carried out in social psychology use some degree of misinformation" (*26*, p. 19), and thus "subvert the possibility of informed consent" (*26*, p. 21). "Prior general consent" or "presumptive consent" (*26*, p. 21) have been proposed to deal with this ethical problem.

Recombinant DNA research makes it at least theoretically possible to combine the genetic characteristics of plant and mammal, to produce a "plammal" or a "mant." We need to find a balance between possibly inadvertently producing the means to cause catastrophe to mankind, and potentially high beneficial developments. The genetic splicing of recombinant DNA technology has already been used to transfer the rat gene for insulin production to bacteria (*27*). This development has the potentially high beneficial consequence of making possible massive commercial production of human (instead of other species) insulin for diabetics. It also has, in the eyes of some, the possibility of catastrophe should insulin-producing bacteria get out of the laboratory into the body of a human, to multiply and throw the person into insulin shock.

One argument is that knowledge is power, and if we do not acquire the knowledge, other countries will. Remember that in World War II the other side was also working on an A-bomb. If we acquire the knowledge, we can also acquire the means to control the knowledge. If we do not, the controls may be in other hands. These, too, are ethical considerations.

As Jonas notes (*28*), generally there is something experimental because tentative about every individual treatment, beginning with the diagnosis itself. He would be a poor doctor who would not learn from every case for the benefit of future patients, and a poor member of the profession who would not make any new insights gained from his treatments available to the profession at large.

In summary, we recognize that acquiring new information while retaining old ethics demands adherence to the fundamental rule that a person should not be subjected to avoidable risk of death or physical harm unless he freely and intelligently consents. The problem is to balance rights against benefits with respect for human dignity in the quest for the cure of human diseases.

References and Notes

1. S. J. Reiser, A. J. Dyck, W. J. Curran, Eds., *Ethics in Medicine* (MIT Press, Cambridge, Mass., 1977).
2. W. A. Silverman, *Sci. Am.* **236** (No. 6), 100 (1977).
3. B. Barber *et al.*, *Research on Human Subjects* (Russell Sage Foundation, New York, 1973).
4. G. J. Annas, *The Rights of Hospital Patients*, American Civil Liberties Union Handbook (Avon, New York, 1975).
5. V. Herbert, in *Proceedings, Western Hemisphere Nutrition Congress IV*, P. L. White and N. Selvey, Eds. (Publishing Sciences, Acton, Mass., 1975), pp. 84–91.
6. E. E. Conn, in *Toxicants Naturally Occurring in Foods* (National Academy of Sciences, Washington, D.C., 1973), pp. 299–308; J. P. Lewis, *West. J. Med.* **127**, 55 (1977); *Fed. Regist.* **42**, 39768 (1977).
7. H. K. Beecher, *J. Am. Med. Assoc.* **159**, 1602 (1955); *Research and the Individual: Human Studies* (Little, Brown, Boston, 1970).
8. J. W. Tukey, *Science* **198**, 679 (1977).
9. J. P. Gilbert, B. McPeck, F. Mosteller, *ibid.*, p. 684.
10. H. C. Black, *Black's Law Dictionary, Revised* (St. Paul, Minnesota, ed. 4, 1968). In "United States of America *v.* Articles of Food and Drug Consisting of . . . apricot kernels . . . amygdalin . . .," Civil No. 77-C-285 (U.S. District Court, Eastern District of Wisconsin, 29 July 1977), Judge Reynolds closed a laetrile factory after holding as a Finding of Fact that, "Anecdotal and testimonial evidence as to cures or effects of treatments on cancer victims as described by lay persons, or persons possessing either an M.D. or Ph.D., but who are not qualified by scientific training and experience as experts in the field of cancer therapy, is not probative or substantial evidence of the safety and efficacy of cancer treatments." Judge Reynolds held as a Conclusion of Law, "The testimony of lay witnesses as to the existence of cancer and the safety and efficacy of an alleged cancer treatment based on their personal experience with the treatment is entitled to no weight and is therefore inadmissible as irrelevant and non-probative evidence." As precedents for this Conclusion of Law, Judge Reynolds cited United States *v.* Hoxsey Cancer Clinic, 198 Fed. Rep., 2nd ser. 273 (5th Cir. Ct., 1952); United States *v.* Wier, 281 Fed. Rep., 2nd ser. 850 (5th Cir. Ct., 1960), and Federal Rules of Evidence 401, 402, 403, and 701.
11. J. Cornfield, *Science* **198**, 693 (1977).
12. J. A. Robinson, *Columbia Law Rev.* **76**, 48 (1976).
13. V. Miké and R. A. Good, *Science* **198**, 677 (1977).
14. L. A. Altman, *N. Engl. J. Med.* **286**, 346 (1972).
15. V. Herbert, *Trans. Assoc. Am. Physicians* **75**, 307 (1962).
16. ———, *Am. J. Clin. Nutr.* **28**, 555 (1975).
17. L. Thomas, *Science* **198**, 675 (1977).
18. S. Barrett and G. Knight, Eds., *The Health Robbers: How to Protect Your Money and Your Life* (Stickley, Philadelphia, 1976), J. W. Miner, *J. Forensic Sci.* **9**, 1 (1964); California *v.* Phillips, 75 Calif. Rep. 720 (1969), certiorari denied, 396 U.S. 1021 (1970).
19. S. 1217. A bill to regulate activities involving recombinant deoxyribonucleic acid, 19 May 1977 (introduced by Senator Edward Kennedy, D-Mass.); Newsletter, *Fed. Am. Soc. Exp. Biol.*, **10** (No. 8), 2 (1977).
20. B. D. Davis, E. Chargaff, S. Krimsky, *Chem. Eng. News*, 30 May 1977, pp. 26–42. The latest evidence is that fears regarding recombinant DNA research may be greatly exaggerated [P. H. Abelson, *Science* **197**, 721 (1977); W. Gaylin, *N. Engl. J. Med.* **297**, 665 (1977)].
21. N. Zinder, hearings before the Subcommittee on Health, U.S. Senate, on S. 1217 (1977).
22. T. M. Powledge, *Hastings Cent. Rep.* **7** (No. 2), 18 (1977); D. Callahan, *ibid.*, p. 20; K. Dismukes, *ibid.*, p. 25.
23. C. Cohen, *N. Engl. J. Med.* **296**, 1203 (1977).
24. R. Goldstein, *ibid.*, p. 1226.
25. G. Robinson and A. Merav, *Ann. Thorac. Surg.* **22**, 209 (1977).
26. S. Milgrim, *Hastings Cent. Rep.* **7** (No. 2), 19 (1977).
27. A. Ullrich *et al.*, *Science* **196** 1313 (1977); N. Wade, *ibid.* **197**, 1342 (1977).
28. H. Jonas, in *Ethics in Medicine*, S. J. Reiser, A. J. Dyck, W. J. Curran, Eds. (MIT Press, Cambridge, Mass., 1977).

Carcinogenic Risk Assessment

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Man is exposed to a variety of natural and synthetic substances that are known to be harmful to experimental animals in high doses and consequently are under suspicion of being harmful to humans in low ones. Exposure to many of these substances, particularly those involving involuntary exposure through food, water, air, or the workplace is subject to regulation by governmental agencies. In some instances the benefits conferred by a suspected substance can be achieved by other safe substances in equally satisfactory ways, in which case the most appropriate regulatory action is an outright ban, no regard being given to the strength of the suspicion. But in many cases important benefits are lost if the agent is banned, and the magnitude of the risk must then be balanced against the benefit conferred. The risk may be of such magnitude that banning is appropriate even in the face of the benefits, or it may be so low at the levels to which humans are exposed that a ban is not considered appropriate. Risk assessment is therefore an essential component of regulatory decisions. It is also a particularly appropriate topic for consideration because of the mixture of statistical, scientific, and public policy considerations that it presents. The problem of risk assessment is the same formally, no matter what the route of exposure, but since much of the exposure is by way of food, I will confine my discussion to that topic.

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Summary. Carcinogenic risk assessment involves a mixture of statistical, scientific, and public policy considerations. Concepts in current use, such as "no observed effect levels" and "virtual safety," and the problems in implementing them by means of dose-response models, particularly the probit-log dose and linear models are reviewed. The upper limits to risk provided by some conservative procedures are inconsistent with coherent balancing of risks and benefits. A common basis to the dose-response curves describing both carcinogenic and noncarcinogenic effects is to be found in deactivating reactions. A simplified model in which a toxic substance is activated and deactivated in separate and simultaneous reactions is presented and the dose response curve implied by the model is deduced. This curve has the general form of a hockey stick, with the striking part flat or nearly flat until the dose administered saturates the deactivation system, after which the probability of a response rises rapidly. Such a curve describes the Bryan-Shimkin methylcholanthrene-tumor incidence dose response curve as well as the probit log-dose model. The concept of a saturation dose is relevant to risk assessments for carcinogenic and noncarcinogenic substances alike.

Two Conceptual Bases for Safety Evaluation

A substance may be carcinogenic or noncarcinogenic and independently it may appear in food as an additive, residue, natural contaminant, or migrant (*1*). There is one public policy governing additives presenting a potential carcinogenic risk and another governing the other three categories. Carcinogenic additives are governed by the Delaney clause that says (*2*):

> . . . no additive shall be deemed safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal. . . .

Such additives are therefore proscribed without regard to the magnitude of the risk at human use levels and without regard to possible benefits. In contrast, food containing a potential carcinogen, but which does not enter the food supply as an additive, for example, peanuts containing aflatoxin, is subject to regulation but is not automatically proscribed. It may not be sold if levels of the substance exceed a certain amount, termed a tolerance, but can be sold if the amount present is below the tolerance. Similarly, any agent presenting a potential noncarcinogenic hazard, whether it appears in food as an additive or in other ways, is acceptable as long as its concentration does not exceed its tolerance.

For all but the potentially carcinogenic food additives covered by the Delaney clause, therefore, the determination of an acceptable daily intake (ADI), or alternatively, of the risk corresponding to a given exposure, is an important part of the regulatory decision-making. Two different procedures have been developed for making such determinations. The first involves the concept of a "no observed effect level" (NOEL) and the use of safety factors and is the standard toxicologic procedure both here and abroad (*3*). A recent document from the Environmental Protection Agency (EPA) states, "the NOEL is defined to be the level (quantity) of a substance administered to a group of experimental animals at which those effects observed or measured at high levels are absent and at which no significant differences between the group of animals exposed to the quantity and an unexposed group of control animals maintained under identical conditions is produced" (*4*). The ADI is obtained by dividing the NOEL by 100, the rule of thumb being that man may be tenfold more sensitive than the experimental animal used and that there may be in addition a tenfold variation in sensitivity among individuals.

The second set of procedures, developed without explicit consideration of the first, are intended to apply specifically to carcinogenic responses. They involve extrapolation downward from observed effects to a risk level deemed virtually safe, the extrapolation involving use of an assumed mathematical model. All models express the probability of a lifetime response, P, as a function of dosage, D [for example, $P = f(D)$], and differ only with respect to the choice of the function, f. They all assume the absence of a threshold, that is, that if proportion p of control animals respond, that $f(D) = p$ only for D equal to zero, and that for any nonzero D, $f(D) > p$. If safety is defined as zero elevation over control risk, then these models require that any nonzero dosage be deemed unsafe, exactly as in the Delaney clause. With this definition of safety, foods containing carcinogenic residues below the limit of analytic detectability, and hence not distinguishable from foods containing no residues, must be deemed unsafe, leaving the regulatory agencies with an impossible enforcement problem. The concept of virtual safety, introduced by Mantel and Bryan (*5*), has provided a way out of this dilemma and has been adopted by the Food and Drug Administration (FDA) (*6*). A dose, D_0, is said to be virtually safe if $f(D_0) \leq P_0$, where P_0 is some near-zero quantity such as 10^{-8}, the Mantel-Bryan proposal, or 10^{-6}, the value adopted by the FDA. The virtually safe dose (VSD), conceptually equivalent to the ADI of the traditional toxicologic procedure is then computed as $f^{-1}(P_0)$. The calculation involved thus requires that we determine the disposable constants of the assumed function, f, from observations in the observable range, and extrapolate down to the unobservable response, P_0, to determine the VSD.

The Probit-Log Dose Model

The major problems with this approach are: (i) The choice of function has a major effect on the VSD, more than 100,000-fold, according to the FDA Advisory Committee on Safety Evaluation (*7*). (ii) Such functions often cannot be distinguished from each other in the observable range. (iii) No firm scientific basis now exists for choosing among them.

The use of probit-log dose function for description of carcinogenic dose-response relations was introduced by Bryan and Shimkin in their classic study of the three carcinogenic hydrocarbons, methylcholanthrene, dibenzanthracene, and benzopyrene (*8*). That function is

$$f(D) = \int_{-\infty}^{\alpha+\beta \log D} (2\pi)^{-1/2} \exp(-x^2/2)dx \quad (1)$$

where α and β are disposable constants, whose values are determined from experimental observations according to any one of a variety of possible statistical methods (*9*). If the probability of a background response is p and response to background and substance are independent,

$$P = p + (1-p)f(D) \quad (2)$$

The argument leading to the probit function is entirely a statistical one. Each experimental animal is considered characterized at the time of the experiment by a tolerance, such that any dose above it will induce cancer and any below it will not. Because of normal biological variation not all animals will have

the same tolerance, and at any given dose, D, only those animals with tolerances below D will respond. If the distribution of tolerances is assumed to be lognormal, then the probit-log dose function results, with the probit slope, β, being the reciprocal of the standard deviation of the log tolerance distribution and α depending in a simple way on the mean as well (*10*).

The major problem with the use of the probit-log dose model for extrapolation is that the normal distribution may not provide as reliable a description in the tails of the distribution as it does in the central part, particularly if one goes as far out as 10^{-6} or 10^{-8}. One does not expect to see 6-inch-tall men or human livers in the picogram range, despite the lognormality of human height or liver weight in the central part of the curve. If the same argument can be applied to the distribution of tolerances, the probit function obtained from the observable range would overestimate the probability of a response at low doses. On the other hand, human tolerance distributions could be more variable than those of inbred strains of laboratory animals, and to allow for this (but not the possible truncation of the tolerance distribution above zero), Mantel and Bryan proposed downward extrapolation using an "arbitrarily low" slope of unity, the rationale being that all observed probit slopes at the time of the proposal exceeded that value (*11*). This allowance, which is the conceptual equivalent of the standard toxicologic allowance of tenfold for human variation could also have been achieved by using some fraction, such as one-half, of the observed slope for extrapolation, thus preserving some contact with the observed dose-response relation. The failure of the Mantel-Bryan procedure to give any weight to the observed slope can be considered a weakness, and the assumption that the tolerance distribution starts at zero lacks observational support.

Low Dose Linearity

The probit-log dose extrapolation, even with the Mantel-Bryan modification, has been criticized (*12*) as insufficiently conservative on the grounds that the extrapolated probability approaches zero with decreasing dose more rapidly than any polynomial function of dose, and in particular more rapidly than a linear function of dose, and hence may overestimate probabilities at low doses. Thus, if at dose D the proportion responding is 2.5 percent above control, a 10^{-6} elevation above control will occur at dose $D/25{,}000$ under a linear extrapolation, at dose $D/620$ under an extrapolation with a probit-log dose slope of unity, and dose $D/10$ with a probit slope of 2.79. The low dose linearity assumption, which thus clearly leads to very much lower VSD, is justified in two different ways. (i) Because carcinogenesis is poorly understood, "conservative" assumptions are required to protect the public safety. (ii) Carcinogenesis is well enough understood to make the low dose linearity assumption a scientifically reasonable one.

The one-hit model provides one possible scientific rationale for low dose linearity (*13*). Whether or not a hit occurs is considered a chance event. If the probabilities of a hit on many exposures are constant and independent, then the Poisson distribution, which is applicable, implies that the probability of one or more hits, and hence of an observable consequence, is given by

$$f(D) = 1 - \exp(-\lambda D) \qquad (3)$$

where λD is the expected number of hits at dosage D. The function (Eq. 3) is also a dose-response curve, which at low response levels, say less than 10 percent, is essentially linear in D with slope λ. The probabilistic component in this dose-response curve arises not from variation in susceptibility of organisms, as in the probit-log dose model, but from whether or not a hit occurs.

In some experiments in carcinogenesis the one-hit model provides a satisfactory description of the dose-response relation in the observable range (*14*), but since the one-hit model and the probit-log dose model with slopes of 1.5 to 2.0 are not readily distinguishable (*15*), this by itself provides no evidence on linearity at low doses. Much larger numbers at low doses are required to distinguish between these models. Such numbers are provided by certain kinds of epidemiologic studies, particularly in cigarette smoking (*16*) and aflatoxin (*17*) and these do appear to exhibit low dose linearity. But errors in reporting dose in the case of smoking, or variations around the average consumption for the village in the case of aflatoxin, will distort any true convex dose-response curve in the direction of linearity (*17*), so that the epidemiologic evidence is inconclusive on this point (*18*). Large numbers at low doses are also available in experiments with radiation-induced carcinogenesis, but there is considerable dispute as to whether these demonstrate linearity (*19*). Furthermore, the applicability to chemical carcinogenesis of even a generally accepted demonstration in radiation carcinogenesis would remain in doubt. Low dose linearity has been found in mutagenesis with chemical carcinogens in bacterial systems (*20*) but not in other cell systems (*21, 22*). Mutagenesis is generally regarded as an early step in the carcinogenic process, but as we shall argue in more detail shortly, the linearity of all other steps can by no means be safely assumed. There is also a well-based mathematical argument due to Crump *et al.* (*23*) which says that if carcinogens in the environment and a newly introduced one are additive, the effect of low doses of the newly introduced one must be linear. But the additivity assumption is a major one that lacks experimental support (*24*).

Thus, none of the above arguments for low dose linearity, singly or in combination, can be regarded as convincing, and the scientific reasonableness of the hypothesis remains in doubt. Another possible justification for it does emerge in my later discussion, however.

On "Conservative" Procedures

The other argument for the low dose linearity assumption, its conservatism in the face of scientific ignorance, raises philosophical rather than scientific issues, and is more difficult to discuss. The same issue of conservatism arises in other ways than as a justification for low-dose linearity. Thus it is "conservative" to use upper confidence limits on the estimated VSD rather than the VSD themselves, and Mantel and Bryan (*5*) and Hartley and Sielken (*12*) have proposed this. Similarly, if an agent is carcinogenic in one species or in one sex but not in another, it is "conservative" to assume that the more sensitive sex in the most sensitive species best describes man. In transferring the VSD from the most sensitive species to man the dosage can be expressed on a body weight or a dietary concentration basis, the latter being more "conservative" since it leads to about a 15-fold lower VSD for man when the experimental animal is the mouse. Although comparison of animal and human results on the same compounds supports the body weight conversion (*14*), the concentration conversion continues to be used (*6*), apparently because of its greater conservatism.

One problem with the conservatism argument is that there is no place at which it can stop. Use of the observed probit slope is almost always less "conservative" than the Mantel-Bryan slope of unity, which is in turn less "con-

servative'' than assuming linearity, which is in turn less ''conservative'' than assuming linearity with a zero slope, which last is consistent with the Delaney clause. Similarly, why stop at using the most sensitive species, the most sensitive strain within species, and the more sensitive sex? Why not use only the most sensitive individual animals, thus obtaining 100 percent incidence at each dose level? Or why stop at the upper 95 or 99 percent confidence limits when an uncountable infinity of more ''conservative'' choices remain? In practice, of course, people do stop, but then it becomes difficult to understand what they mean by being conservative.

A more fundamental problem, no matter where one stops, is that ''conservative'' risk assessments distort the cost-benefit analysis since an exaggerated estimate of risk cannot be balanced against a sober analysis of benefit. The principles of decision-making under uncertainty are well-known, and, although difficult to apply in practice, leave no doubt as to the inappropriateness of ''conservative'' risk assessments in decision-making, since they indicate that expected risks and expected benefits, rather than upper limits, are required (*25*). Thus, the appropriateness of confidence limits for general decision-making purposes was questioned by Savage more than 20 years ago (*26*), and subsequent developments have strengthened his argument. These principles also establish the necessity of separating scientific assessments, such as the assignment of probabilities, from value judgments, such as assignment of utilities to the consequences of decisions. It appears, however, that conservative assessments embody value judgments in a not clearly identifiable way (in the use, for example, of upper rather than lower confidence limits on risk) and should not be imposed on the decision-maker who balances risks and benefits in the guise of ''conservative'' mathematical assumptions.

An example will perhaps illuminate this general argument. Consider a single observed no-effect level, which for simplicity we regard as consisting of 0 animals affected out of n observed. The ''conservative'' analysis remarks that such a result is consistent with the existence of a small probability of risk, say $1/2n$, and regards the upper confidence limit as the proper quantification of this remark. From a decision point of view the appropriate expression of the uncertainty is the expected risk, given the observation 0 out of n (*27*). If a uniform prior distribution is assumed, the expected risk is known to be $1/(n + 2)$, that is, 1/3 for $n = 1$ and 1/102 for $n = 100$. Thus, $1/(n + 2)$ is the appropriate Bayesian risk assessment at the no observed effect level for a uniform prior distribution. If, however, one uses as the estimated risk the upper confidence limit for some selected value of the confidence coefficient, $1 - \alpha$, namely $1 - \alpha^{1/n}$, this is equivalent to selecting a prior distribution with expectation above $1 - \alpha^{1/n}$, that is, above 0.99 for $\alpha = .01$ and $n = 1$. Such a prior distribution would rarely correspond to anyone's real beliefs and seems to reflect instead a concealed value judgment, that is, assignment of great weight to the risk, without regard to possible benefit. Such value judgments can not and should not be avoided, but they should be made explicit and not introduced in so intellectually muddled a way that no one knows which are the facts and which the judgments.

Carcinogenic and Noncarcinogenic Toxicity

A reason often assigned for the use of different safety evaluation procedures for carcinogenic and noncarcinogenic substances is that the classical toxicological procedures are useful for assessing acute, reversible, nonprogressive effects but not for the chronic, progressive, and irreversible effects of carcinogenesis (*28*). A corollary to this view is that while population thresholds may exist and can be estimated for noncarcinogenic substances, no such estimation is possible for carcinogens, since even one molecule might be sufficient to initiate the process. This distinction may not be as clear-cut as it seems at first sight if one considers such toxic substances as lead or such disease states as emphysema and atherosclerosis. But more fundamentally it is not clear why chronic, progressive, irreversible effects must lead to qualitatively different dose-response curves from those found for acute, short-term reversible effects, since from the point of view of establishing ADI it is only the dose-response curve that matters. An alternative to this dualistic view regards dose-response curves for carcinogenic and noncarcinogenic substances alike as reflecting the saturation of protective biological mechanisms, such as detoxification and DNA repair, and considers differences on the acute-chronic or reversible-irreversible axes as simply reflecting detailed differences in the kinetics of the reactions involved [see also (*17*) and (*29*)]. Thus, even if one molecule of carcinogen is sufficient, the carcinogen will often be a metabolite of the compound administered, and, as Miller and Miller (*30*) put it, much of the dose of the compound administered ''may be dissipated in deactivation reactions'' so that it may be impossible for one molecule of the administered compound to lead to one molecule of carcinogenic metabolite. A mathematical analysis of this argument is of interest in view of its implications for the development of more rationally based safety evaluation procedures for carcinogenic and noncarcinogenic agents alike. It need hardly be emphasized that the only objective is to explore the qualitative implications for safety evaluation of some reasonable biological assumptions, and not the development of a universal kinetic model for all toxic reactions.

A Simple Kinetic Model

Two reactions are considered here. In the first, d moles of toxic substance combine with s moles of free substrate to form x moles of an activated complex, which in turn reversibly disassociates into toxic substance and substrate. Forward and back reactions are governed by rate constants k and k_-. The amount of activated complex formed in the forward reaction is thus kds and the amount lost in the back reaction is k_-x, and since in the steady state these two amounts are equal we have

$$kds - k_-x = 0 \quad (4)$$

In the second reaction d moles of free toxic substance are simultaneously deactivated by t moles of free deactivator to form y moles of toxin-deactivator complex, which in turn reversibly disassociates into toxic agent and deactivator, the governing rate constants being k^* and k^*_-. In the steady state we thus also have

$$k^*dt - k^*_-y = 0 \quad (5)$$

The total moles of toxic substance in the system is $d + x + y$, which we denote by D; the total moles of substrate is $s + x$, which we denote by S; the total moles of deactivator is $t + y$, which we denote by T, leading to the balance equations

$$\begin{aligned} D &= d + x + y \\ S &= x + s \\ T &= t + y \end{aligned} \quad (6)$$

Denoting k_-/k by K and k^*_-/k^* by K^* we rewrite Eqs. 4 and 5, using Eq. 6, as

$$(D - x - y)(S - x) - Kx = 0 \quad (7)$$

$$(D - x - y)(T - y) - K^*x = 0 \quad (8)$$

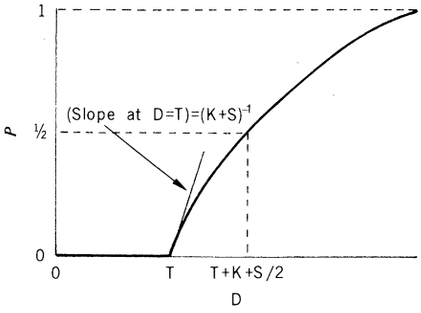

Fig. 1. Dose-response relation under a model of irreversible deactivation.

where from Eq. 6, $x \leq \min(D,S)$ and $y \leq \min(D,T)$.

The probability of a toxic reaction in an organism exposed to the toxic substance, P, is considered proportional (*29*) to amount of activated complex x, and since $\lim_{D\to\infty} x = S$, we take as the constant of proportionality $1/S$, so that

$$P = x/S \tag{9}$$

We thus embody in the model the assumption that even one molecule of x could lead to a toxic reaction. We are interested in the relation between P and D defined by Eqs. 7, 8, and 9, this relation yielding the dose-response curve implied by the system. The quantities S, T, K, and K^* are parameters and x and y variables to be eliminated.

A direct solution yields an explicit relation between P and D but more insight results from first considering an implicit solution for P for the case $K^* = 0$, that is, the case in which there is no back deactivation reaction. It is then easily verified that Eqs. 7, 8, and 9 are satisfied by the following solution: For

$$D \leq T,\ P = 0$$

$$y = D \tag{10a}$$

and for

$$D \geq T,\ P = \frac{D - SP - T}{D - SP - T + K}$$

$$y = T \tag{10b}$$

Since $P = 0$ for all $D \leq T$, the dose-response curve yielded by this solution has a threshold at $D = T$, but for $D > T$ it increases with decreasing slope from $P = 0$ to $P = 1$. Such an asymmetric sigmoid curve is shown in Fig. 1.

Although D, S, and T in Eq. 10 are expressed in moles, and K is dimensionless, multiplication of numerator and denominator by any constant needed to convert moles to any other unit, such as milligrams, leaves the form of the relationship unaffected and converts the parameters S and T to milligrams and K to milligrams per mole. To see whether Eq. 10 provides a satisfactory description of an observed dose-response curve, it is therefore sufficient to estimate S, T, and K and to compare the observed values of P with those computed from Eq. 10. This is done in Table 1 for the lifetime tumor incidences in mice subcutaneously injected with various doses of methylcholanthrene as reported by Bryan and Shimkin (*8*). The parameters S, T, and K were estimated, somewhat crudely, by equating the P yielded by Eq. 10 with the P yielded by the fitted probit curve at values of $P = 0.05$, 0.50, and 0.95. It will be observed that the description provided by Eq. 10 is satisfactory despite its neglect of possible animal to animal variation in the values of S, T, and K. This might be considered scarcely surprising, given the three disposable constants in Eq. 10, but there is no a priori reason why the values estimated for these constants must be positive, as the model requires, and as they are in this case. Thus, if the model is to be rejected, it cannot be because of failure to describe the methylcholanthrene dose-response curve. Since we are here interested in qualitative implications, and not detailed statistical procedures, I shall not consider the modifications of Eq. 10 required to allow for animal variation in parameter values, although it is clear that without them the possibility of negative estimates of S, T, and K cannot be excluded.

An Expanded Kinetic Model

Not all deactivating reactions are irreversible. In the hydrocyanic acid-thiosulfate-cytochrome oxidase system, for example, a back deactivation reaction exists, which although quite slow compared to the forward reaction (*31*) should

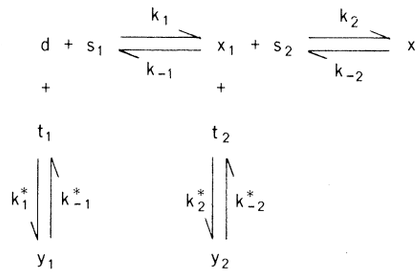

Fig. 2. Model of a two-step chain of protective reactions.

not be disregarded. To see the effect of such a reaction we now relax the assumption that K^* in Eq. 8 is equal to zero. A simple, though perhaps inelegant, way to investigate this more general case is to note that for small D,

$$S - x \cong S \text{ and } T - y \cong T \tag{11}$$

in which case Eqs. 7 and 8 become linear in x and y, leading immediately to the solution

$$P \cong \frac{D}{S + K\left(1 + \dfrac{T}{K^*}\right)} \quad \text{for } D \leq T \tag{12}$$

Thus, for small D, P is linear in D, with slope approaching zero as K^* approaches zero. For $D > T$ we use Eqs. 7 and 9 to obtain

$$P = \frac{D - SP - y}{D - SP - y + K} \tag{13}$$

for $D > T$, where, by eliminating $D - x - y$ from Eqs. 7 and 8 we find

$$y = KPT/[KP + K^*(1 - P)] \tag{14}$$

for $D > T$.

Thus a reversible deactivation reaction implies low-dose linearity. If the kinetics for the system are known, the slope of the linear portion can be calculated from Eq. 12, but for a very low K^*

Table 1. Comparison of observed and estimated lifetime tumor incidence at various doses, D, of methylcholanthrene for Eq. 10 and probit-log dose curve.

D (mg)	Observed	Eq. 10*	Probit-log dose†
1	20/20	0.9964	1.0000
0.5	21/21	0.9926	0.9997
0.25	21/21	0.9843	0.9962
0.125	21/21	0.9644	0.9728
0.062	17/21	0.9044	0.8808
0.031	13/20	0.6955	0.6680
0.0156	6/18	0.3686	0.3782
0.0078	3/17	0.1490	0.1457
0.0039	0/19	0.0283	0.0360
0.002866‡		0	0.0165
0.00195	0/19	0	0.0055
0.00098	0/41	0	5.0×10^{-4}
0.00024	0/79	0	8.9×10^{-7}

*$P = \dfrac{D - (.02904)\,P - .002866}{D - (.02904)\,P - .002866 + .003475}$

†As calculated from the Bryan-Shimkin equation [see (*8*)]. ‡Calculated saturation dose.

as in the case of the hydrocyanic acid-thiosulfate-cytochrome oxidase system, it will be negligible (*32*). But when the kinetics are not known and the slope must be inferred from the observed dose-response curve, the threshold argument provided by Eq. 10 can no longer be sustained. That argument assumes, however, one step between the toxin and the organism's toxic reaction, while in fact numerous steps may exist (*29, 30*).

It is an interesting mathematical exercise to deduce the consequences of assuming a chain of n reactions, each of the type previously considered. It is sufficient, however, to consider the case $n = 2$ in order to demonstrate that (i) irreversible deactivation in any one step in the chain leads to a threshold for the function $P = f(D)$, and (ii) that even in the absence of irreversible deactivation, the addition of a step reduces the low-dose slope. In what follows, the first step can be thought of as a detoxification reaction and the second as DNA repair. The model is shown in Fig. 2. The balance equations are:

$$\begin{aligned} D &= d + x_1 + y_1 + x_2 + y_2 \\ S_1 &= s_1 + x_1 + x_2 + y_2 \\ T_1 &= t_1 + y_1 \\ S_2 &= s_2 + x_2 \\ T_2 &= t_2 + y_2 \end{aligned} \tag{15}$$

so that

$$\begin{aligned} x_1 &\leq \min(D, S_1) \\ y_1 &\leq \min(D, T_1) \\ x_2 &\leq \min(D, S_1, S_2) \\ y_2 &\leq \min(D, S_1, T_2) \end{aligned} \tag{16}$$

The equations of the system are:

$$\begin{aligned} [D - (x_1 + y_1 + x_2 + y_2)]\ [S_1 - (x_1 + x_2 + y_2)] - K_1 x_1 &= 0 \\ [D - (x_1 + y_1 + x_2 + y_2)]\ [T_1 - y_1] - K_1^* y_1 &= 0 \\ x_1(S_2 - x_2) - K_2 x_2 &= 0 \\ x_1(T_2 - y_2) - K_2^* y_2 &= 0 \\ P = x_2/S_2 \end{aligned} \tag{17}$$

where $K_1 = k_1/k_{-1}$ and $K_1^* = k_1^*/k_{-1}^*$. Then, for the case $K_2^* = 0, K_1^* \geq 0$ and $D \leq \min(S_1, T_2)$, Eqs. 17 are satisfied by $x_1 = 0$, $x_2 = 0$, $y_1 = 0$, and $y_2 = D$, so that $P = 0$ for all $D \leq \min(S_1, T_2)$. Similarly, for the case $K_1^* = 0, K_2^* \geq 0$, and $D \leq T_1$, Eqs. 17 are satisfied by $x_1 = 0$, $x_2 = 0$, $y_2 = 0$, and $y_1 = D$, so that $P = 0$ for all $D \leq T_1$. Thus irreversibility in either of the steps leads to a threshold.

To find the solution for $K_1^*, K_2^* > 0$, we generalize the argument used in the one-step case starting with Eq. 11, thus making Eqs. 17 linear in x_1, x_2, y_1, and y_2 and find that, for $D \leq \min(S_1, T_1, T_2)$

$$P \cong D \Big/ \left[\frac{K_1 K_2}{S_1} (1 + T_1/K_1^*) + S_2 + K_2(1 + T_2/K_2^*) \right] \tag{18}$$

But the two-step steady state system of Fig. 2 reduces to a one-step system for $S_1 > 0$ and $K_1 = 0$, since in that case $y_1 = D - (x_1 + y_1 + x_2 + y_2) = 0$ satisfies the first two parts of Eq. 17 and no D remains in step 1. But from Eq. 18 P is greatest for $K_1 = 0$, in which case it reduces to Eq. 12, thus demonstrating that the existence of an additional step ($K_1, S_1 > 0$) reduces the low dose slope. These results are easily extended to cover an n step system.

Thus, for a chain of n protective reactions the resulting dose-response curve is shaped much like a hockey stick, with the striking part flat or nearly flat and the handle rising steeply once the protective mechanisms are saturated. Gehring and Blau (*29*), using a kinetic system not unlike the present one, eight simultaneous reactions, typical rate constants selected from the literature, and a computer simulation found exactly such a curve with a saturation dose of about 10^{-4} mole/kg.

Discussion

This analysis establishes that even if carcinogenesis is an irreversible one-hit phenomenon between the ultimate carcinogen and DNA, an assumption embodied in Eq. 9, the existence of a no effect or threshold level for the carcinogenic compound administered is not precluded. Whether such levels do or do not exist depends on the presence of at least one irreversible protective reaction, but there seems no present reason for believing that all carcinogenic processes are characterized by the absence of such reactions and all or most noncarcinogenic processes by their presence. We have thus found no analytic basis for the sharp distinction drawn between the two classes of toxic reaction by present safety evaluation procedures. Other bases, perhaps in the realm of value judgments, may exist, but they do not appear to have been made explicit.

Although many observed dose-response curves are consistent with the existence of thresholds, for example, the data in Table 1, no finite set of dose-response observations could establish this. All present safety evaluation procedures, whether involving the use of NOEL's, or of some favored non-threshold dose-response function with a "virtually safe" level, must be regarded as mathematical formalisms whose correspondence with the realities of low-dose effects is, and may long remain, largely conjectural. But regulatory decisions must be made, and formalisms with more theoretical or experimental support, or both, should be preferred to those with less. In this spirit I suggest that another formalism, with at least as much claim to reality as those now in use, is provided by the saturation dose defined by Eq. 10, and that the development of efficient statistical procedures for computing the posterior expectation of the saturation dose may find a place in safety evaluation procedures.

References and Notes

1. Residues include such substances as pesticides left on crops and diethylstilbesterol from beef; natural contaminants include the aflatoxin found in groundnuts and corn; migrants include such compounds as those from packaging materials, for example, vinyl chloride or acrylonitrile.
2. *U.S. Code* **21**, 348(c)(3).
3. See *Code of Federal Regulations*, title 21, sect. 121.5; B. L. Oser, *Food Cosmet. Toxicol.* **7**, 415 (1964).
4. Attachment to letter to Chairman, EPA Environmental Health Advisory Committee from Assistant Administrator of the EPA, Office of Water and Hazardous Substances, 19 April 1977.
5. N. Mantel and W. R. Bryan, *J. Natl. Cancer Inst.* **27**, 455 (1961).
6. *Fed. Regist.* **42** (No. 35), 10412 (22 February 1977).
7. Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation. Panel on Carcinogenesis: "Report on cancer testing in the safety evaluation of food additives and pesticides, *Toxicol. Appl. Pharmacol.* **20**, 419 (1971).
8. W. R. Bryan and M. B. Shimkin, *J. Natl. Cancer Inst.* **3**, 503 (1943).
9. D. J. Finney, *Probit Analysis: A Statistical Treatment of the Sigmoid Response Curve* (Cambridge Univ. Press, London, 1952).
10. An alternative, equally descriptive, route to the probit-log dose function is provided by the work of H. Druckery [in *Potential Carcinogenic Hazards from Drugs, Evaluation of Risks*, R. Truhaut, Ed. (Union Internationale Contre le Cancer Monogr. Ser. No. 7, Springer-Verlag, New York, 1967)] and of R. E. Albert and B. Altschuler [*AEC Symp. Ser.* CONF-720505 (1973)]. In studying the dose dependence of time to tumor for a number of carcinogenic agents Druckery noted that they were all characterized by the empirical relation Dt^n = a constant, where t is median time to tumor and n is a constant varying between 1 and 4. Albert and Altschuler extended Druckery's work by considering various statistical distributions of time to tumor, in particular the lognormal. It is easy to show, however, that the Druckery relation in combination with the Albert-Altschuler assumption of a lognormal distribution of time to tumor implies that the probability of a tumor at dose level D by any time, T, such as the life span of the experimental animal, is given by Eq. 1 with α and β dependent in a simple way on n, T, and the two constants of the lognormal distribution of time to tumor. The probit–log dose model therefore gives a more appropriate expression of time to tumor than is sometimes realized.
11. It is known that measurement errors, although normal in the central part of the distribution, tend to occur with above normal frequency in the tails [H. Jeffreys, *Theory of Probability* (Clarendon Press, Oxford, ed. 1, 1939), sect. 5.77.] and this makes lower slopes in the tails seem more plausible to some, even though the relevance of the distribution of measurement errors to that of tolerance is questionable.
12. H. O. Hartley and R. L. Sielken, Jr., *Biometrics* **33**, 1 (1977).
13. A hit is any event necessary for the production of an observable consequence. The event might be a bacterium landing on an agar plate or a gamma ray penetrating a chromosome, the consequence being the growth of a colony or a chromosome breakage. In a one-hit model a

single hit is sufficient to produce the consequence.
14. National Academy of Sciences, *Contemporary Pest Control Practices and Prospects* (National Academy of Sciences, Washington, D.C., 1975), vol. 1.
15. S. Peto, *Biometrics* **9**, 320 (1953).
16. H. A. Kahn, in *Natl. Cancer Inst. Monogr. No. 19* (1966), p. 1.
17. J. Cornfield, F. W. Carlborg, J. Van Ryzin, *Proceedings of the First International Toxicology Congress*, in press.
18. An unpublished calculation by J. Van Ryzin applying the continuous multi-hit generalization of the one-hit model (*17*) to the Dorn smoking-lung cancer results [see (*16*)] leads to an estimate of 0.7 hit. A less than one-hit model, for which there appears to be no biological rationale, is easily explained on the reporting error hypothesis, so that this result adds empirical support to that hypothesis as a theoretical explanation of the epidemiologic results.
19. B. Wolfe, *Science* **196**, 1387 (1977).
20. J. McCann and B. N. Ames, in *Occupational Carcinogenesis*, U. Saffiotti and J. K. Wagoner, Eds., published in *Ann. N.Y. Acad. Sci.* **271**, 5 (1976).
21. B. E. Matter and J. Grauwiler, *Mutat. Res.* **23**, 239 (1974); D. J. Kilian *et al.*, *ibid.* **44**, 97 (1977).
22. A. W. Hsie, *et al.* in preparation.
23. K. S. Crump, D. G. Hoel, C. H. Langley, R. Peto, *Cancer Res.* **36**, 2973 (1976).
24. To distinguish between independent and additive effects of two or more agents one has to make large numbers of observations. The use of the cell systems for investigating joint effects in mutagenesis would supply large numbers and seems promising. Summaries of results of experiments in combination carcinogenesis can be found [Health and Welfare Canada, *The Testing of Chemicals for Carcinogenicity, Mutagenicity and Teratogenicity* (March 1973); D. Schmähl, *Oncology* **33**, 73 (1976); J. C. Arcos, in *Chemical Carcinogenesis*, P. O. P. Ts'o and J. A. DiPaolo, Eds. (Dekker, New York, 1972), part A.]
25. The designation "conservative" is clearly inappropriate since it is not conservative to forego benefits—which may be more than monetary, as in the antimalarial effect of DDT. The strict Bayesian decision procedure, which requires assignment of prior probabilities to all the possible scientific hypotheses, utilities to all the possible consequences, the computation of an expected utility for each possible decision, and the selection of the decision with maximum expected utility may be well beyond the capacity of any scientifically, legally, or politically oriented decision-maker short of Plato's philosopher king, even though it is the only coherent one [see D. V. Lindley, *Making Decisions* (Wiley, New York, 1971); and B. Altschuler, in *Environmental Health, Quantitative Methods*, A. Whittmore, Ed. (Society for Industrial and Applied Mathematics, Philadelphia, 1977)].
26. L. J. Savage, *Foundations of Statistics* (Wiley, New York, 1954).
27. This assumes that utility is linear in probability of risk, a reasonably acceptable assumption for the small probabilities of concern, but of doubtful generality and, of course, ludicrous as the probability approaches unity.
28. *Summary Report: Drinking Water and Health*, a report of the Safe Drinking Water Committee, Advisory Center on Toxicology, Assembly of Life Sciences (National Research Council, National Academy of Sciences, Washington, D.C., 1977).
29. P. J. Gehring and G. E. Blau, *Proceedings of the First International Toxicology Congress*, in press.
30. J. A. Miller and E. C. Miller, *J. Natl. Cancer Inst.* **47** v (1971).
31. L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics* (Macmillan, New York, 1970).
32. This model thus explains low-dose linearity for mutagenicity in some cellular systems and nonlinearity for carcinogenicity in mammals by the existence of deactivating mechanisms, such as detoxification by the liver ($T > 0$) in the latter, but not in the former ($T = 0$). A striking example of this is given by Hsie (*22*), who studied the mutagenic effects of ethyl methanesulfonate in Chinese hamster ovary cells both in vitro and in vivo. The dose-response curve for the former was linear, but for the latter showed an apparent threshold.
33. The preparation of this manuscript was supported by NIH grant 15191.

The Code of the Scientist and Its Relationship to Ethics

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Several decades ago, Paul Valéry, poet and essayist, declared (*1*):

> Never has humanity known so much power and so much confusion, so much worry and so much play, so much knowledge and so much uncertainty. In equal measure does now anguish, now futility, command the hours of our days.

These words were undoubtedly appropriate when Valéry gave pen to them. Yet today they are perhaps even more apposite. Indeed, they seem to apply to three distinct spheres of human action.

In the first place, we live in a time in which the industrialized countries are experiencing unparalleled technological development, in large part the fruit of science. However, the benefits of new technologies are distributed in a grossly unbalanced manner, not only within individual industrialized countries, but also among all the nations of the world. Overcrowding and environmental degradation are already significantly reducing the quality of life in the developed nations and give stark evidence of their inability to confront the problems of the future and its planning. Excess population and famine are on the increase in some regions, while in others there are those who enjoy material goods and leisure as never before. In a word, our inability to regulate the processes of cultural and technological development poses a grave threat to our ability to achieve a decent and humane future.

In the second place, as we all are aware, the trends toward nationalism, and its opposite, multinational industrialization, are growing. Many will agree with me that if a universal world order of some type is not achieved by agreement based upon reason and economic justice, the prospect is that it may be imposed by force.

And third, science is now in a state of siege. Those who in the past have praised its contributions to human understanding and material well-being are now questioning many facets of the scientific enterprise. Some even go so far as to ask whether it does not contain the potential for destroying civilization.

In this article I center my discussion on something which I shall argue is common to each of these problems, namely, the operating and ethical code of the scientist. First, I discuss some aspects of the situation of scientists and the possibilities for preserving the norms of science. Second, I deal with an even broader question: could there be a relationship between the ethical stance of the scientist, *qua* scientist, and the problem of fostering humane socioeconomic development? In turn, these reflections will prepare the way for a brief examination of the possible relationship between science and a unified world-order of some type.

Formulation of an Operational and Ethical Code of the Scientist

Scientists have developed characteristic rules of procedure that help to produce the intended outcome of their activity, which is certified knowledge. These rules also guide the conduct of individual investigators toward each other in their capacity as scientists. In 1942, Robert Merton formulated these rules as the

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