The Makeham constant "A" presumably represents age independent causes of death.

2. *Rate of Loss of Function* (see Table 1). The determination by Shock, et al. (6, 9, 13, 14, 16, 17, 18, 21, 22, 23) of the change in physiological properties of human males of age 30 or more, as measured by renal, pulmonary, cardiovascular, neurologic, muscular and psychometric function tests, show a great deal of variation among individuals. However, the decade averages show a decline of function with age that is approximately linear (see Fig. 2).

The linear rate constants for loss of physiologic function have been evalu-

TABLE 1

Calculation by Three Techniques of the Linear Decay Constant for 10 Physiologic Functions in Human Males

(See text for references)

Physiologic Function (F_i)	Units	Value at Age 30	Change in Function/ Yr.	Hypothetical Extrapolated Value At Age 0	Lowest Measured Value	Fraction of F_i^{30} Lost/Yr.	Fractionof "Reserve" Lost/Yr.	Age 80-90 Average Value—$\bar{F}_i^{80}$	Fraction of "Reserve" Lost/Yr.
(F_i)		(F_i^{30})	$\Delta F_i/\Delta t$	(F_i^0)	(F_i^L)	$\frac{\Delta F_i/\Delta t}{\Delta t(F_i^{30})}$	$\frac{\Delta F_i/\Delta t}{\Delta t(F_i^{30} - F_i^L = B_i)}$	$\bar{F}_i^{80}$	$\frac{\Delta F_i/\Delta t}{\Delta t(F_i^{30} - \bar{F}_i^{80})}$
Standard Renal Plasma Flow (Diodrast)	ml./min. × 1.73 M²	620	6.74	822	150	.0109	.0100	126	.0097
Standard Renal Plasma Flow (PAH)	ml./min. × 1.73 M²	525	7.29	743	120	.0139	.0087	4	.0099
Standard Glomerular Filtration Rate	ml./min. × 1.73 M²	130	.90	157	33	.0069	.00725	31.8	.0072
Tubular Maximum (Glucose)	mg./min. × 1.73 M²	330	2.2	396	170	.0066	.00973	128	.0082
Tubular Maximum (PAH)	mg./min. × 1.73 M²	90	.96	119	27	.0107	.0104	14.4	.0091
Vital Capacity	liters	4.2	.038	5.3	1.05	.0091	.00895	.98	.0088
Maximal Breathing Capacity	liters/min.	120	1.30	159	23	.0108	.00956	0.6	.0082
Cardiac Index	liters/min.× 1.73 M²	3.7	.025	4.45	1.7	.0068	.00910	1.24	.0078
Nerve Conduction Velocity	M/sec.	59	.20	65	42	.0034	.00869	41.0	.0083
BMR	Cal/M² × hr.	39	.137	42.60	29	.0035	.0101	20.75	.0066
$\Delta F_i/\Delta t(\bar{F}_i^{30})$ $N = 10$		$\Delta F_i/\Delta t(\bar{F}_i^0 - F_i^L)$ $N = 10$				$\Delta F_i/\Delta t(\bar{F}_i^0 - F_i^{80})$			$N = 10$
Mean = .0083		Mean = .00925				Mean = .0084			
Standard deviation = .00324		Standard deviation = .000554				Standard deviation = .000985			
Standard deviation/mean = .390		Standard deviation/mean = .0588				Standard deviation/mean = .116			
Standard Error of Mean = .00102		Standard Error of Mean = .000171				Standard Error of Mean = .00031			

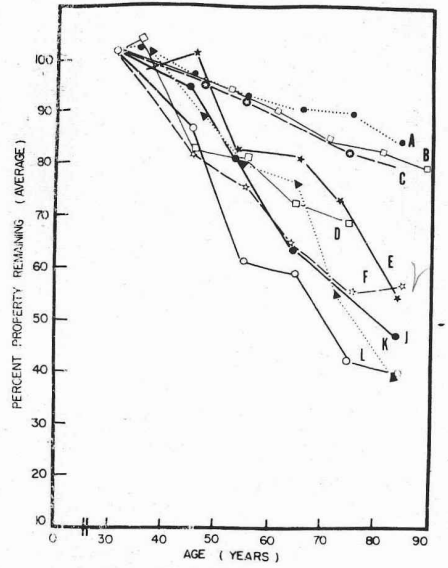

FIG. 2. Percent of initial (age 30) physiologic function remaining versus age for man (See text for references.)

A. Nerve conduction velocity
B. Basal metabolic rate
C. Standard cell water
D. Cardiac index
E. Standard glomerular filtration rate (inulin)
F. Vital capacity
J. Standard renal plasma flow (diodrast)
K. Standard renal plasma flow (PAH)
L. Maximal breathing capacity

ated in two ways (Table 1). Firstly, they are expressed as the fraction of the initial (age 30) function lost per year. Alternately, each constant may be expressed as the fraction of the "reserve physiologic function" lost per year. This "reserve physiologic function" is defined as the difference between the

hypothetical extrapolated value at age 0 and the lowest value compatible with life. Although it is difficult to measure this lower limit, it may be approximated either by the lowest measured individual value in a large series of individual measurements, or by the average value at some advanced age (e.g., 80–90) minus two standard deviations. These latter methods of calculation produce considerably less variation among the estimated constants for diverse physiologic function. Moreover, although they entail an additional minor assumption, the values obtained are more analogous to the quantities used in certain of the theories here discussed.

The values for the linear attrition coefficient B derived by the above methods are summarized below:

A) Fraction of original age 30 function lost per year.

$$.0034 \leq \frac{\Delta \bar{F}_i}{(\bar{F}_i^{30})\Delta t} \leq .015 \qquad \begin{matrix} \text{Mean} = .0083 \\ \text{S.D.} = .0032 \end{matrix} \tag{3}$$

B) Fraction of original (age 0) reserve capacity lost per year (lowest individual value method).

$$.0072 \leq \frac{\Delta \bar{F}_i}{(\bar{F}_i^{0} - F_i^{L})\Delta t} \leq .0104 \qquad \begin{matrix} \text{Mean} = .0093 \\ \text{S.D.} = .00055 \end{matrix} \tag{3}$$

C) Fraction of original (age 0) reserve capacity lost per year (2 sigma method).

$$.0072 \leq \frac{F_i}{(\bar{F}_i^{0} - F_i^{2\sigma})\Delta t} \leq .0099 \qquad \begin{matrix} \text{Mean} = .0084 \\ \text{S.D.} = .00099 \end{matrix} \tag{5}$$

$\bar{F}_i$ = decade average of physiologic function i.
$\bar{F}_i^{30}$ = age 30 decade average of physiologic function i.
$\bar{F}_i^{0}$ = hypothetical (extrapolated to age 0) value of physiologic function i.
F_i^{L} = lowest measured value of physiologic function i.
$F_i^{2\sigma}$ = age 80–90 average minus 2σ of physiologic function i.

3. *Relationship between Slope* (α) *and Intercept* (R_0) *of Gompertz plot* (Fig. 3). For human subpopulations, there is an inverse relationship between R_0 (the extrapolated mortality rate at zero time) and α (the Gompertz slope) (7, 26); i.e.,

$$\frac{dR_0}{d\alpha} < 0. \tag{6}$$

Actually, from Fig. 3 $\qquad -140 \leq \frac{d \ln R_0}{d\alpha} \leq -75 \tag{7}$

Thus, countries with higher initial mortality rates (presumably due to poorer environments) also are characterized by a slower rate of increase of mortality rate (i.e., longer doubling times). This unexpected relationship was first predicted by the Strehler-Mildvan theory (7, 25, 26).

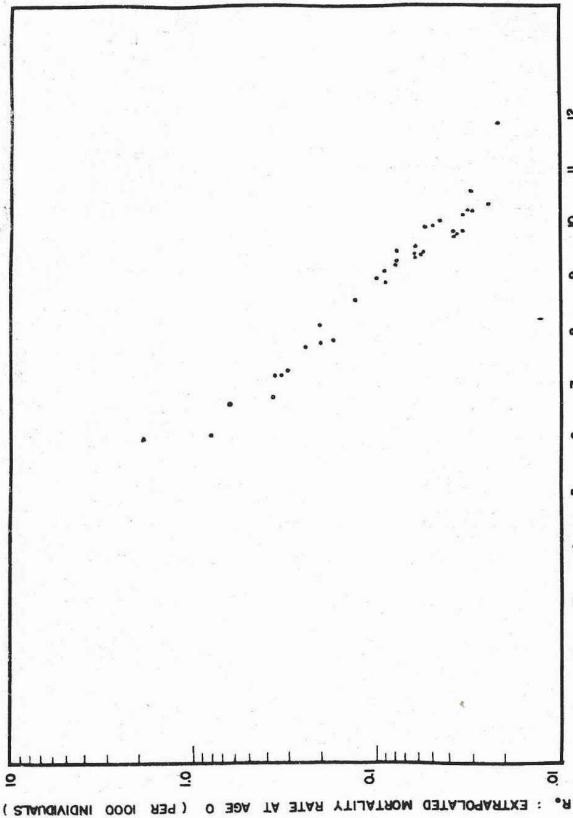

FIG. 3. Hypothetical extrapolated mortality rate at age 0 (R_0) versus Gompertz slope (α) for the males of 35 nations (7).

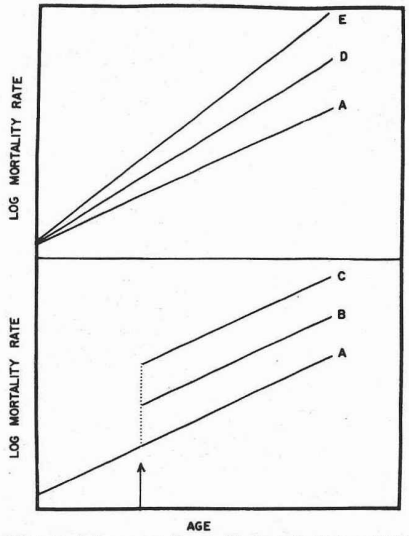

FIG. 4. Effect of radiation on mortality rate (idealized after Berlin and DiMaggio (1).) Upper graph shows in a highly idealized and simplified form, the effect of low chronic radiation dosage on the Gompertz slope of an animal population.

Curve A: Control
Curve D: x roentgens/unit time
Curve E: $2x$ roentgens/unit time

Lower graph represents the effect of high acute radiation dosage on Gompertz intercept at the time indicated by the arrow.

Curve A: Control
Curve B: Radiation dose y
Curve C: Radiation dose $2y$

4. *Relation between Continuous or Instantaneous Radiation Dosage and Gompertz Slope and Intercept* (Fig. 4). It has been observed in experimental animals that continuous exposure to high energy radiation increases the Gompertz slope, without affecting the intercept (1, 2, 4). Conversely, a single dose is said to increase the intercept without appreciably affecting slope.

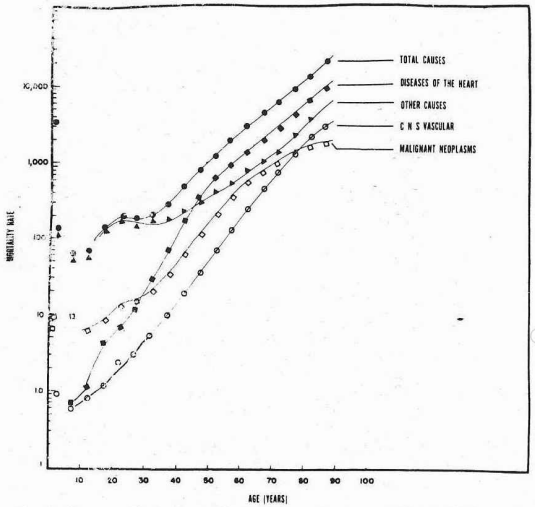

FIG. 5. Cause specific death rates for the three major causes of death in U. S. males in 1952 (28).

These observations, in a highly idealized and simplified form, are summarized in Figure 4.

5. *Application of Gompertz's Function to Cause Specific Mortality Rates.* Simms (24) and Jones (12) have pointed out that cause specific mortality rates in humans tend to increase approximately exponentially with time (Fig. 5). This somewhat less reliable data is by no means as clearly an exponential function, however, as is the total mortality rate (28).

6. *Decreased Gompertz Slope at Great Ages* (Fig. 1). At extremely advanced age, the mortality rate curves of several species rise at a rate progressively lower than exponential (26, 27); i.e.,

$$\frac{d \ln R_m}{dt} < \alpha \qquad \text{for} \qquad t \gg 0. \tag{8}$$

It should be pointed out that three of these observations (2, 3, 5) were made exclusively on man. Moreover, the most reliable mortality statistics

(involving very large sample sizes) and the only extensive physiological and pathological data have come from studies on this species.

We wish to emphasize also that none of the theories here considered make quantitative predictions regarding *all* of these observations. However, it is important to bear in mind the restriction that no acceptable theory should be in essential disagreement with *any* of these observations.

STATEMENT AND CRITIQUE OF THEORIES

A. *Brody-Failla Theory* (3, 8).

1. *Statement.* The theory suggested by Brody and formalized by Failla states that the mortality rate is inversely proportional to the vitality, a physiologic property which itself decays at a rate proportional to the amount present (i.e., first order).

V = vitality at time t

V_0 = vitality at time $t = 0$

$$\frac{dV}{dt} = -\alpha V \tag{9}$$

Integrating,

$$\ln V = -\alpha t + \text{constant} \tag{10}$$

$$\ln \frac{V}{V_0} = -\alpha t, \qquad \text{thus} \qquad V = V_0 e^{-\alpha t} \tag{11}$$

Now according to the theory

$$R_m = \frac{k}{V} = \frac{k}{V_0 e^{-\alpha t}} = \frac{k}{V_0} e^{\alpha t} \tag{12}$$

Defining

$$R_0 = \frac{k}{V_0} \tag{13}$$

we obtain $R_m = R_0 e^{\alpha t}$.

2. *Critique.*

a) Thus, the theory correctly accounts for observation 1.

b) However, by combining equations 12 and 13, we obtain $R_m/R_0 = V_0/V$. Since the observed value of R_m/R_0 for most human populations is approximately 300 between ages 30 and 80, it follows that $V_0/V = 300$ or that the vitality at age 30 would be $^{299}/_{300}$ gone by age 80. Few human physiologic functions decrease to this low value during a lifetime. Moreover, assuming a linear approximation, the decay constant would be 2%/year which is somewhat above the observed rate (observation 2). Moreover, the theory assumes first order loss of vitality which is contrary to observation 2, if we assume that vitality decays linearly as does physiologic functional capacity.

c) According to observation 3, countries with poor environments have high R_0's and lower α values. In order to fit this observation, the Brody-

Failla theory would require a lower starting vitality in a poor environment which is a reasonable assumption (see equation 13). However, the theory would also require a lower first order rate constant for loss of vitality (α) in a poor environment than in a good one. This is patently an unreasonable assumption, for one would certainly expect the rate constant for loss of vitality to be greater in a poor environment than in a good one.

Because of its inconsistency with observations 2 and 3, the Brody-Failla theory fails to meet the criteria that a satisfactory theory should meet.

B. *Simms-Jones Theory* (24, 12).

1. *Statement.* In 1940, Simms and, more recently, Jones suggested that the exponential form of mortality curves might be explained by an autocatalytic accumulation of damage and disease. In Jones' words, "We may regard the lessening of vitality as the accumulation of damage. The rate at which damage is incurred is proportional to the damage that has already been acquired in the past." (12)

Mathematically, $$V = V_0 - cD \tag{14}$$

D = damage at time t

and $$\frac{dD}{dt} = \alpha D \tag{15}$$

Integrating $$\ln D = \alpha t + \text{constant} \tag{16}$$

$$\ln \frac{D}{D_0} = \alpha t \tag{17}$$

D_0 = damage at time $t = 0$

$$D = D_0 e^{\alpha t} \tag{18}$$

thus $$V = V_0 - cD_0 e^{\alpha t} \tag{19}$$

Assuming that mortality rate

$$R_m = kD \tag{20}$$

where k = constant

$$R_m = kD_0 e^{\alpha t} \tag{21}$$

If $$kD_0 = R_0, \tag{22}$$

then $$R_m = R_0 e^{\alpha t} \tag{1}$$

2. *Critique.*

a) The theory is consistent with observation 1.

b) The theory predicts that

$$V = \text{Vitality} = V_0(1 - ce^{\alpha t}) = V_0 - D_0 c e^{\alpha t}.$$

Although the value of V cannot be estimated quantitatively, its rate of loss would increase exponentially which is in conflict with observation 2.

c) Further, in order to account for observation 3, the theory requires the illogical assumption that the growth constant of damage is slower (i.e., α is lower) in a poor environment than in a good one. It is thus in essential conflict with observation 3.

d) Finally, from the basic postulates of the theory, we would expect a marked effect on subsequent mortality behavior of exposure of young animals to severe diseases or damage. Curtis and Healy (5) have tested this prediction on rats with negative results.

Hence, despite its parsimony, this theory makes three incorrect predictions and is therefore apparently unsatisfactory according to the above criteria.

C. *Sacher Theory* (20).

1. *Statement.* An ingenious theory proposed by Sacher incorporates a linear decay of mean physiologic state into its postulates. Although the mean physiologic state declines at a constant rate with time, random or Gaussian displacements occur about this mean at all times. Death occurs when a displacement of the physiologic state extends below a certain limiting value.

The probability of dying increases with age because, as the mean moves toward the limiting value, more and more of the random displacements cross the limiting value.

Certain properties of the mean physiologic state are required. Firstly, it has a lower limit below which death occurs, but no upper limit. Thus, it is unlike blood pH or blood sugar, but more like maximal breathing capacity, etc. Secondly, the mean physiologic state must never closely approach the limiting value. Otherwise the approximations required to fit the theory to Gompertz kinetics are not valid.

Definitions:

L = lower limit of physiologic state (constant)

M = mean value of physiologic state at time t

M_0 = mean value of physiologic state at time $t = 0$

$\lambda = M - L$ = difference between mean and limit

$\lambda_0 = M_0 - L$ = initial difference between mean and limit

$\Delta\lambda = \lambda - \lambda_0 = M - M_0 = \Delta M$

g, σ are constants

R_m = mortality rate

B = linear decay constant of mean physiologic state $= \dfrac{-\Delta\lambda}{\lambda_0 \Delta t}$

Mathematically, using the above postulates, definitions, and basic probability considerations, the following equation has been derived by Sacher for the rate at which members are removed from the population as a function

of the difference (λ) between their mean physiologic state and the limiting physiologic state (20).

$$R_m = \frac{g}{\sigma}\lambda\left(\frac{2}{\pi}\right)^{1/2}\exp -\frac{\lambda^2}{2\sigma^2} \tag{22}$$

In order to fit Gompertzian kinetics (observation 1), the following steps, which were taken by Sacher, are here expanded for clarity.

$$\lambda = \lambda_0 + \Delta\lambda \tag{23}$$

$$\lambda^2 = \lambda_0^2 + 2\lambda_0\Delta\lambda + \Delta\lambda^2 \tag{24}$$

If $\Delta\lambda \ll \lambda_0$, the following approximations can be made:

$$\lambda^2 \doteq \lambda_0^2 + 2\lambda_0\Delta\lambda \tag{25}$$

$$\lambda \doteq \lambda_0 \tag{26}$$

$$R_m = \left[\frac{g}{\sigma}\lambda_0\left(\frac{2}{\pi}\right)^{1/2}\right]\exp -\frac{(\lambda_0^2 + 2\lambda_0\Delta\lambda)}{2\sigma^2} \tag{27}$$

$$R_m = \left[\frac{g}{\sigma}\lambda_0\left(\frac{2}{\pi}\right)^{1/2}\exp -\frac{\lambda_0^2}{2\sigma^2}\right]\exp -\frac{\lambda_0\Delta\lambda}{\sigma^2} \tag{28}$$

It is postulated that:

$$\Delta M = -k\Delta t \tag{29}$$

Therefore,

$$\Delta\lambda = -k\Delta t \tag{30}$$

$$R_m = \left[\frac{g}{\sigma}\lambda_0\left(\frac{2}{\pi}\right)^{1/2}\exp -\frac{\lambda_0^2}{2\sigma^2}\right]\exp\frac{\lambda_0 kt}{\sigma^2} \tag{31}$$

Let

$$R_0 = \left[\frac{g}{\sigma}\lambda_0\left(\frac{2}{\pi}\right)^{1/2}\exp -\frac{\lambda_0^2}{2\sigma^2}\right] \tag{32}$$

Let

$$\alpha = \frac{\lambda_0 k}{\sigma^2} \tag{33}$$

Therefore,

$$R_m = R_0 e^{\alpha t} \tag{1}$$

2. *Critique.*

a) The theory apparently accounts for observation 1, the Gompertz function.

b) The theory correctly predicts an inverse relationship between α and $\ln R_0$ (observation 3). (See equation 40.)

c) The theory assumes a linear rate of loss of "vitality" which is qualitatively consistent with observation 2.

d) However, in order to fit a Gompertz function, the theory requires

assumptions which are inconsistent with the quantitative relationship between R_0 and α and requires rates of loss of physiologic function which are inconsistent with observation 2.

This may be shown as follows:

Using the postulates of Sacher's theory, we now evaluate the actual change in the "mean physiologic state."

$$k = -\frac{\Delta\lambda}{\Delta t} \qquad \text{(from equation 30)}$$

Therefore,

$$\alpha = -\frac{\lambda_0}{\sigma^2}\frac{\Delta\lambda}{\Delta t} = \left(\frac{\lambda_0^2}{\sigma^2}\right)\left(\frac{-\Delta\lambda}{\lambda_0\Delta t}\right) \tag{34}$$

Let $B = (-\Delta\lambda/\lambda_0\Delta t)$ = the linear decay constant of the mean physiologic state

Therefore,

$$\alpha = \frac{\lambda_0^2}{\sigma^2}B \tag{35}$$

$$\frac{\alpha}{B} = \frac{\lambda_0^2}{\sigma^2} \tag{36}$$

$$\lambda_0 = \sigma\left(\frac{\alpha}{B}\right)^{1/2} \tag{37}$$

Substituting equation 37 into equation 32, we have:

$$R_0 = g\left(\frac{\alpha}{B}\frac{2}{\pi}\right)^{1/2}\exp -\frac{\alpha}{2B} \tag{38}$$

Taking logarithms

$$\ln R_0 = \ln g\left(\frac{\alpha 2}{B\pi}\right)^{1/2} - \frac{\alpha}{2B} \tag{39}$$

Differentiating equation 37 with respect to α:

$$\frac{d(\ln R_0)}{d\alpha} = \frac{1}{2\alpha} - \frac{1}{2B} \tag{40}$$

Therefore, from a plot of $\ln R_0$ vs. α for various countries (fig. 3), we can evaluate B thus:

$$-140 \leq \frac{d(\ln R_0)}{d\alpha} \leq -75 \tag{7}$$

Therefore, $.0035 \leq B \leq .0058$ or $.0035 \leq \frac{-\Delta\lambda}{\lambda_0\Delta t} \leq .0058$ (41)

These values are somewhat lower than the decline constants of observation 2.

Further, by setting $\Delta t = 70$ years, one obtains

$$-.25 \geq \frac{\Delta\lambda}{\lambda_0} \geq -.41 \tag{42}$$

Since the mean physiologic state may decrease by as much as 25 to 41% of the total difference between original state and limiting value in 70 years, we may conclude that the approximations made in equations 25 and 26 are not justified.

Thus, although the theory is qualitatively consistent with several key observations, it requires assumptions which are in quantitative disagreement with other observations.

D. *Strehler-Mildvan Theory* (25, 26).

1. *Statement.* The fourth theory considers an organism to be composed of a number of subsystems which are subject to displacements by internal or external stresses. These displacements result in the expenditure of energy generally directed toward the re-establishment of the original condition. The maximum rate at which energy can be expended to restore the original condition in a subsystem is termed the vitality of that subsystem. The vitality of the organism, as a whole, is the "weighted average" of the vitalities of all the subsystems.

Whenever a demand or stress surpasses the ability of a subsystem to put out work, the environment of the other subsystems changes until they, in turn, find themselves incapable of meeting the demands placed on them, and death occurs.

The central assumption of the theory is that these fluctuations in demand for energy expenditure are principally due to random fluctuations in the energetic environment (or internal environment) of the organism. These stresses are thus assumed to be distributed exponentially as is a Maxwell-Boltzmann distribution of kinetic energy among gas molecules. That is, the frequency of stresses of a certain magnitude, or greater, increases exponentially as their energy decreases linearly. The rate of death is assumed to be proportional to the frequency of stresses which surpass the ability of a subsystem to restore initial conditions. This assumption and observation 1 (Gompertz's mortality kinetics) form the basis of the Strehler-Mildvan theory.

Since the rate of death (R_m) is proportional to the frequency of stresses that can kill (X), we have the following:

$$R_m = CX \doteq CK' \exp -\frac{\Delta H}{RT} \quad \text{if} \quad X \doteq K' \exp -\frac{\Delta H}{RT} \tag{43}$$

ΔH = size of energetic fluctuation just sufficient to kill = vitality
RT = average size of energetic fluctuation. C, K, and K', are appropriate constants.

Combining this assumption with observation 1 (Gompertz kinetics), we obtain

$$R_m = R_0 e^{\alpha t} \doteq CK' \exp -\frac{\Delta H}{RT} \doteq K \exp -\frac{\Delta H}{RT} \tag{44}$$

which is the basic equation of the theory from which all other relationships are derived.

2. *Critique.*

a) The theory assumes observation 1 and, hence, is consistent with it.

b) The theory predicts a linear decline of vitality with age, thus:

If $$R_m = R_0 e^{\alpha t} = K \exp -\frac{\Delta H}{RT}$$

solving for vitality (ΔH) as a function of time, letting ΔH_0 = vitality at time 0, we obtain

$$\Delta H = \Delta H_0 \left(1 - \frac{\alpha t}{\ln \frac{K}{R_0}}\right).$$

Since α, K and R_0 are constants, we may set

$$\frac{\alpha}{\ln \frac{K}{R_0}} = B \tag{45}$$

which is the linear decay constant of vitality. Thus,

$$\Delta H = \Delta H_0(1 - Bt). \tag{46}$$

The theory permits two independent calculations of the rate of loss of function (B) purely from mortality statistics (vide infra). The values thus calculated are, moreover, in good quantitative agreement with the B values given in observation 2 (see Fig. 6 also).

c) The theory predicts an inverse relationship between α and $\ln R_0$ and is thus consistent with observation 3. Thus, by substitution of

$$\Delta H = \Delta H_0(1 - Bt)$$

in equation 44, we obtain

$$R_m = K \exp -\frac{\Delta H_0}{RT} \exp \frac{\Delta H_0 Bt}{RT} = R_0 e^{\alpha t}. \tag{47}$$

Setting

$$t = 0, \quad R_0 = K \exp -\frac{\Delta H_0}{RT} \tag{48}$$

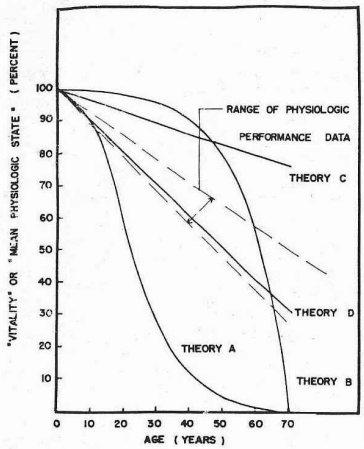

FIG. 6. Comparison of observed and four theoretical time courses of physiologic function.

Theory A: Brody-Failla
Theory B: Simms-Jones
Theory C: Sacher
Theory D: Strehler-Mildvan

Solving for α, we have

$$\frac{\Delta H_0}{RT} B = \alpha \quad \text{or} \quad \frac{\alpha}{B} = \frac{\Delta H_0}{RT} \tag{49}$$

Substituting for $\Delta H_0/RT$ in equation 48 and taking logarithms, we obtain

$$\ln R_0 - \ln K = -\frac{\alpha}{B} \tag{50}$$

Differentiating, we have

$$\frac{d \ln R_0}{d\alpha} = -\frac{1}{B} \tag{51}$$

This is qualitatively consistent with observation 3.

Plotting α against $\ln R_0$ for various countries (27), one obtains values of B, according to equation 51 ranging from .0093 to .013/year (Fig. 3). Alternatively (since $0.6 < K 2.0$), making the independent and reasonable assumption that K, the maximum possible observable mortality rate is $\cong 1$, one may calculate $B = .0097$.

Both of these calculated B values are in good quantitative agreement with observation 2.

E. *Other Theories.*

The discussion has been limited to theories which have relatively parsimonious mechanistic implications. Thus, although power series of time (15) and overlapping Gaussian distributions (19) may give reasonable approximations to observation, they are regarded as curve fitting rather than as physical theories which predict other functional relationships between measurable variables.

Similarly, we will not discuss, in detail, theories such as that of Yockey (29), which make explicit assumptions regarding the relationship of such quantities as "information content" to death and implicit assumptions which cannot, at present, be judged physically (e.g., distribution of information or rate of loss of information in a population).

Yockey has reinterpreted radiation-survivorship curves of non-aging populations in terms of information theory. He has then extended these interpretations to aging populations.

When applied to Gompertzian populations, however, Yockey's interpretation requires the assumption of an exponential growth with age of the probability of finding individuals with the lower limit of information necessary for viability. α is therefore a measure of this increasing probability.

It should be pointed out, however, that even in their present form, certain of Yockey's postulates appear to be inconsistent with observation 3, for they require the unlikely assumption that the rate constant for information loss is less in a bad environment than in a good one in order to account for the observed decrease in α in an inhospitable environment.

Since no assumptions are made relating environment to the lower limit of information necessary to continued life, Yockey's interpretation can not be subjected to a more detailed test at present.

In a similar manner, the recently published theory of Szilard (27) is not stated in a form which permits its evaluation in terms of the above observations.

DISCUSSION AND SUMMARY

Of the six theories of mortality rates discussed in the foregoing, four were comprehensive enough to permit detailed analysis. Three of these, although making certain predictions in keeping with the observation, fall short of com-

plete consistency with certain of the primary observations relating time, physiologic function and mortality (Fig. 6).

The fourth theory (25, 26) has been shown to fit, or predict, Gompertzian mortality kinetics (observation 1), a linear decay of physiologic function at the observed rate (observation 2), and an inverse relation between Gompertz slope (α) and intercept (R_0) (observation 3). This latter theory, and the Sacher theory, also can be shown to predict observation 4 which relates radiation exposure to life shortening, if it is assumed that radiation damage results in a loss of vitality (function) or mean physiologic state proportional to the total dose (20, 26).

None of the theories considered are in conflict with exponential cause specific death rates (observation 5). The Sacher theory and the Strehler-Mildvan theory do qualitatively predict curvature (decreased Gompertz slope) under certain conditions at great ages (observation 6). However, neither of the latter two theories, nor the data, are sufficiently refined to permit exact quantitative comparisons to be made. It may well be that any statistical theory of mortality, which must deal with variable populations, will break down as the number of individuals remaining decreases.

Thus, as discussed in detail elsewhere (26), a selection of a hardy group of individuals would either affect the mean value of the initial vitality or of the decline constant for vitality. An improved environment for older individuals, or a selective perpetuation of certain individuals in a subenvironment would affect slope by affecting the average environment.

Qualitative evidence of a potential contribution by all of such variations is at hand. Unfortunately, it has been impossible up to now to assign an appropriate weight to each factor.

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