Letters

Toxicological Testing Dilemma

The controversy over the priorities of research conducted at the National Cancer Institute to reduce the time required to perform bioassay tests and the high cost ($47 million) of the Institute's carcinogenesis program (News and Comment, 7 May, p. 529) underscore the problems currently associated with testing procedure for carcinogens and other toxic substances. Before new chemicals manufactured for human consumption can be registered, federal regulatory agencies require a long (3 to 10 years) series of toxicological tests: the acute, a single dose with a range of concentrations; the subchronic, repeated doses or exposures administered for up to 90 days; and the chronic, lasting 2 to 10 years, depending on the species being tested. Routes of administration are selected on the basis of the most likely mode of human contact (such as ingestion, inhalation, or skin contact) (*1*). Several species and large numbers of animals are required for statistical reliability and to assess interspecific variation in the reactions to toxic substances. Human health evaluation according to the standard, accepted protocols currently costs more than $500,000 per compound. Wildlife, aquatic, plant, and domestic animal toxicity evaluation (*2*) costs are additional. Twelve government agencies conduct toxicological testing and research and spend probably more than $100 million annually; private industry probably spends much more. If the $100 million the federal agencies now spend were devoted to human health effects research alone, testing of only about 200 compounds could be started each year. However, many thousands of chemicals are in need of toxicological evaluation (*3*). Obviously, the current federal allocation is insufficient to test the majority of these chemicals.

Many toxicologists agree that faster and less costly testing procedures are urgently needed (*4*) and that research should be devoted to evaluating in vitro testing methodologies (*5*). Moreover, the acute test is being challenged, since a single exposure is much less likely to occur in an environmental or an occupational situation than repeated low level exposures. The chronic test is often conducted using the lowest effective concentration determined in the subchronic test and a one or half log dilution below that. Since two dilutions provide sufficient empirical data in approximately 95 percent of the cases, why conduct the chronic test, which is six to ten times more expensive than the subchronic? The answer is because lifetime studies are the accepted procedure for assessing carcinogenic and other possible toxic effects, including reproductive malfunctions (*6*). However, less expensive batteries of mutagenic screening tests (*4*) could be employed that would estimate the potential for carcinogenicity.

Furthermore, in vivo tests are subject to interspecific variation in test animals. Species have different strategies to deal with toxicity. Measurable toxic effects often represent exposure levels higher than concentrations of pollutants actually found in the environment. More sensitive tests, such as those based on behavioral toxicology, are being developed (*7*), but few are widely accepted. The National Center for Toxicological Research and other agencies are developing such new and rapid tests, and the National Institute of Environmental Health Sciences is evaluating the possible substitution of the traditional, long-term, in vivo tests with rapid screening methods. The Committee for In Vitro Toxicity Testing of the Tissue Culture Association is defining and validating the presently available in vitro tests. Although faster and cheaper tests are being developed, we wonder whether we can afford to wait? The Toxic Substances Control Act will soon be implemented (*8*). Many potentially useful chemicals remain unevaluated.

We propose that a more decisive step be taken: a team of expert toxicologists and scientists from related fields should be assembled to evaluate existing technology and identify a battery of the most predictive screening tests, including in vitro systems, animal models, and chemical behavior (*5*). A combination of quick tests could replace the conventional protocols, whereas any single test might not. This team could also perform cost-benefit analyses and estimate how much, if any, sacrifice of confidence would result from using a battery of screening tests at this time. Use of a combination of screening tests might allow a tenfold reduction in cost and a fivefold reduction in time for toxicological testing. We would expect little or no sacrifice of safety, since most of the tests tend to err on the side of false positives. Standard methods could still be employed if indicated by the screening results.

The findings of the "blue ribbon" team should be presented to a national referendum symposium of decision-making toxicologists representing all the federal agencies, academic institutions, and private industries involved in toxicological testing. The prevailing opinion could then be presented to the regulatory agencies for their consideration and the current requirements modified.

If a battery of screening tests were to be accepted, we would find the process of testing many thousands of chemicals a more manageable task. At present it looks pretty hopeless.

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Recombinant DNA: Unknown Risks

Bernard D. Davis's letter (6 Aug., p. 442) makes interesting reading in a week in which 25 Legionnaires have died and more than 100 are still ill—some critically—of a disease of unknown ori-

gin, unusual virulence, and unprecedented epidemiology. If scientists do not conclude from this juxtaposition that it would be good to face up to ignorance in areas in which we have no experience, instead of engaging in facile speculation, I hope the public will.

I am not claiming that the mystery disease is a result of genetic manipulation, since obviously no one knows its cause. But I wish to point out that to pretend to know more than we do about causes and prevention of disease can only discredit science and scientists. (At this writing, infectious and toxic agents have in turn been ruled out as causes of "Legionnaire's Disease" and today's newspaper talks about Fort Detrick and possible unknown varieties of infectious agents.)

A further point: *if* a recombinant (and perhaps short-lived) coliform organism ever were to produce an outbreak of an epidemic, it might well be nearly impossible to identify or to culture as the cause in the presence of all the other, normal strains of *Escherichia coli* that grow in us.

Davis suggests that medical history shows such risks must be taken and implies that the high child mortality rate of a century ago was reduced through medical intervention. This is not true. Almost nine-tenths of the decline in the combined death rate from scarlet fever, whooping cough, diphtheria, and measles in children under age 15 occurred before the introduction of specific therapies or vaccinations; and similarly with tuberculosis, cholera, typhoid, and most other infectious diseases. The most probable reasons for these reductions were improvements in nutrition and public health measures—better housing, clean water, and so forth. The specific medical measures of the last three to four decades only clipped the tail off the asymptotic curve. This is not to underrate the importance of every life saved. Furthermore, those risks were taken to cure known diseases, not to create new ones.

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Computers: Reassuring, but Dispensable

Paul Chernoff's insightful letter on understanding mathematical proofs (23 July, p. 276) includes a remark that is perhaps misleading. He states that Shanks spent years calculating pi to 707 decimal places and implies that it was only after the advent of computers that the last 200 digits were found to be wrong. But it did not take computers to inspire verification. As early as 1854 Shanks' approximation was verified to 500 decimal places. In 1945 it was found to be in error past 527 places. D. F. Ferguson, of the Royal Naval College and the University of Manchester, extended the result to 808 places, cowardly resorting to the mechanical calculator to obtain the last 300 or so. In 1949, George W. Reitwiesner and his colleagues verified the work, extending the approximation to 2035 figures on the Electronic Numerical Integrator and Calculator (ENIAC) at the Aberdeen Proving Ground. The computer was convenient and reassuring, but hardly indispensable to uncover the error.

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Open Debate

I can only assume that Frank J. Munger (Letters, 30 July, p. 358) had no opportunity to express his "concern for freedom of information" while National Science Foundation (NSF) officials physically barred a member of our staff from attending a meeting of the former advisory committee for research, of which he was a member, since the meeting was held behind closed doors, in violation of the Federal Advisory Committee Act.

I must also assume that he was unaware of the nearly unanimous criticism of the committee's operation, as reflected in letters from past committee members, which the committee reluctantly agreed to supply but which were not included in their report.

Munger also calls for "open debate" on issues such as "fewer but larger grants," which Nicholas Wade correctly reported in his article (News and Comment, 28 May, p. 872) was among the suggestions offered by NSF officials as a potential way of cutting administrative costs.

Unfortunately, such open debate in the scientific community would require access to information on plans and problems, which NSF has been so unwilling to provide in the past. Thanks, in part, to such discussion of the issues, NSF has, in recent weeks, come closer to being the open-door, nonsecret organization that it should be.

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