Finally, a debatable question must be raised based on the premise that there must be some avocations in a capitalistic society that are not tied in to the profit motive, and that scientific research, based on the socialistic principle of funding for the public good, must be one of them.

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Cancer Risk Assessment

The controversy over the appropriate method for assessing cancer risks, as described in *Science* (News and Comment, 25 May, p. 811), cannot be resolved satisfactorily without considering the diverse causes that can lead to an apparent positive result in a bioassay for carcinogenicity. Indeed, the very term "bioassay" is unfortunate, in that it implies that chemicals which are "active" share one particular characteristic that can be quantified and mechanically extrapolated to yield an estimate of risk. Such interpretations, though possibly appealing to the decision-maker, lack credibility. If experiments were perceived as "investigations" of biological activities, rather than as "bioassays," studies would be designed differently and would yield information more meaningful to risk assessment. The resulting estimates, based on recognition of the differing kinds of effects chemicals can exert on the whole animal, would appear more believable than the rigid mathematical interpretations currently proposed.

A helpful perspective on the issue is afforded by considering certain analogies to infectious disease. Bacteriologists distinguish between pathogenic organisms and those incapable of causing illness. They also recognize "opportunistic" pathogens, those capable of infecting a host only if the defense of the host has been weakened. Virulence depends upon several factors, including the host species, and bacteriologists will pause before concluding that the risk to humans is the same as that observed for another mammal. They certainly do not view all pathogens as representing an equal health hazard and know that the progression of an infection depends upon more factors than just the size of the inoculum (exposure). Death associated with infectious disease, just as death from cancer, frequently occurs under conditions (impaired defenses) which indicate that such infection should be viewed as a symptom rather than the cause of an organism's failing. Nobody

proposes to cleanse our environment of all potential pathogens; yet it is recognized that some must be scrupulously avoided.

"Positive" results in a carcinogenicity bioassay may arise for a variety of reasons. The chemical tested may be a potent carcinogen (true "pathogen"). It may be an "opportunistic" carcinogen detectable only because the defense of the host was weakened, for example, by senility or stress induced by a drug overdose; or the test substance may have *provided* the opportunity for an environmental or endogenous carcinogen to express itself. Any treatment which significantly influences the physiology of the rodent can change the pattern of background lesions in the senile animal. Insofar as tumors are a part of the disease pattern observed in old rodents, a difference in tumor distribution between medicated and control animals does not necessarily have a mechanistic basis that calls for zero exposure of humans.

The possibility that hormonal imbalance can influence tumor formation is well recognized (*1*). Stress alone can affect the tumorigenic response in mice (*2*), and it has been reported that the tumor incidence was higher in mice housed one per cage than in those housed five per cage (*3*). Some chemicals, particularly at high doses (*4*), may support tumor formation in rodents through stress-related mechanisms. The term "stress" may stand for several phenomena including the pharmacological activity of a chemical or the depletion of sulfhydryl groups needed for deactivating metabolites. Statistical artifacts are another source of difficulty that can lead to results incorrectly perceived as positive (*5*).

The results from carcinogenicity studies in our laboratories with many chemicals clearly indicate that no one mode of interpretation can serve adequately in every case. We have encountered chemicals that caused carcinoma at a time when untreated animals were still in robust health. Only relatively few animals were needed to detect this effect. When tests for mutagenicity (*6*) are positive, it is reasonable to conclude that such substances are "true" carcinogens (pathogens) in rats. Whether or not these chemicals would have the same effect in humans, or even in another rodent species, can, of course, only be a matter of speculation at this time. It is, however, prudent *policy* to assume that carcinogenic potential which coincides with mutagenic activity might also be expressed in humans, although differences in metabolism and host susceptibility make the estimation of potency in the human situation tenuous at best (*7*). In any case, prudence dictates that precautions should be taken to minimize human exposure to such chemicals.

We have also studied chemicals that appeared to influence the tumor *pattern* normally observed in old animals. Assessing the risk of such physiologically active agents requires a very different approach from that for genotoxic chemicals. One example, a potentially valuable drug, was labeled "carcinogenic" and barred from further development, although in a certain segment of the relevant patient population it would have been the treatment of choice. This compound was inactive in a battery of mutagenicity tests. Numerous observations established that it affected the endocrine balance of rodents. In a mouse experiment lasting 20.5 months, malignant uterine tumors were found only in control animals, and mammary carcinoma only in medicated females. Numerically, an untreated mouse had a threefold greater probability of dying with uterine tumor than a medicated mouse did of dying with a mammary carcinoma. The mammary carcinomas were seized upon to label the drug carcinogenic, although the incidence of all tumors, when results from both sexes were pooled, was 46 percent in control mice and 36 percent in the highest dose level group. The appropriate conclusion should have been that the drug at the high doses administered altered the pattern of tumor *distribution* by upsetting the hormonal homeostasis. Such data can only be meaningfully assessed in a manner very different from that appropriate for mutagenic carcinogens. Any application of one-hit or similar models is clearly inappropriate, while considerations familiar to pharmacologists of dose-response and interspecies differences most probably yield a realistic and credible estimate of the human hazard.

Other data support the thesis that a complete "biological" evaluation of carcinogenicity "bioassay" results is needed. For example, we know of compounds that appear to suppress tumors. A hypoglycemic agent showed such effects in mice and rats. Another agent, known to affect prostaglandin concentrations, caused diminished occurrences of spontaneous pulmonary tumors in mice, without concomitant increase in other tumors. Such findings clearly indicate that, while statistical treatments are valuable tools, they cannot be used in isolation from other facts in deciding whether or not a chemical should be considered a hazard. Pharmacological studies, tests for mutagenicity, and metabo-

lism experiments are essential in elucidating what causes tumors in the animal model. The implications to public health differ depending on whether one is dealing with a potent direct-acting carcinogen, or an opportunistic carcinogen capable of doing harm only to mammals of severely impaired resistance, or an agent providing the opportunity for ubiquitous carcinogens to become effective. The "bioassay" approach imposes a dogmatic and narrow interpretation of tumor incidences and discourages broader studies needed to advance our knowledge of what contributes to tumor formation. Only full consideration of physiological effects on a case by case basis can lead to credible risk assessment. An encouraging note is that Food and Drug Administration's advisory committees have provided flexible responses to "bioassay" data, pointing the way to more balanced risk assessments (*8*).

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2. V. Riley, *Science* **189**, 465 (1975).
3. C. Peraino, R. J. M. Fry, E. Staffeltt, *J. Natl. Cancer Inst.* **51**, 1349 (1973).
4. "Maximum tolerated doses" (MTD) are generally insisted upon for inclusion in carcinogenicity bioassays, and their effects are considered relevant to risk assessment. This appears to be an inappropriate application to biology of the mass law as known in chemistry. The MTD concept can be expressed as

$$\frac{(\text{animals}) \times (\text{chemical})}{(\text{tumor})} = K$$

In chemistry the mass law in this form holds only as long as first-order kinetics prevail. As it is well known that in biology the ranges for linear kinetics are limited, and because the development of tumors in response to an animal's exposure to a chemical involves many enzymatic and other processes, application of the mass law to tumor formation seems unsound, unless linearity of the relevant reactions has been demonstrated.
5. D. S. Salsburg, *J. Tox. Environ. Health* **3**, 611 (1977). "Using the standard formulation of tests of hypothesis, it is shown that there is a 20–50% chance of having a false positive. . . ." These are irreproducible artifacts. I would like to define a reproducible artifact as one which, though real, is not relevant to the question of risk from low-level exposure. A good example appears to be NTA (nitrilotriacetic acid), a chemical useful as a detergent additive which caused bladder tumors in rats when fed in concentrations above 0.7 percent in the diet. At these dosage levels NTA concentrations are so high in the urine as to cause the formation of calculi; R. L. Anderson, "Discontinuities of dose response curves in toxicological testing," paper presented at the Soap and Detergent Association 52nd Annual Convention, Boca Raton, Fla., 25 to 28 January 1979.
6. Rigorous proof for the causal relationship between carcinogenic and mutagenic activities of chemicals is still missing. However, attractive mechanistic theories and the generally good correlation between such activities suggest that short-term mutagenicity tests are useful for the assessment (as opposed to identification) of carcinogenic risk, in that probable mechanisms of action may be defined. Since many mutagenic and tissue-transformation tests are designed to be exquisitely sensitive, positive results in such experiments are expected to be obtained with those mutagens and/or carcinogens also, which should be designated as "opportunistic," that is, capable of doing harm to cells and organisms only under the most unusual circumstances.
7. The work of R. W. Hart and R. B. Setlow [*Proc. Natl. Acad. Sci.* **71**, 2169 (1975)] suggests a greater resistance of humans to carcinogens affecting DNA because of a greater capability for DNA repair by the human cell as opposed to that of the rodent cell.
8. See the summary minutes of the Food and Drug Administration's Toxicology Advisory Committee meeting on the role of prolactin in mammary carcinogenesis (12 to 13 May 1977) and the minutes of the FDA Endocrinology and Metabolic Drug Advisory Committee meeting on clofibrate-like drugs (15 to 16 February 1979) (available from the Supervisor, Public Records and Documents, Food and Drug Administration, Rockville, Md.). The FDA Drug Advisory Committee on Pulmonary-Allergy Drugs proposed (3 to 4 May 1977) the use of a class of drugs, some of which had caused tumors in rodents, and did not distinguish between "tumorigenic" and "nontumorigenic" compounds.

Mercury in Sperm Whale Meat

Japanese whaling interests have long resisted international whale conservation initiatives. A major argument used by the Japanese to support their plunder of great whale stocks has been that the meat is needed for human consumption (even though whale meat supplies less than 1 percent of yearly Japanese protein consumption) (*1*). However, data released by Masashi Taguchi of the University of Tokyo's College of Fisheries, at the June 1979 meeting of the International Whaling Commission in London, indicates that sperm whale meat offered for sale in Japanese food stores contains unsafe levels of organic mercury. The whale meat contained mercury levels of 2.3 parts per million, which is six times the level the Japanese government considers acceptable (0.4 part per million). . . .

Because of modern industrial activity, the world's oceans are polluted with mercury. This is not so important a factor in the contamination of fish with short life-spans. However, sperm whales live for 60 years and concentrate mercury in their flesh. When humans consume contaminated whale meat, the lipid soluble methylmercury is concentrated in the cells of the nervous system and very slowly eliminated from the body, even when all intake is stopped.

It is hoped that the Japanese will act on Taguchi's data. Their action could have the double benefit of protecting public health (*2*) and preventing threatened whale species from diminishing further.

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2. *Brit. Med. J.* **1**, 599 (1978).