LETTERS

Vitamin C

The report "Academy turns down a Pauling paper" (News and Comment, 4 Aug., p. 409) contains the following incorrect and misleading statement: "Pauling himself, for example, has published in the PNAS [*Proceedings of the National Academy of Sciences*] on vitamin C twice in the last 2 years. Even though his papers were accepted with what Edsall terms 'extreme mental reservations,' the overriding feeling was that Pauling had a right to express his views, in spite of the fact that most other NAS members took issue with their scientific validity."

In the first of these two papers, "Evolution and the need for ascorbic acid," I presented a new argument, based on the nature of the evolutionary process, about the optimum intake of vitamin C for the best health. Not one paper taking issue with the scientific validity of this article has been published, and not a single member of NAS has taken issue with me about its scientific validity.

In the second paper, "The significance of the evidence about ascorbic acid and the common cold," I reported a statistical analysis of all published double-blind studies of the effect of ascorbic acid, regularly ingested in daily amounts of more than 100 milligrams, as compared with that of a placebo, in decreasing the incidence and integrated morbidity of the common cold for subjects exposed to cold viruses in the ordinary way and without colds when the test period began. No paper taking issue with the scientific validity of this article has been published, and no NAS member has taken issue with me about its scientific validity.

I doubt that *Science* questioned most of the 900 NAS members. I am sure that the statement that most NAS members took issue with the scientific validity of these papers is false. The statement made by *Science* is derogatory to me; I attribute its publication to carelessness on the part of *Science* rather than to malice.

In 1913 the NAS as a whole set the policy for PNAS that papers by members would not be refereed. I feel that no one but the NAS as a whole has the right to refuse publication of a paper by a member.

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Narcotic Antagonists

Some of the conclusions in Thomas Maugh's report on narcotic antagonists (Research News, 21 July, p. 249) are based on inaccurate assumptions. Maugh states that "Most important, perhaps, it has recently been shown that one of the antagonists exhibits great potential for preventing abuse of such drugs as methadone and paregoric" because naloxone blocks the effects of methadone when taken intravenously, but not when taken orally. He concludes that "Addition of naloxone to methadone could thus conceivably curb all the intravenous abuse of methadone in maintenance programs." The problem, however, is not intravenous abuse, but oral abuse. In New York City, where there are the greatest number of narcotic addicts and addicts in methadone treatment in the country, and considerable diversion of methadone, virtually all methadone abuse is oral, not intravenous—all 98 methadone overdose deaths in 1971 resulted from oral consumption. Intravenous paregoric abuse is a problem of minimal significance.

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Biological Effects of Chemical Agents

Dinman's article (4 Feb., p. 495) was a welcome approach to pollution toxicity on a more quantitative and microscopic level than is common in these somewhat frenetic times. However he neglected to mention a point which is the very one most central to the problem. For most and quite possibly all substances (including carbon monoxide) in the natural environment (but probably

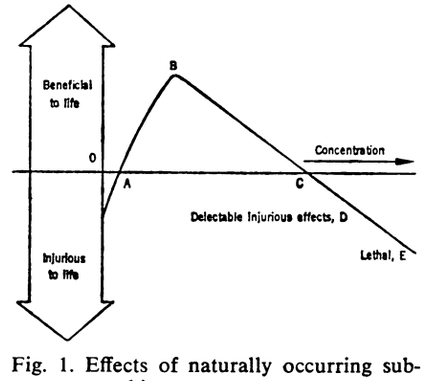

Fig. 1. Effects of naturally occurring substances on biosystems.

not for certain man-made pollutants alien to the environment), far from being linear, the curves representing the effects on biosystems are complex, as in Fig. 1. While large concentrations are injurious, trace concentrations can be necessary for life. The "toxic" heavy metals, vanadium, iron, manganese, cobalt, nickel, copper, zinc, and perhaps arsenic, tin, and lead are all necessary for life. Another highly publicized example is fluoride ion—small amounts reduce tooth decay (point B on the curve), larger amounts cause tooth mottling (point D), and in massive amounts it is the major ingredient of some rodent poisons (point E). Concentrations corresponding to points E and D are known for a few substances for a few organisms, including man, but the really important concentration level, point C, is known for none. Certainly it is not at the origin, that is, at zero concentration. Rather than none or even one threshold, there are at least three (points A, C, and D). Much more attention should be devoted to defining these curves for various substances (and types of radiation). We must be careful in "cleaning-up" environmental situations, for we may precipitate more biological and ecological damage by removing a vital "pollutant" below a critical level than might result from a moderate excess of the same pollutant.

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Dinman's criticism of the "non-concept" of "no-threshold" for environmental pollutants totally ignores the fact that this concept has been put forth not as an absolute, literal, and totally verified biochemical truth, but as a prudent assumption for establishing pollution standards and policies in the absence of thorough information. I have never heard any environmentalist claim that one "foreign" molecule entering a cell necessarily has a harmful effect. Dinman's invocation of stochastic structure-function models to bolster his statement that there "may not" be any harm done leaves only one unanswered question: So what?

Dinman criticizes proponents of the no-threshold concept for not reasoning quantitatively. Yet his own "quantitative" estimate of a threshold—about 10^4 molecules per cell—in practice is indistinguishable from the no-threshold view. For the case he discusses at length (mercury in a liver

cell), Dinman's threshold amounts to less than 1 part per billion, that is, one or two orders of magnitude below levels observed in persons unexposed to any artificial mercury (*1*). Were we ever to attain such levels, I doubt if many environmentalists would quibble as to whether or not the remaining mercury was still causing any harm.

Finally, Dinman implies that the logical conclusion of the no-threshold concept is that any disturbance whatever, or even any sensory stimulus, shortens the life of the organism. He conjures up Faustian images lest we be tempted to seek an immortality at such cost. Yet I failed to note any references to advocates of the other side of this question. Indeed, environmentalists commonly argue against the sterility and blandness of an environment in which we seek to eradicate insect pests, rather than control them, or in which a variety of natural habitats, including some "disturbing" ones, are systematically replaced by the uniformity and drabness of most modern cities (*2*).

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2. See R. Dubos, *Man Adapting* (Yale Univ. Press, New Haven, Conn., 1965).

B. D. Dinman presents some useful facts and ideas. I agree that extrapolation of data on dosage response to very low levels of treatment is biologically unsound. However, another concept could have been emphasized more. The hypothesis that all poisons are stimulatory in small quantities was introduced by Schulz in 1888 (*1*) and has since become the basis of the Arndt-Schulz law (*2*). Southam and Ehrlich (*3*) proposed the term hormesis to define a stimulatory effect of subinhibitory concentrations of any toxic substance on any organism.

Hormesis is a common and widespread phenomenon. Insecticides have been shown to stimulate growth of insects as well as plants, and fungicides can stimulate growth of fungi. A wide variety of herbicides can stimulate plant growth when applied at low concentrations (*4*).

Hormesis is often ignored in toxicological considerations. Legislative and regulatory decisions affecting ordinary toxicants should be made with an awareness of this phenomenon. Potential carcinogens present a different problem, which can only be resolved with additional scientific evidence.

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2. T. D. Luckey, in *ibid.*
3. C. M. Southam and J. Ehrlich, *Phytopathology* **33**, 517 (1943).
4. S. J. Wiedman and A. P. Appleby, *Weed Res.* **12**, 65 (1972).

I agree with Horne that there are probably several thresholds of response. Indeed, the concerns of the toxicologist and the nutritionist constitute different sides of the same coin. That we can "clean up" the environment to the point where we might precipitate damage by making such traces unavailable is, I believe, a bit overdrawn. This implies extractive activities beyond any possible economic return or technologic capability.

Inherent in Lockeretz's letter are the gut responses of the environmentalists which prompted my article. I refer to his statement that the "no-threshold" concept is a ". . . prudent assumption for establishing pollution standards and policies in the absence of *thorough* [italics mine] information." If conceptually the scientific basis for "no-threshold" is open to serious question, how can the proposition become prudent for *any purpose*? Particularly so, since Lockeretz inserts the reservation that ". . . thorough information" is required before a threshold is permissible. It is well known that for any discrete area of knowledge, characterization of what constitutes "thorough" is always debatable. Therefore only "no-threshold" can be "prudent."

As to the threshold at 10^4 molecules per cell, I left open the nature of the response (see the letters from Appleby and Horne). Lockeretz doubts ". . . if many environmentalists would quibble . . ."; I do not doubt it. Consider the recommendations by some for carbon monoxide air-quality standards approaching 5 to 6 parts per million—or lower—despite the reality that the internal environment is in equilibrium with endogenous carbon monoxide at such concentrations.

Lockeretz's last argument about the problems of our modern cities is interesting. I have been long concerned that the extreme environmentalist position inherent in the "no-threshold" stance has drawn our attention and resources from what I consider to be the prime global environmental problem, that is, the quality of human life in the conurbation (*1*). The fruitless pursuit of "no-threshold" has needlessly siphoned off our finite resources from their application to what should be our common concern.

The problem with the Arndt-Schulz law, mentioned by Appleby, is that there have been at least as many exceptions as supporting instances (*2*). While Carlson and Jackson (*3*) and Sacher and Trucco (*4*) present persuasive evidence in support of that law, I did not lean heavily on the principle in my article since I believe it is presently open to question.

With respect to carcinogens, it is interesting to note that the Millers (*5*) present an argument similar to those in my article regarding interfering substances, that is, that "non-critical nucleophiles" in the cell may trap ultimate carcinogens.

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Virtuous Noun Verbed

Whoever allowed a previously respectable noun to be verbed should be violenced [see 18 Aug., p. 616—"a major part of the ventromedial nucleus of the hypothalmus has been *lesioned*" (italics mine)]. Good nouns are hard to keep virtuous, and their prostitution should be crimed. In his defense, whoever is responsible might claim that he should not be clubbed, axed, or gunned, as usage has justified similar seductions.

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