Letters

NCI Bioassay Program

R. Jeffrey Smith's articles on the National Cancer Institute's bioassay program (News and Comment, 22 June, p. 1287) give the reader an unbalanced view of the program. Smith distorts some admitted problems and does not adequately credit the program for the enormous progress it has made. Worse, his opening paragraphs suggest the bioassay results may be invalid, although pages later he admits that "NCI is running the program better now than it ever has." The implication of his opening paragraph is not validated in the article, nor do I believe it ever could it be.

Many of the problems Smith describes need to be considered in light of the way NCI's chemical testing programs developed. These programs evolved from research activities intended primarily to develop testing systems. As the development of these systems continued, public interest in them increased, and it was recognized that no other government agency was systematically on a large scale testing chemicals for carcinogenicity for regulatory purposes. As a result, NCI's chemical testing research programs have gradually taken on a "production" or "service" function. This conversion from activities designed for research purposes to activities designed to serve the needs of regulators is at the heart of what I believe to be Smith's misrepresentations.

For example, there are not "hundreds of completed tests languishing in NCI files," a statement Smith attributes to a member of Congress. Tests conducted for purposes of research, many of them in the early days of the chemical testing program, have always been and still are reported in traditional articles published in scientific journals. The chemicals in this category are mistakenly said to constitute an "additional backlog," unfairly implying that their results have not been reported. The statement that another Tris could be lurking in a backlog, also attributed to the congressman, reflects lack of understanding and is untrue.

Those tests conducted as a service to regulatory agencies are reported in the form of specially designed technical documents of a specific format. The reports go through an extensive review process in which regulatory agencies participate at every stage. The tests rank with the best performed anywhere in the world.

Although the technical reports are formally printed and announced in the *Federal Register*, they are given in final manuscript form to regulatory agencies well in advance of these later publication steps. Regulatory agencies can act and have acted on the basis of either scientific articles or technical reports. They have also acted on the basis of technical reports in manuscript, before their final printing or announcement in the *Federal Register*. The Consumer Product Safety Commission acted to ban Tris before the technical report was published. Regulatory action also was taken before publication of technical reports on toxaphene, ethylene dibromide, and other chemicals in the so-called "backlog."

As to the 51 tests on chemicals Smith states "are so deficient they cannot be written up in technical reports," 32 of these were carried out more than 4 years ago on anticancer agents thought at the time to be potentially carcinogenic. Although some of the results of these tests were incomplete, the results, as Smith's article notes, were published in the scientific literature in 1975. These agents were not retested because many were dropped from consideration as chemotherapeutic agents and others had such limited use that retesting was unwarranted. In the group of 51, nine additional chemicals, many of which were already known carcinogens, were part of a research study on combinations of two or more chemicals and were not routine bioassays. Although it is unfortunate that all tests were not reportable by today's standards, the vast majority of the 51 tests have indeed been reported, contrary to Smith's implication.

At the National Cancer Institute we are firmly committed to our chemical testing program. All major problems have been solved, and the validity of the tests conducted for regulatory purposes is unmatched. We look forward to continuing the program and expanding it at the NCI, within the framework of the new National Toxicology Program.

ARTHUR C. UPTON
National Cancer Institute, Bethesda, Maryland 20205

Smith's article "NCI bioassays leave a trail of blunders" contains a number of errors. It purports to reflect the substance of both a General Accounting Office (GAO) and a Department of Health, Education, and Welfare (HEW) Inspector General's report on the Eppley Institute's contractual arrangements with the National Cancer Institute (NCI). While we do not agree with everything in the GAO report, we feel it is, by and large, an objective appraisal with a positive approach attempting to improve administrative arrangements between Eppley and NCI; the HEW report finds no fault either with methods of contract award or with the propriety of relationships between Eppley staff members and NCI staff. Smith refers to the contract between Eppley and NCI as a "prime contract" and equates it with the contracts awarded to Tracor-Jitco and the Frederick Cancer Research Center. It is not and never has been a prime contract. It is implied that Eppley undertook a contractual agreement with the NCI to perform bioassays according to set protocols, and that we refused to honor this agreement and to send progress reports. None of this is true. In fact, during the first 12 years of these contracts, NCI had no set protocols.

The Eppley Institute is a cancer research institute built and endowed mainly with local funds. Unlike the other organizations mentioned, it has performed "cut-price bioassays" for NCI without profit. Our contract with NCI started in Chicago in 1962 and was transferred to Omaha with the encouragement of the originator, K. Endicott. Its funding derived from the amalgamation of many peer-reviewed grants. The bioassays undertaken were part of a research and training program and preceded other bioassay efforts in the United States by more than a decade.

Many notable discoveries were made under this contract, among them the presence of polycyclic aromatic hydrocarbon carcinogens in charbroiled meat (*1*); the carcinogenicity of metronidazole (*2*); and the inhibition of nitrosation in nitrited products by vitamin C (*3*). From 1974 to 1976, Eppley published between

30 to 40 percent of the output of the extramural contract program of NCI's Division of Cancer Cause and Prevention for 5 percent or less of their budget.

Our personal contributions to the area began in the late 1940's. Certainly Smith must be familiar with the review article in *Cancer Research (4)* urging that carcinogenicity testing be made part of chronic toxicity testing. One of us (P.S.) can justifiably claim a major role in urging, via the National Advisory Cancer Council and the National Cancer Advisory Board (NCAB), that more funds be alloted to investigate environmental carcinogenesis. We also had a major role in training many of those now engaged in this field, including Saffiotti, Lijinsky, Tomatis, Della Porta, Mirvish, Toth, Montesano, Cabral, Keefer, Rappaport, and Magee.

The real reasons for the blunders Smith assigns to NCI are not likely to be discovered through audits by GAO, HEW, and so forth. The problems are a reflection of the present state of the sciences that underwrite this program. Individual bioassays pose separate scientific problems and, more crucial, there is a need for new approaches and a careful evaluation of procedures.

The developments during the present decade have been much more complex than they appear from Smith's oversimplified article. Debates have been held at the NCAB; discussions have taken place during congressional hearings; new legislation has been enacted. Great confusion has been engendered about the role of NCI and that of the regulatory agencies. Implications of responsibility have been made where none have existed, and roles have been entirely misunderstood.

If *Science* is to represent the scientific community, any discussion of carcinogen testing should surely include the scientific merits of such a procedure. Nowhere does Smith even ask whether routine testing should be done at all. Finally, a distinction should be made between an academic cancer institute such as Eppley and a commercial testing facility.

PHILIPPE SHUBIK
DAVID B. CLAYSON
Eppley Institute for Research in Cancer, University of Nebraska Medical Center, 42 and Dewey Avenue, Omaha, Nebraska 68105

References

1. W. Lijinsky, P. Shubik, *Science* **145**, 53 (1964).
2. M. Rustia, P. Shubik, *J. Natl. Cancer Inst.* **48**, 721 (1972).
3. S. Mirvish, L. Wallcave, M. Eagen, P. Shubik, *Science* **177**, 65 (1972).
4. P. Shubik, J. Sice, *Cancer Res.* **16**, 728 (1956).

Risks and Public Policy

The Three Mile Island nuclear reactor accident has dramatized not only the role of nuclear power but that of other complex, science-based technologies in our society. It is important, therefore, to draw the maximum lesson from the accident, and the President, Congress, the Nuclear Regulatory Commission (NRC), and the nuclear industry have announced investigations in order to do just that. As a result, a lowering of the risk to the public from nuclear power reactors is to be expected.

Looking beyond nuclear power to the general issue of risks/benefits to the public from applying complex technologies, there appears to be one conclusion from Three Mile Island that can be made already: Accurate multidisciplinary assessments of any highly complex technology cannot be guaranteed until after a period of trial and error. The unavoidable risks during that period should therefore be countered with extra, defense-in-depth safety measures.

In the case of the Three Mile Island accident, the most noteworthy fact, in my opinion, is not that material and human malfunctioning apparently were encountered along with bureaucratic and organizational inefficiencies (although the NRC should be commended for its choice of procedure of cooling down the reactor), but that the reactor got into a potentially dangerous failure mode that had not been foreseen. This failure mode was (i) unanticipated; (ii) metastable; and (iii) potentially dangerous to the public.

To an impartial observer, before the accident the NRC would appear to have done all that it could reasonably be expected to have done to learn the potential failure modes of operating light water nuclear reactors. It had available the $1-million-plus Rasmussen study, an independent evaluation of it by a special group of the American Physical Society, several evaluations by special interest groups, and a recent additional review of the Rasmussen study that was sponsored by the NRC itself. In none of these studies was the NRC led to believe that a large bubble of hydrogen would form inside a reactor vessel.

The general public may well wonder if this is the best it can expect from the scientific community. The answer, of course, is, No. Scientists can pay more attention to the discipline of risk assessment; they can recommend designs incorporating more monitoring instrumentation and defense-in-depth safety measures designed to avoid a broader spectrum of failure modes. Also, a wider