Letters

Wisdom of Cyclamate Ban

Inhorn and Meisner, in their letter "Cyclamate ban" (7 Nov.), refer to "overwhelming evidence that cyclamate causes no deleterious effect on humans [and they] . . . find it inconceivable that when there is so much human data available, that cyclamate be discarded on the basis of experiments employing only 12 rats." Such widespread misconceptions prompt this reply.

The editorial "Chemicals and cancer" by Abelson in the same issue properly refers to the difficulty of assessing carcinogenic hazards from chemicals because of the generally long interval between exposure and subsequent effect. For example, the average latent period is 18 years between occupational exposure to aromatic amine carcinogens and the induction of bladder cancer (*1*). As wide-scale dietary use of cyclamates is relatively recent, the retrospective Connecticut data, to which Inhorn and Meisner refer, indicating that there has been no increase in mortality from bladder cancer, are hardly relevant. In fact, the *incidence* of bladder cancer in Connecticut has increased in the last 20 years; in men it has approximately doubled (*2*). For the reasons given below, we endorse rigorous restriction of cyclamates.

In spite of a caution from the National Academy of Sciences in 1962 on the inadequacy of toxicological data on cyclamates (*3*), production in the United States increased from 5 million pounds in 1963 to 15 million pounds in 1967 and, if unrestricted use were to continue, would total an estimated 21 million pounds by 1970 (*4*). More recently, an interim report reemphasized this warning with particular reference to cyclohexylamine, a major human metabolite of cyclamate, and "recommended that adequate tests of carcinogenic potential of these materials and their metabolites be completed" (*4*, p. 49).

The ultimate decision to restrict cyclamates was based in part on the Abbott-sponsored 2-year study which indicated induction of bladder cancer in 7 of 20 male rats at risk following feeding with a mixture of cyclamate and saccharin (10 : 1) at concentrations approximately 50 times greater than the estimated human exposure levels. This study can be reasonably criticized on the grounds that the rats should have been fed cyclamates only, but it cannot be criticized on the grounds that high dose levels were tested.

Let us assume that a carcinogen, such as a food additive or pesticide, at actual human exposure levels induces cancer in as many as 1 out of 10,000 humans, then the chances of detecting this in test groups of 20 to 50 rats exposed at these actual levels would be very low; indeed, many more than 10,000 rats, depending on their spontaneous tumor incidence, would be required to demonstrate a statistically significant increase in the cancer incidence if we assumed that rats and humans have similar sensitivity to the carcinogen being studied. For these reasons, it is routine practice to test for carcinogenicity at concentrations higher than human exposure levels. Apart from the Abbott data, reexamination (*5*) of the histopathology of the 1951 FDA chronic toxicity studies (*6*) suggests the carcinogenicity of cyclamates when tested alone. More recently, cyclamate salts fed to rats produced bladder cancer in 3 out of 23 rats and extensive hyperplasia and polyps in the bladders of 10 of 20 rats; no such changes were noted in comparable numbers of controls (*7*).

In addition to the legal basis for restrictions on cyclamates based on the Delaney Amendment, there are serious and unresolved questions as to the potential teratogenicity and mutagenicity of cyclamates. Data on the teratogenicity of both cyclamate and cyclohexylamine in the chick embryo (*8*) have to be contrasted with the lack of available mammalian data on the teratogenicity of cyclohexylamine. The demonstration of in vivo cytogenetic damage to rat germinal and somatic cells by microgram doses of cyclohexylamine is presumptive evidence of genetic hazard.

The decision to restrict cyclamates to the general public and to terminate a mass human experiment for which there are no demonstrable matching benefits is clearly proper. We concur that food additives be banned from products unless they have been proven safe, and either significantly improve the quality or nutritive value of the food or lower the food cost (*9*). Finally, our experience with cyclamates emphasizes the critical need for reviewing procedures concerned with potential hazards due to chemicals to which we are currently exposed and which have never been adequately tested.

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References and Notes

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3. *Policy Statement on Artificial Sweeteners* (Food and Nutrition Board, National Academy of Sciences, Washington, D.C., 1962).
4. *Interim Report on Non-nutritive Sweeteners* (Food Protection Committee, National Academy of Sciences, Washington, D.C., November, 1968).
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6. O. G. Fitzhugh, A. A. Nelson, J. P. Frawley, *J. Amer. Pharm. Ass.* **40**, 583 (1951).
7. Food and Drug Administration, unpublished data.
8. M. Legator, K. A. Palmer, S. Green, K. W. Petersen, *Science* **165**, 1139 (1969).
9. D. M. Kendall, *A Summary of Panel Recommendations*, Report of Panel on Food Safety to the White House Conference on Food Nutrition and Health (22 November 1969), p. 19.

Uphill Road for New Drugs

In "Prognosis for the development of new chemical birth-control agents" (24 Oct., p. 468), Djerassi is critical of the fact that appeals to rulings of the Food and Drug Administration (on clinical tests of contraceptives, for example) can be made only through the courts. He suggests that the ultimate authority should be vested with independent bodies of experts.

Judging the safety and efficacy of

lrugs is more than a purely scientific lecision. It is a complex process involvng morals, ethics, and law. Courts can :valuate testimony from experts in all hese fields and are therefore the proper ıltimate authority. The Nuremberg rials demonstrated that very effectively.

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Djerassi challenges current objections o testing potentially injurious comounds on healthy individuals. If soiety would regard the testing of conraceptives as a form of employment ıttended by a certain hazard, the volunteer could be compensated for his or ıer cooperation commensurate with the isk involved, just as in other fields of employment. The pay could be a nonthly stipend or a health and life nsurance policy, or both. Such wages would be part of the budget for research on contraceptives, but since society will oe the ultimate and prime beneficiary of this work, the cost should be met by public funds. This approach would ease recruitment of volunteers, discourage esting of imitative compounds, and most important, would counteract the dea that the poor or ignorant donated their health for the comfort of the well-off, be they individuals or nations.

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Permeation of Polyethylene Bags

Since 1963 we have handled and stored more than 80,000 samples of solid organic chemicals in amounts averaging much less than 1 gram each. These samples were placed in small polyethylene bags to prevent breakage, reduce handling, shipping charges, and storage space—all methods to effect savings. Unfortunately, we learned a painful lesson. The bags were permeable to some compounds if stored for a long time at room temperature. Although it is an excellent moisture barrier, the polyethylene film (0.005 centimeter) is penetrated by a variety of solid organic compounds, even though the penetration may not be observed for many months. Salts of amines can also penetrate the polyethylene, apparently by dissociation and recombination.

The problem first appeared when we noticed finger stains after handling bags of colored organic compounds which had been stored about 1 year. In the literature we found many papers on the permeation of liquid hydrocarbons through polyethylene, but none pertained to solids (*1*). Like rotten apples in a barrel, the permeation to other samples occurs because the bags are often stored in tight bundles. After the saving is realized from shipping the samples in such bags, I recommend that the contents be transferred to the fragile, bulky, heavy, but impenetrable old faithful glass containers for permanent storage.

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Man's Rights over Nature

Fahnestock's letter (3 Oct.) and preceding letters help to bring man's rights on earth back to public attention. If the conservation zealots had been as active a century ago as they are today in the United States they would have succeeded in setting aside the Great Plains as a National Buffalo (Bison) Park, and we would be importing most of our wheat.

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Fahnestock is correct that man must have air, water, food, and shelter. If this is all he wants, we might be able to maintain today's human population and even part of the next decade's deluge. However, he is naive to think that the threatened extinction of the eastern bald eagle from DDT poisoning is in itself the major cause of alarm among professional ecologists. Its far greater significance is that something is wrong with calcium metabolism and steroid hormone function in eagles because of DDT. The effects happened to appear first in certain raptorial and pelagic birds, but since life processes are essentially similar in all organisms, it seems likely other creatures will suffer as world usage (U.S. usage is declining) of DDT increases. . . .

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Fahnestock's attitude toward ecological change and its effect on other organisms is sophisticated in presentation and superficially far less objectionable than the concept of the conservationist "as a yellow-bellied sapsucker," but I believe that it stems from the same rationale. What man is doing to the world is different by many orders of magnitude from what the dinosaurs did; one need not read any further than that issue of *Science* to have this point brought home. It is inevitable that man's increasing population and increasing degradation of nature will destroy him. The time may vary with the rate of population increase, but the ultimate solution to the problem of man seems inevitable if man continues on his present course.

The need for other life forms has to be put on a simple economic basis; I fully agree that emotionalism does not help. Of course, it does not hurt to cut down a few old redwoods and other such trees useless to the practical man. However, we do not live entirely in a plastic world. Without vegetation to produce oxygen, man dies; there must be a point where the smog becomes so thick that it is economic not to destroy trees. In the same sense, a complex interrelationship of organisms which has taken millions of years to evolve can probably survive having some of the life strands snapped by artificial extinction. Still, a single crop agriculture will eventually be destroyed by a disease mutation, since this evolutionary process will continue regardless of what man does. All the eggs in one basket makes it ever so much easier to wreck the eggs.

Perhaps the best nonemotional reason for seeking to retain a few species is for the practice it may give in picking what should be saved. If man cannot save the bald eagle and other frills, it follows that he will never be able to save himself. It is not much of a jump from making a choice among species to making a choice among racial, religious, or economic groups.

A final pragmatic point to make is the biological truism that no organism can survive on its own waste products. Every movement toward changing the world to a place for man to the exclusion of other living organisms leads to this end. A world aimed at being exclusively ours will be a world in which man cannot survive. . . .

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