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RESEARCH ARTICLES

Alcoholism and Mortality Kinetics

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Abstract □ Gompertz plots of age-specific mortality rates *versus* age were compared in alcoholics and the general population. Alcoholism had a dual effect, apparently increasing vulnerability to death while slowing the aging rate (longevity is a two-dimensional function). It was hypothesized that the apparent slowing of the aging rate was an artifact, resulting from population heterogeneity in vulnerability. It is recommended that in future studies, attempts be made to categorize alcoholic subjects with respect to alcoholic habit. Longitudinal studies would also be useful.

Keyphrases □ Kinetics, mortality—effects of alcoholism □ Alcoholism—effects on mortality kinetics

It has long been recognized that alcoholism has serious consequences for health and longevity. Excess mortality in alcoholics has been reported for all major disease categories, particularly cirrhosis, cancers of the upper respiratory and digestive tracts, accidents, and suicide (1). The alcoholic environment probably promotes injury by exacerbating existing pathological tendencies, with the extent of deterioration being a weighted sum of the several kinds of injury produced in the constituent systems. The progressive and irreversible accumulation of informational entropy is hastened in alcoholism, and chances for survival are lessened. Death occurs when one or more subsystem is incapable of meeting the demands placed on it, producing a fluctuation in the physiological state of the organism of such magnitude as to exceed the limits within which homeostatic regulation can occur (2-6). The cybernetic failure or escape of one of these subsystems to a more likely configuration (death) is analogous to the transition of an activated complex over the activation energy barrier, implying an inherently stochastic component to the process. The situation is similar to a group of identical radioactive atoms, in which each atom has λdt probability of disintegrating in the interval dt. Alcoholic subjects are characterized by a hypothetical mean physiological state[1], which is more unstable than that in normal subjects and, therefore, more likely to undergo a biological fluctuation that produces death. This increased actuarial risk could result from two kinds of parameters governing longevity: rate of aging and vulnerability (7). These parameters are investigated in this report.

THEORETICAL SECTION

The measure of age-specific mortality rate is the actuary's q_x (7-10):

$$q_x = \frac{1}{h}\frac{L_x - L_{x+h}}{L_x} \qquad \text{(Eq. 1)}$$

where h is the length of the time interval, L_x is the number living at age x, and

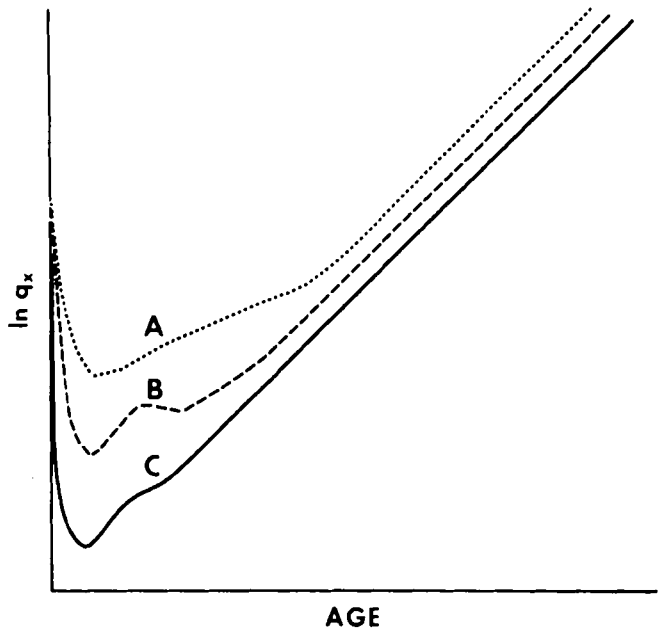

Figure 1—*Age-specific mortality rate plotted semilogarithmically against age for three populations; all populations have the same aging rate parameter but differ with respect to the vulnerability parameter (see text for discussion).*

[1] Mean physiological state can be described by specifying the mean values of certain essential physiological variables in a theoretical as opposed to an operational sense (see Refs. 3 and 5 for development of this concept).

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Table I—Parameter Estimates for the Gompertz Equations in Alcoholics and General Populations [a]

Population	Sex	Reference	Regression Line: Slope, years^{-1}	Regression Line: Intercept, years^{-1}	T_d, years^{-1}	1000 q_0, years^{-1}	Ratio, Alcoholic:Population: T_d	Ratio, Alcoholic:Population: q_0	t-Test: Slopes [b]	t-Test: Intercepts [b]
South Africa										
Caucasion alcoholics	M	23	0.0423 (0.0160[c])	1.46 (0.728)	16.4	4.32[c]				
Caucasion population	M	23	0.0816 (0.00228)[c]	−1.72 (0.118)	8.49	0.178[c]	1.93	24.3	$0.025 < p < 0.05$	$p < 0.001$
Ontario, Canada										
Alcoholics[d]	M	24, 25	0.0599 (0.00576)[c]	−0.0197 (0.309)	11.6	0.980[c]				
General Population[e]	M	24, 25	0.0931 (0.00251)[c]	−2.56 (0.142)	7.45	0.0775[c]	1.56	12.6	$p < 0.001$	$p < 0.001$
Alcoholics[d]	F	24-26	0.0301 (0.0118)[f]	1.36 (0.583)	23.0	3.89[f]				
General Population[e]	F	24-26	0.0918 (0.000638)[f]	−3.05 (0.0364)	7.55	0.0474[f]	3.05	82.1	$p < 0.001$	$p < 0.001$
Working class alcoholics[g]	81% M	27	0.0587 (0.00941)	−0.264 (0.489)	11.8	0.768				
Working class population[h]	M, F	27	0.0967 (0.00182)	−2.82 (0.0988)	7.17	0.0599	1.65	12.8	$0.001 < p < 0.005$	$p < 0.001$
Middle class alcoholics[g]	79% M	27	0.0556 (0.00854)	0.234 (0.442)	12.5	1.26				
Middle class population[h]	M, F	27	0.0966 (0.00199)	−2.79 (0.109)	7.18	0.0614	1.74	20.5	$p < 0.001$	$p < 0.001$
England and Wales										
Alcoholics[i]	M	28	0.0437 (0.00365)[c]	1.25 (0.198)	15.9	3.49[c]				
General Population[j]	M	28	0.0981 (0.00198)[c]	−2.97 (0.126)	7.07	0.0515[c]	2.25	67.8	$p < 0.001$	$p < 0.001$
Alcoholics[i]	F	28	0.0482 (0.00406)[f]	0.837 (0.222)	14.4	2.31[f]				
General Population[j]	F	28	0.0987 (0.00150)[f]	−3.53 (0.0957)	7.02	0.0292[f]	2.05	79.1	$p < 0.001$	$p < 0.001$

[a] Numbers in parentheses are *SD*s of the parameter estimates. [b] All tests are between alcoholics *versus* the general population. [c] Male data fitted by Eq. 4; see text for discussion. [d] A t test of slopes for male *versus* female alcoholics detected differences ($p < 0.05$), whereas a t test of intercepts failed to detect differences ($p > 0.05$). [e] A t test of slopes for male *versus* female populations failed to detect differences ($p > 0.6$), whereas a t test of intercepts detected differences ($p < 0.005$). [f] Female data fitted by Eq. 4; see text for discussion. [g] t Tests of slopes and intercepts for working class *versus* middle class alcoholics failed to detect differences ($p > 0.4$). [h] t Tests of slopes and intercepts for working class *versus* middle class populations failed to detect differences ($p > 0.8$). [i] t Tests of slopes and intercepts for male *versus* female alcoholics failed to detect differences ($p > 0.4$ and $p > 0.1$, respectively). [j] A t test of slopes for male *versus* female populations failed to detect differences ($p > 0.8$), whereas a t test of intercepts detected differences ($p < 0.005$).

L_{x+h} is the number living at age $x + h$. This is an estimate of the instantaneous mortality rate or force of mortality, $\rho(x)$ (5, 9):

$$\rho(x) = -\frac{1}{N(x)}\frac{dN(x)}{dx} \qquad \text{(Eq. 2)}$$

where $N(x)$ is the number of individuals surviving to age x. $\rho(x)$ is also the probability of an individual of age x dying over the interval from x to $x + dx$. Characteristically, q_x is high during infancy, falls to a minimum at ~10 years of age, and increases at an accelerated rate thereafter. Figure 1 illustrates typical semilogarithmic age-specific mortality curves for different populations. Goldman (11) has noted the similarity of these curves to failure curves for manufactured articles. High values of q_x occur during infancy and may be due to birth defects, immune deficiencies, incomplete gestation, *etc.* These are analogous to initial failures of manufactured products, resulting from faulty steps in the manufacturing process, defective parts, *etc.* After the curve bottoms out, but before it becomes exponential, chance failures predominate. In mortality curves and for manufactured goods, these chance failures are due to factors which are just as likely to be operative at any one time as at any other[2]. In mortality curves, this could be due to rare but fatal exposure to toxicants (chemicals, bacteria, *etc.*), accidents, *etc.* At some point in time, chance failures become exceedingly small relative to first-order wear-out failures, and the curve becomes exponential. Wear-out failures in manufactured articles are due to the effects of the duration of the service of the article. In mortality kinetics, wear-out failures are due to biological changes induced by processes we collectively lump under the heading of aging. In those Western societies with good standards of living, first-order mortality kinetics are generally first observed between the ages of 30 and 35 years. The appropriate mathematical relationship, termed the Gompertz equation, is (5, 7, 9, 12-17):

$$q_x = q_0 \cdot e^{\alpha x} \qquad \text{(Eq. 3)}$$

where q_x is the death rate at age x (age-specific death rate), q_0 is the extrapolated value of the death rate at age zero, and α is an aging rate parameter. The q_0 term is a measure of the initial vulnerability (7, 15) of the population to senescent-mediated causes of death in adults, *i.e.*, it measures the vulnerability of the population before the onset of aging. It is not an estimate of the death rate at birth, but rather is a theoretical parameter that is indicative of environmental influences and vigor of the genotype. Note in Fig. 1 that group A is more vulnerable than group B or C. The α term specifies the rate of increase of age-specific mortality; the doubling time (T_d) of age-specific mortality rates is equal to $(\ln 2)/\alpha$. In humans, T_d is ~8.5 years[3] (18). In a homogeneous population, an 8.5-year T_d means that a typical 50-year-old individual has twice the probability of dying during the course of one 24-h period than does a typical 41.5-year-old individual.

Sacher (7) has investigated the effects of various treatments (ionizing radiation, drugs, *etc.*) that contribute to the shortening and prolongation of life and has noted that although some treatments may affect both vulnerability (q_0) and rate of aging (α), most treatments affect predominantly one or the other (pharmacological agents usually affect q_0). In life prolongation, efficacious pharmacological therapies such as chronic procaine administration

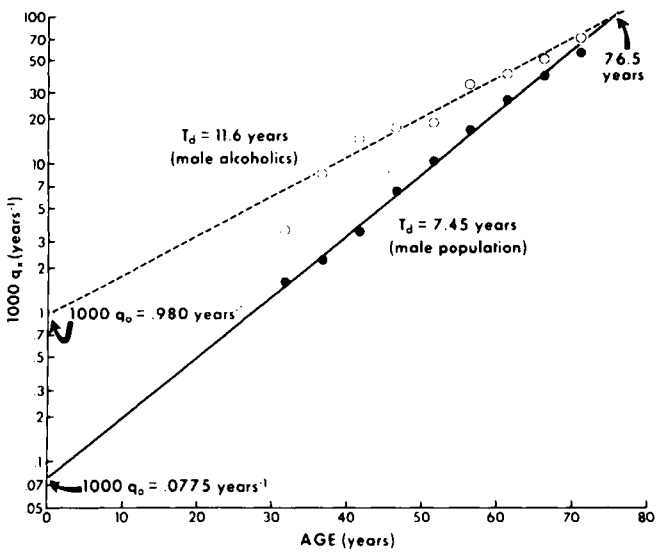

Figure 2—*Gompertz plots of age-specific mortality rates* versus *age for male alcoholics and the male general population in Ontario, Canada. See Fig. 3 for sample sizes and statistical weights in alcoholics (data are from Refs. 25 and 26).*

[2] This zero-order loss accounts for the age-independent term in the so-called Gompertz-Makeham equation (7, 12, 13), $q_x = q_0 e^{\alpha x} + A$, which characterizes age-specific mortality in this region and beyond; q_0 and α are defined with Eq. 3, and A is the zero-order component to mortality.

[3] In the data collated by Strehler and Mildvan (12), T_d ranged from 5.82 years in people from Trinidad and Tobago to 11.3 years for Algerian Moslems.

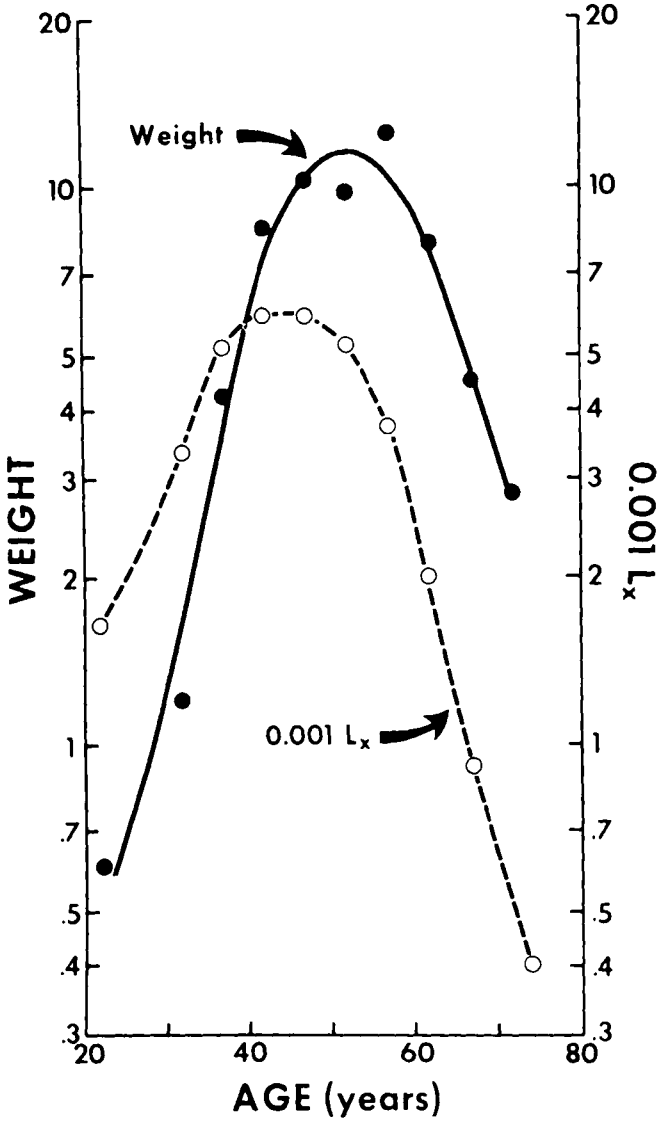

Figure 3—*Statistical weights and sample sizes (L_x) for alcoholic age-specific mortality data in Fig. 2 (data are from Refs. 25 and 26).*

achieve their effects by reducing q_0, whereas smoking in humans (7, 19) shortens life by increasing q_0. Strehler and Mildvan (12), on the other hand, have developed a general theory of mortality and aging which predicts an inverse relationship between q_0 and α.

Although the disease we term alcoholism is not generally regarded as a pharmacological treatment, mortality kinetics arising from it can be analyzed and discussed in that context; the results of such an analysis are reported.

EXPERIMENTAL SECTION

Mortality data in alcoholics was acquired by exhaustively searching the literature; this search ended in December 1982. In all cases, data were also presented on the general population as a whole[4], including all individuals of the same sex living in designated geographical areas.

Literature mortality data were generally collated for individuals in 5-year age groups; age-specific mortality rates were plotted semilogarithmically against age (Gompertz plot), where age was taken as the midpoint for the group. Data prior to the exponential phase were not used. Generally, this meant using only data obtained at or beyond the age of 32 years. A linear transformation of Eq. 3 is:

$$\ln q_x = \alpha x + \ln q_0 \qquad \text{(Eq. 4)}$$

Equation 5 was fitted to each set of data by the method of weighted, linear least-squares (21); parameter estimates and standard deviations were obtained for α and q_0. The weighting factor used for $\ln q_x$ was the reciprocal of its variance, and this was estimated by (9):

$$w = \frac{1}{v} \cong \frac{N_x P_x (\ln P_x)^2}{1 - P_x} \qquad \text{(Eq. 5)}$$

where w is the statistical weight, v is the sampling variance, N_x is the sample size, and P_x is the calculated probability of surviving the interval ($1 - P_x = q_x$). Differences between parameter estimates for alcoholics *versus* the general population were detected by t tests (Eq. 17 in Ref. 22).

[4] The population itself contains alcoholics, and a popular estimate of the point prevalence of alcoholism in Western societies is 7% (20). The lifetime prevalence rate is higher.

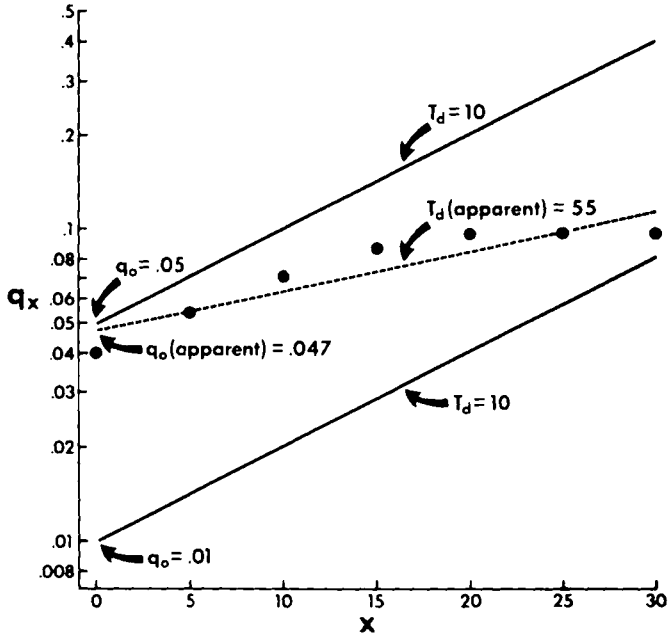

Figure 4—*Hypothetical Gompertz curves (—) for two strata of alcoholic subjects (arbitrary units). One group ($q_0 = 0.05$) is highly vulnerable to the mortality effects of alcohol, whereas the other group ($q_0 = 0.01$) mimics the general population; both groups have a T_d of 10. By taking the vulnerable group to comprise 75% of the alcoholic population and the invulnerable group to comprise 25%, pooling of the alcoholic subject data gives rise to the q_x data points between the two solid lines. The dashed line arises from a linear least-squares analysis of the pooled data. Note that the T_d (apparent) is considerably increased (see text for discussion).*

RESULTS AND DISCUSSION

Influence of Alcoholism on Vulnerability and Aging.—Parameter estimates obtained from analysis of Gompertz plots are summarized in Table I. Curves for alcoholics and the general population from one representative study are shown in Fig. 2. Figure 3 depicts sample size and statistical weights for those data points from alcoholics in Fig. 2. A cursory examination of these data indicates two significant effects of alcoholism on the Gompertz parameters. First, the vulnerability parameter, q_0, is ~10-80 times higher in the alcoholic populations. Second, there appears to be a concomitant reduction in the aging rate parameter, α (see below). Although T_d in the general male population is ~7.7 years, an ostensible T_d of ~14.6 years is noted for male alcoholics.

The apparent increases noted for q_0 and T_d in male alcoholics are also seen in females. In the one study in which alcoholic subjects were categorized as either "working class" or "middle class," there were no differences in Gompertz plot slopes ($p > 0.8$) or intercepts ($p > 0.4$); in working class *versus* middle class general populations, slope ($p > 0.9$) and intercept ($p > 0.8$) values also did not differ.

Considerable variability exists between q_0 values in both normal male and female populations (an approximate threefold range). Aside from the genetic component, q_0 is affected by environmental factors (air and water quality, disease-carrying insects, *etc.*) and medical intervention (inoculations against disease, antibiotic therapy, *etc.*). Variability is also seen in a comparison of the influences of alcoholism on the T_d and q_0 parameters, particularly the latter. Values of q_0 are increased 12.6-fold over normal values in male alcoholics from Ontario, Canada, whereas there is a 67.8-fold increase in male alcoholics from England and Wales. Part of this diversity may be due to the variables mentioned above, as well as genetic factors predisposing individuals to alcoholism. In addition, several types of alcoholism do exist. Jellinek (29)

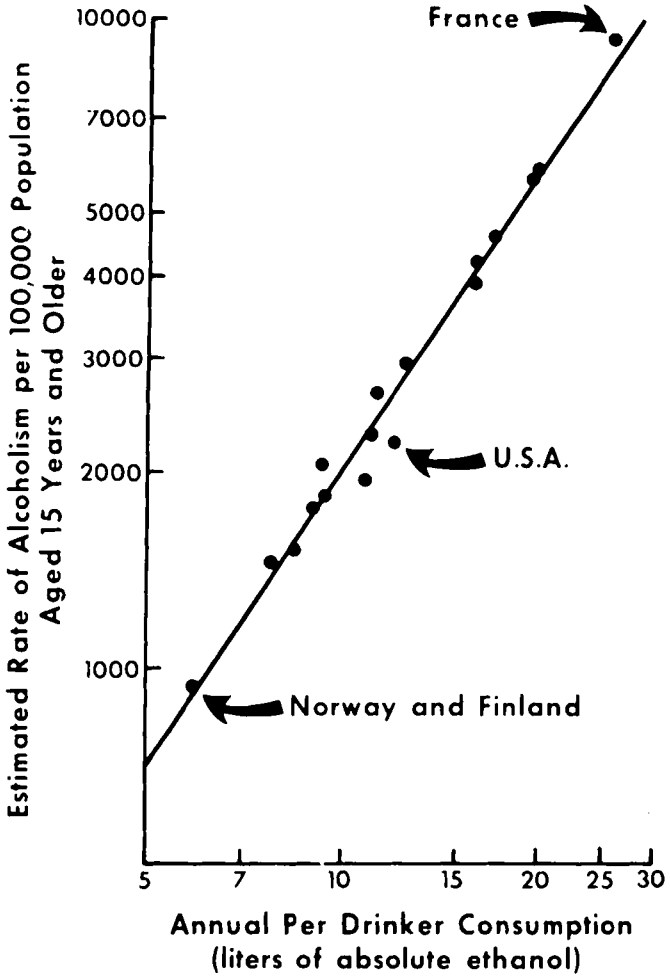

Figure 5—*Double logarithmic plot of the estimated rate of alcoholism in a country* versus *the annual per drinker consumption of alcohol. The equation consistent with this plot* ($y = \theta_1 y^{\theta_2}$) *was fitted by least-squares analysis (data from Ref. 30) and is* $y = 61.5\ x^{1.52}$; $r = 0.990$; $p < 0.01$.

has divided alcoholics into four major and several minor categories. The four major classifications are: (*a*) alpha alcoholism, a purely psychological continued dependence on the effects of alcohol to relieve bodily or emotional pain; (*b*) beta alcoholism, a condition in which alcoholic complications such as polyneuropathy, gastritis, and cirrhosis of the liver may occur without either physical or psychological dependence on alcohol; (*c*) gamma alcoholism, physical dependence and loss of control over the use of alcohol, a disease in and of itself; and (*d*) delta alcoholism, which is similar to gamma alcoholism, except instead of loss of control, there is inability to abstain (inveterate drinking)[5]. Therefore, alcoholics constitute a markedly heterogeneous group, with different drinking pattern and disease entities. Additionally, it is well known that the risk of getting cancer, cirrhosis of the liver, *etc.*, due to excessive alcohol use varies greatly among individuals. Those alcoholics who survive the age of, for example, 60 years in effect will be the least vulnerable, and their average vulnerability should be much lower than the average vulnerability in the general population at the same age. The range increases observed for q_0 in different populations probably reflects this heterogeneity[6].

To help explain this anomaly of an apparent slowing of aging in alcoholics, consider a hypothetical situation in which the alcoholic population consists of two strata, one highly vulnerable and one invulnerable to the effects of alcohol. In the latter group, the Gompertz curve is identical to that for the general population. In the former, the aging rate (α) is the same, but the vulnerability parameter is larger. For all alcoholics taken together, age-specific mortality rates will lie somewhere in between the two subgroups. This is illustrated in Fig. 4, in which q_0 for the invulnerable group is 0.01 (arbitrary units), and for the vulnerable group is 0.05. Note that the doubling times (T_d values) for the two subgroups are identical ($T_d = 10$ arbitrary units). If we take the vulnerable group ($q_0 = 0.05$) to comprise 75% of the alcoholic population and the invulnerable group ($q_0 = 0.01$) to comprise 25% of the alcoholic population, pooling of the data results in the q_x data points observed between the two Gompertz functions. Although the data points are best characterized by a curve, a linear function may be reasonably well fitted to the data, and this is indicated by the dashed line ($r = 0.92$) (Fig. 4). Note that the apparent T_d is now 55. After a number of years, the vulnerable alcoholics will become more or less extinct, and only the invulnerable ones will remain. At this age, the curve for all alcoholics would conicide with the one for the invulnerable group and, therefore, also for the general population. The larger the average vulnerability of the alcoholic group, as compared with the general population, the greater the apparent increase in T_d. This hypothetical illustration is no doubt simplistic (there are probably several strata), but it does serve to illustrate how an erroneously high T_d for alcoholics could be obtained. Although other possibilities exist to explain the increase in T_d, the grouping of heterogeneous alcoholic population is, by far, the most likely explanation.

If we assume the unlikely possibility that alcoholics are relatively homogeneous with respect to mortality parameters, we conclude that those factors causing or resulting from alcoholism also slow the aging rate. The Strehler–Mildvan theory of mortality and aging (12), mentioned above, interrelates the values of q_0 and α and predicts that a high initial mortality rate (q_0) should be associated with as low rate of increase of mortality rate (reduced α); this represents yet another interpretation of the data.

In future studies of alcoholic mortality, attempts should be made to categorize the various types of alcoholics. Another problem is that all studies have heretofore been based on age-group cohorts (not longitudinal data). Data from chronic, progressive alcoholics are therefore lumped with those from individuals who have a fluctuating course or a limited single alcoholic episode. This may have contributed to the postulated heterogeneity in vulnerability, producing the postulated artifactual increase in T_d. Longitudinal studies, therefore, would be very useful.

Drinking Habits, Alcoholism, and Aging—The fact that alcoholism affects apparent values of α and q_0 suggests that there might be some correlation between drinker consumption of alcohol in a given country and these parameters. Data from 16 countries (12, 30) were used to test this hypothesis. Correlation analyses were conducted on data for per drinker consumption *versus* α or q_0. Correlation coefficients were <0.02, indicating no correlations whatsoever. Similar results were obtained when rates of alcoholism in various countries were compared with α or q_0. This analysis implies that the drinking habits of a nation will not affect the overall Gompertz parameters for that nation. As expected, annual drinker consumption of alcohol did correlate with the rate of alcoholism (Fig. 5). For each twofold increase in per drinker alcohol consumption, alcoholism increases 2.87-fold.

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[5] Current research programs are investigating the possibilities of several other or different types of alcoholism.

[6] Considerable heterogeneity also exists within each of the major categories with respect to the following variables: age of onset of heavy drinking, cumulative period of drinking, alcohol consumption, smoking habits, social and financial status, marital status, availability and cost of alcohol, social mores, genetic constitution, geographical location, treatment intervention, ethnicity, accessibility and availability of health care, amount of exercise and sleep, and environmental stress.

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Solubility and Complexation Behavior of Griseofulvin in Fatty Acid–Isooctane Mixtures

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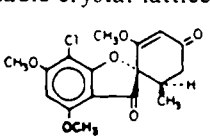
Received January 17, 1983, from the *Faculty of Pharmacy, University of Toronto, Toronto, Ontario M5S 1A1 Canada.* Accepted for publication August 1, 1983.

Abstract □ The influence of complex formation on the solubility behavior of griseofulvin in the straight-chain fatty acids was investigated by using phase solubility analysis in isooctane (2,2,4-trimethylpentane) at 25°C. The apparent molar solubility of the proton acceptor griseofulvin ($[A]_t$) was determined spectrophotometrically in the presence of various total molar concentrations ($[D]_t$) of each of the proton donors (acetic, propanoic, butanoic, hexanoic, and octanoic acids). Increasing $[D]_t$ caused a pronounced increase in $[A]_t$ according to a biphasic log-log relationship, suggesting the formation of two complexes, AD_m and AD_n. The data are in close agreement with a simple mathematical model which assumes that two complexes, AD_m and AD_n, are formed and that $[D]_t \approx 2[D_2]$, where D_2 refers to the fatty acid dimer. Linear regression analysis showed that the data best fit the complexation models with $n = 5$ or 6 and $m = 0$, 1, or 2, depending on the fatty acid. Assuming values of the dimerization constants of the fatty acids as reported in the literature, the stability constants of the complexes, K_n and K_m, were calculated and found to decrease with increasing chain length of the fatty acids. The proposed model was critically appraised. An alternative model, which takes into full account the fatty acid monomer while assuming that only one complex is formed, leads to unacceptable conclusions.

Keyphrases □ Molecular complexes—griseofulvin and straight-chain alkanoic acids, isooctane solution, solubility □ Carboxylic acid dimerization—influence on molecular complexation, griseofulvin and straight-chain fatty acids, isooctane solution □ Griseofulvin—solubility in isoocatane solution, straight-chain fatty acids

Complex formation, a valuable method for increasing the solubility, dissolution rate, and bioavailability of sparingly soluble drugs (1), also leads to a modification of the rate of transfer of certain drugs through lipid barriers (2). Griseofulvin (I) exhibits a poor bioavailability due to its low aqueous solubility (3). The stable crystal lattice of griseofulvin can, however, be broken down by proton-donating solvents, such as chloroform (4) and the fatty acids (5), which presumably form hydrogen-bonded complexes. Some of these complexes appear to exist in the solid state as solvates or inclusion compounds (6–8). Phenobarbital, a weak acid, also forms a solid complex with griseofulvin (9). Soluble complexes are formed between griseofulvin and phenols in carbon tetrachloride (10) and between certain steroidal drugs and organic solvents (11).



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The purpose of the present work is to investigate further the complexation of griseofulvin with the straight-chain alkanoic acids. The solubility method of Kostenbauder and Higuchi (12) was employed, and isooctane (2,2,4-trimethylpentane) was used as the inert solvent.

EXPERIMENTAL SECTION

Materials—Griseofulvin[1] was >99% pure, as described previously (5). Chloroform[2], acetic acid[3], *n*-butanoic acid[3], and *n*-octanoic acid[3] were reported to be >99% pure. Propanoic acid[4] and *n*-hexanoic acid[3] were distilled by using a glass apparatus. Isooctane (2,2,4-trimethylpentane)[4] was ≥99% pure.

Solubility Determinations—A mixture of griseofulvin (in excess of its solubility) and 5 mL of isooctane–fatty acid was shaken at 25.0 ± 0.05°C. Aliquots of 0.1–1.0 mL were diluted with chloroform, and the concentration of griseofulvin was determined (in duplicate) spectrophotometrically[5] at λ_{max} = 289.5 nm[6]. Saturation equilibrium was attained in <24 h. Each value (*e.g.*, $[A]_t$) is the mean of three separate determinations.

Analysis of the Solid Phases—A sample of the solid was removed from the equilibrated saturated solution, and the crystals were immediately placed on filter paper. The following methods of analysis were applied to all samples: X-ray diffraction (9), hot-stage microscopy (9), thermogravimetry (8), and

[1] ICI Ltd., Pharmaceuticals Division, Macclesfield, Cheshire, U.K.
[2] J.T. Baker Chemical Co.
[3] BDH Chemicals Ltd.
[4] Fisher Scientific Co. Ltd.
[5] Model PMQ II UV-visible spectrophotometer; Zeiss.
[6] Model 118 UV-visible spectrophotometer; Cary.

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