with unusual psychological orientation and imaginative, romantic proclivities. Without denying the "reality" of responses in such people, it has proved scientifically unwise to assume that such responses are typical of those experienced by all individuals under all circumstances.

That generalizations from volunteer groups are *necessarily* invalid, however, is a nihilistic and pessimistic view as untenable as claiming that volunteer data are infallibly transferable to all other situations. For example, the results obtained in a study of drug-induced mood changes in young healthy male volunteers in our laboratory were quite comparable with those obtained in a similar study in elderly patients hospitalized for chronic disease (*13*). In addition, distinct and reproducible patterns of response could be discerned in the volunteer group (*14*). This apparent predominance of drug effects, cutting across personality differences, suggests that the modifying effects of personality and motivation may be relatively minor at times or may affect details without obscuring larger patterns of response. *How* important the modifying nondrug factors are needs to be determined, if possible, in each specific situation. It is obvious that an awareness of the problems involved and care in eliciting and describing data will help in avoiding error and improving precision.

A final word should be said about the possibility of using to good purpose the very characteristics of certain volunteers that render them different from their fellows. As previously pointed out, the total spectrum of a drug's effects is often apparent only when "abnormal," as well as "normal," states are studied. Purposeful focusing on subjects with "addict potential," or anxiety, or depression should render more easily detectable the effects of drugs on such parameters.

References and Notes

1. This work was supported by a grant from the Medical Research and Development Board of the U.S. Army, contract No. DA-49-007-MD-92 (made to Henry K. Beecher).
2. D. Brower, *J. Gen. Psychol.* **39**, 145 (1948).
3. A. H. Maslow, *J. Soc. Psychol.* **16**, 259 (1942).
4. ——— and J. M. Sakoda, *J. Abnormal and Social Psychol.* **47**, 259 (1952).
5. C. C. Fry, personal communication.
6. C. C. McArthur, personal communication.
7. D. Funkenstein and S. King, personal communication.
8. The entire problem of the operationist approach in pharmacology and psychiatry has been ably discussed by Wikler (*9, 10*).
9. A. Wikler, *Am. J. Psychiat.* **108**, 590 (1952).
10. A. Wikler, *Neuropsychiatry* **2**, 87 (1952).
11. E. K. Marshall, Jr., personal communication.
12. A. Huxley, *The Doors of Perception* (Harper, New York, 1954).
13. L. Lasagna, J. M. von Felsinger, and H. K. Beecher, unpublished data.
14. It is of interest, however, that those subjects in the study who gave "atypical" response to drugs were, in general, the more "abnormal" members of the group. (For example, the number of "anxiety-hostility" responses of the "atypical" reactor was likely to be higher than the median group score.) In this sense, therefore, the more "abnormal" volunteers increased the difficulty of observing distinct patterns of response within the group.

Toxicity of Cations toward Living Systems

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THE correlation of metal-ion toxicity with some physical or chemical property of the metals presents a challenging problem. Biologists, physiologists, and toxicologists have expressed widely divergent opinions (*1, 2*) concerning the possibility of such a correlation. Some have argued that the complexity of the living organism precludes any simple relationship. Others have pointed out that complexity has been encountered in other fields of science and explained.

In an important paper, A. P. Mathews (*3*), basing his arguments on data obtained for the eggs of the fish *Fundulus,* demonstrated a significant relationship between metal-ion toxicity and "electrolytic solution tension" (standard electrode potential). J. R. Erickson Jones subsequently made careful measurements with the planarian (*4*) *Polycelis nigra* and the stickleback (*5*) (a fish). He again observed a rough correlation with standard electrode potential. W. Seifriz (*2*) presented an excellent discussion of the problem with particular reference to the slime mold.

The purpose of this investigation (*6*) is to describe a simple physiochemical model of the toxicological process and attempt to correlate the available data in terms of this model.

Consider an enzyme E_1 at a total molar concentration e_1 confined in a living cell. The enzyme finds itself in an environment containing its substrate s_1 with which it reacts at a rate $V_1{}^{s}$ to form a product s_2. Assuming that the enzyme obeys Michaelis-Menten kinetics, the following mechanism pertains:

$$E_1 + s_1 \underset{r_1}{\overset{f_1}{\rightleftharpoons}} \sigma_1 \xrightarrow{d_1} E_1 + s_1, \qquad (1)$$

where σ_1 is the enzyme-substrate complex, f_1 the rate-constant for the forward reaction, r_1 the rate-constant for the reverse reaction, and d_1 the rate-constant for the decomposition reaction.

By conventional mathematical treatment,

$$V_1^u = \frac{d_1 e_1 s_1}{s_1 + K_m^1}, \quad K_m^1 = \frac{r_1 + d_1}{f_1}. \tag{2}$$

If now an inhibitor I is injected into the cell at a concentration I, one may write for a competitive inhibition (*7, 8*):

$$E_1 + I \rightleftharpoons E_1 I, \quad K_i^1 = (E_1 I)/(E_1)(I), \tag{3}$$

and the reaction rate in the presence of the inhibitor V_1^i becomes

$$V_1^i = \frac{d_1 e_1 s_1}{s_1 + K_m^1[1 + K_i^1(I)]}. \tag{4}$$

It will prove convenient to define an inhibition index (*7*) ϕ_1 as follows:

$$\phi_1 = \frac{V_1^u}{V_1^i} - 1 = \frac{K_m^1 K_i^1 (I)}{s_1 + K_m^1}. \tag{5}$$

The relationship between ϕ and the conventional percentage inhibition, percent, is given by

$$\text{percent}_1 = \frac{100}{1 + 1/\phi}; \tag{6}$$

also

$$V_1^i = \frac{1}{1 + \phi_1} V. \tag{7}$$

V_1^i, then, represents the rate at which s_2 is produced in the presence of the inhibitor I. It will next be assumed that s_2 is essential to the metabolism and life of the cell, and if it is not produced at an adequate rate the cell dies. That is, if

$$V_1^i \leqq V_1^*, \tag{8}$$

death results. Here V_1^* is the rate of s_2 production that is just inadequate to support life. Equation 8 constitutes a criterion for death.

In the absence of the inhibitor, the rate of the enzyme-catalyzed reactions is V_1^u. As the inhibitor concentration increases, ϕ_1 increases (Eq. 5). As ϕ_1 increases, V_1^i decreases (Eq. 7). Finally, enough inhibitor I^* may be added so that $\phi_1 = \phi_1^*$, which makes $V_1^i = V_1^*$ (Eq. 8), and death results. Under these conditions, Eq. 5 can be rearranged to read (*8*):

$$pI^* = \left(p\phi_1^* + \log \frac{K_m^1}{s_1 + K_m^1}\right) + \log K_i^1. \tag{9}$$

Here p refers to the negative logarithm of the quantity involved. This equation may be rewritten, using new symbols, as

$$L = S + T; \tag{10}$$

that is, the lethality L equals the sum of the susceptibility S (the term in parentheses in Eq. 9) and innate toxicity T. The justification for this interpretation of Eq. 9 may be made as follows. The susceptibility term involves the amount ($p\phi_1^*$) that the key enzyme system must be inhibited for death. If s_2 production must be closely regulated for the life of the cell, even a slight decrease in its rate of formation may be fatal (that is if ϕ_1^* is small, $p\phi_1^*$ is large and S is large). The second term in the parentheses in Eq. 9 shows that the susceptibility depends on the concentration of s_1. If it is assumed that s_1 depends on the nutritional state of the organism, one is forced to the conclusion that a well-fed organism is less susceptible to poison than a starved one. Thus the susceptibility S refers to the particular organism; T is simply the logarithm of the equilibrium constant for the inhibition reaction (Eq. 3). Since the loss in the free energy of inhibition is

$$-\Delta F_i = RT \ln K_i^1, \tag{11}$$

one may conclude that the innate toxicity T represents the thermodynamic affinity of the inhibitor for some key functional group in the enzyme's catalytically active site.

In applying the theory to cation toxicity, several additional assumptions (*9*) are needed: (i) In the cases presented here, metallic cations are toxic because they combine with a sulfhydryl group that is part of the key enzyme's catalytically active site. (ii) The driving force $-\Delta F_i$ (*8*) behind this reaction,

$$\begin{matrix} S(-) \\ \diagup \\ E \\ \diagdown \\ S(-) \end{matrix} + M^{++} \rightleftharpoons \begin{matrix} S \\ \diagdown \\ E \\ \diagup \\ S \end{matrix} M, \tag{12}$$

is linearly related or proportional to the driving force $-\Delta F_s$ behind the analogous reaction

$$S^{--} + M^{++} \rightleftharpoons MS, \tag{13}$$

where M^{++} represents the metal ion, and MS the corresponding metal sulfide. The more insoluble the sulfide,

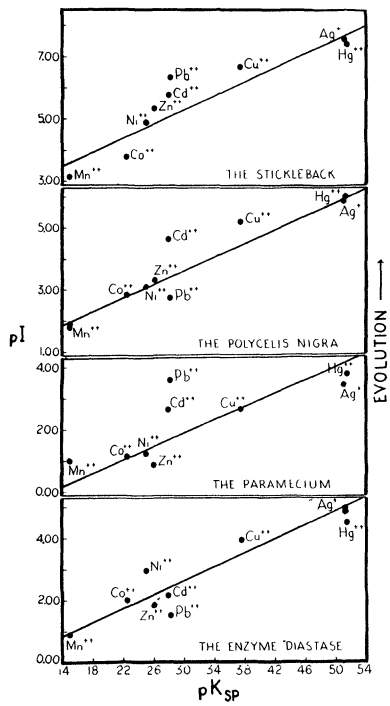

Fig. 1. Correlation of the toxicity (pI) of metal ions toward various organisms with the insolubility of the corresponding sulfide (pK_{sp}).

the farther reaction 13 proceeds to the right (and, by assumption ii, the same applies to reaction 12). The loss in free energy accompanying the formation of the insoluble sulfide is given by

$$-\Delta F_s = 2.303\ RT\ pK_{sp}. \quad (14)$$

Here K_{sp} is the solubility product constant for the metal sulfide, and T is the absolute temperature. Then, according to assumption ii, and Eqs. 9, 10, 11, and 14, it follows that

$$T = log\ K_i = (m) \times (pK_{sp}), \quad (15)$$

where m is a proportionality constant and T is the innate toxicity,

Equation 9 may then be written as

$$L = pI^* = S + (m)\ pK_{sp}. \quad (16)$$

This equation predicts that a plot of the negative logarithm of the metal-ion concentration just necessary to produce death against pK_{sp} will be linear. The theory also allows only one adjustable parameter (S) per organism. Regardless of the organism studied, therefore, the innate toxicity of a particular ion will be the same; but the susceptibilities of the various organisms to poisoning by the ion will be expected to differ. Thus, a plot of pI^* versus pK_{sp} for the various organisms should result in a family of straight lines with the same slope m but with different intercepts.

Typical results obtained for the enzyme "diastase" (*10*), the paramecium (*11*), the planarian (*4*), and the stickleback (*5*), are presented in Fig. 1. The lines have all been drawn with the same slope. Completely analogous results have been obtained for *Fundulus* eggs (*3*) and the enzyme urease (*8*).

A thorough statistical treatment of these and other data taken from the literature is being made and will be presented elsewhere. Numerous qualitative and semiquantitative observations have been and are being collected from a great variety of fields. The results obtained thus far seem to indicate a rather widespread applicability of the theoretical treatment.

References and Notes

1. R. H. True, *Proc. Am. Phil. Soc.* **69**, 231 (1930).
2. W. Seifriz, *Science*, **110**, 193 (1949).
3. A. P. Mathews, *Am. J. Physiol.* **10**, 290 (1904).
4. J. R. E. Jones, *J. Exptl. Biol.* **17**, 408 (1940).
5. ———, *ibid.* **16**, 425 (1939).

6. I wish to acknowledge with gratitude the generous support from Research Corporation of New York and the University of Texas Research Institute that, in part, made possible this investigation. This report was presented as a paper before the Texas chapter of the Society of the Sigma Xi, 9 Feb. 1954.

7. G. B. Kistiakowsky and W. H. R. Shaw, *J. Am. Chem. Soc.* **75**, 866 (1953).
8. W. H. R. Shaw, *ibid.*, in press. The other types of inhibition have also been treated in this paper.

9. Several other important factors are doubtless involved, but space does not permit their detailed consideration here. For example, as a first approximation, it has also been assumed that (i) the concentration of the toxic ion within the organism is the same or a constant fraction of its external concentration; (ii) all the metals considered attack the same key enzyme; (iii) the affinity of the metal for the —SH group is independent of the enzyme to which the group is attached.

10. H. McGuigan, *Am. J. Physiol.* **10**, 444 (1903).
11. L. L. Woodruff and H. H. Bunzel, ibid. **25**, 190 (1909).

Howard Bishop Lewis, Biochemist

THE death of Howard Bishop Lewis on 7 March 1954, following an illness of 14 months, brought to an end the illustrious career of a great biochemist, an ardent scholar in many fields, and a warm human being.

Dr. Lewis was born in Southington, Connecticut, on 8 November 1887, the son of Frederick A. and Charlotte R. (Parmelee) Lewis. At Yale, the award of the Chamberlain prize for the best entrance examination in Greek, followed by prizes in chemistry, the calculus, and Latin composition during his undergraduate years, gave early evidence of his brilliant mind.

After completing his doctoral work at Yale under the supervision of Lafayette B. Mendel, he served for 2 years as an instructor of physiological chemistry at the University of Pennsylvania (1913–15), and then joined the staff of the Chemistry Department at the University of Illinois, where he remained until 1922. At this time, because his inspirational leadership, sound research, and outstanding talent as a teacher had become nationally recognized, he was called to the University of Michigan as chairman of the Department of Physiological Chemistry in the Medical School. He held this position until his death in 1954. In addition to his duties in the department, Dr. Lewis was also the director of the College of Pharmacy from 1933 to 1947.

The scope of his activities outside the university are too numerous to present in detail. Because of an unusual breadth of knowledge and skill of expression, his editorial work was most noteworthy. He has served on editorial boards of five national journals.

His broad interests in the fields of medicine and nutrition may be judged by his national committee assignments. From 1936 until his illness, he was a member of the council on foods and nutrition of the American Medical Association. In 1941–42, he served on the council of the American Institute of Nutrition, as vice president of the institute in 1941–42 and as its president in 1943–44. From 1945 to 1948 he was a member of the Division of Medical Sciences of the National Research Council, and from 1947 to 1952 he was chairman of the Michigan Nutrition Council. In December 1952, shortly before his illness, he served as