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Risks, research, and reason[1]

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This paper will discuss some aspects of ecological problems with primary emphasis on human health. Although these problems are of enormous importance, it will focus on human health problems. It seems to me that the American public has developed "the expectation of perfection" in its consideration of chemicals, be they drugs, industrial chemicals, pesticides, or whatever. The concept that these chemical compounds were perfect started out with the articles in *Readers Digest* about 20–30 years ago that told us each month there was a new miraculous cure for this disease or for that condition. There was no mention, as I remember these stories, of the fact that many of these cures—talking about drugs for the moment—had serious adverse effects. Some of the early drugs, the sulfonamides, streptomycin, penicillin, had serious deleterious effects. It came as a great shock to the American public to realize this was, in fact, true. Similarly, the pesticide DDT was presented as a perfect pesticide; and yet even in 1941–1942, which is really quite a long time ago, there were documented reports of the extremely high toxicity of DDT for fish. These miraculous cure stories created in the minds of the American public a concept that chemicals were perfect.

There were also the advertisements —again, perhaps about 30 years ago— about "better things for better living through chemistry," and I think that many of us believed this. We believed that chemicals—drugs, pesticides, transformer fluids, plasticizers—were a single-edged, rather well-guarded razor blade. It came as a rather profound shock and sense of betrayal to realize that many of these compounds are, in fact, two-edged swords. This is particularly interesting because I think the American people are willing to undertake many kinds of risks: driving automobiles here, taking the limousine from Philadelphia, and eating raw clams and oysters at the local seafood houses. But somehow we are uneasy and insecure about the risks from invisible chemicals.

Let me briefly describe the origin of these risks to try to provide a slightly different view as to how research can help and to point out where we need reason. The phrase I mentioned before—"better things for better living through chemistry"—does epitomize one side of the coin. The technological revolution of the past few decades, the chemical revolution, has involved the synthesis and worldwide distribution of a great number of totally new chemical entities. The first industrial revolution was the result of the increased ease and economy of the remaking, the reshaping, or the remolding of the existing materials, materials to which man had been exposed for generations. In the United States alone in 1969 we synthesized over 1 billion pounds of phthalic acid esters, over 600 million pounds of monochlorobenzene, 460 million pounds of tricresylphosphate, and 80 million pounds of the polychlorinated biphenyls. Compare, for example, the production of the most widely used pharmaceutical agent, 37 million pounds of aspirin, and 61 thousand pounds of corticosteroids. These industrial chemicals, all new to man, have become ubiquitous, and man is exposed to these agents to a greater or lesser extent. Sometimes the extent of this exposure is known, but unfortunately often even the fact of exposure is unknown. It is interesting to contrast this massive exposure with man's exposure to foreign organic compounds over the past hundred generations. The primary source of exposure a millennium ago must have been through food. We know that many plants and many animal tissues contain highly toxic compounds. However, because of the dispersed human population and the fairly localized distribution of the edible plants and animals, ingestion of toxic food stuffs, even toxins with delayed effects, would only have affected a small segment of the human population. Today, it is important to realize that the new pollution can be virtually worldwide.

POLYCHLORINATED BIPHENYLS

Let me describe two examples of the sorts of problems that exist today. First, consider the polychlorinated biphenyls. These are not one or two or a few compounds. Two hundred and ten different isomers of varying chlorination are possible. They are important because they are fascinating industrial compounds with an enormous number of uses. They are highly heat resistant. They have a high dielectric constant, and this has led to great utility and commercial sales. They were first put into production in the late 1920's; they are now used to insulate most of the large transformers and capacitors. This use is vital. The substitute for the PCB's would probably be mineral oil which has a high fire hazard. Other uses of the PCB's are as plasticizers in paint and paper, as lubricants for certain high temperature applications, as hydraulic system fluids, and as heat transfer fluids. The *Internal Revenue Service Form 1040* at one time contained almost 4% of PCB's.

It is interesting to note there was no appreciation that the polychlorinated biphenyls were even present in the environment at all until about 1967, four decades after their introduction. In 1967 Jensen noted in Scandanavia high concentrations of PCB's in the liver and fat of seabirds. In 1967 and 1968 there was a peculiar disease identified in Japan, called Yusho, which turned out to be the result of contamination of rice cooking oil by polychlorinated biphenyls. The PCB's had been used as a heat transfer fluid that

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MUNS 082396

heated this oil to drive off unpleasant odors. This system leaked and the polychlorinated biphenyls contaminated the oil. There were at least 1,000 cases of Yusho directly related to that contaminated oil. The primary symptoms included a painful skin disease, similar to chloracne, and liver disease, and reports suggest that this liver disease is chronic. Some contaminated Great Lakes salmon were fed to mink, and there was an enormous mortality in young in the mink farms of the Midwest.

The United States population contains very likely one or more parts per million of PCB's in its fat and liver. In some random samples, up to 100 ppm of PCB's have been detected.

Fortunately, very fortunately, the polychlorinated biphenyls as they appear in the environment do not seem to be highly toxic to mammals, but they are fairly toxic to some birds; this is another problem.

The first comprehensive toxicity study on these compounds began in 1968, some 40 years after their introduction. Polychlorinated biphenyls in the United States are now restricted to controllable enclosed applications, primarily as electrical insulating fluids.

PHTHALIC ACID ESTERS

Let us turn to the phthalic acid esters. Last year over 1 billion pounds were produced in the United States. These esters are widely used as plasticizers, and they make the plastics pliable. Up to 60 or 70% of the plastics may in fact be phthalic acid esters. Their detection I think first was from the fact that there were peculiar peaks in gas chromatographs from rat liver perfusion experiments where the blood was passed through plastic tubing. It turned out that these peaks were the phthalates that leach out of plastic tubing into protein- or fat-containing solution. They leach out of blood bags, and one can achieve up to 5 mg/100 ml in stored blood. Their concentration in man is more like 1 ppm, and these compounds are very widely distributed indeed. An interesting side light: the fog on the inside of the windshield of many cars is not necessarily due to cigarette smoking but is often due to the phthalic acid esters that have volatilized out of the plastic upholstery and deposited on the inside of the windshield. There have been some toxicity studies with these compounds; they were done about 25 years ago, rather short term, using oral administration. They appeared on the basis of these studies to have a very low hazard. On the other hand, man's exposure to most of the phthalates is probably by inhalation rather than by ingestion. There are no inhalation studies as yet reported, and there are no long-term modern chronic toxicity studies reported. Again, I think phthalates are not a hazard, but this also is not a reassuring story.

The lesson we must learn is that the incessant demands of technology must not exceed the boundary established by proper toxicological evaluation. There exists a natural and proper conflict between the immediate and specific needs of man as expressed by vigorous technological advancement and the long-term comfort, safety, health, and well-being of man as dictated by the potential human hazards of the products, effluents, and by-products that are the inevitable result of our vigorous technology. Technological development must not be stifled, and yet technology must not erode human health and well being.

A PROGRAM FOR SURVEILLANCE

How can we do this? I think this is a critical question, and I shall present a series of possible answers. We need to develop a new form of toxicological research which I shall describe shortly. But toxicological research alone is inadequate. It must be buttressed both by technological surveillance—in other words, what is going into the environment today—and by an ecological surveillance. The latter is in a sense a monitoring program. Let me describe what is needed in terms of toxicological surveillance. First, we need much better quicker, more economical toxicity testing systems. Approximately 300-500 new chemical entities are introduced into the environment every year. If we were to try to test these for toxicity by our standard method, we would run out of pathologists and toxicologists in about 90 days. There simply are not enough people, facilities, funds, or laboratories to test, by the old-fashioned methods, the large number of compounds that enter the environment. We need to develop simplified in vitro systems or simplified in vivo systems that will give us a presumptive index of safety or toxicity. A number of these systems are being developed; Heidelberger and DePaolo are developing in vitro carcinogenesis testing systems. These systems are interesting and, although they are not ready for use yet on a broad scale, they must be explored. Malling is developing an interesting mutagenesis test system, utilizing a rat liver microsome suspension with *Escherichia coli*. If metabolism of the compound occurs in the whole animal, it may also occur in vitro and mutagenesis can be documented for compounds that are mutagenic only if metabolized. We need these presumptive tests to screen out those compounds that are most likely to be toxic and that we can study more intensively. These tests also should serve to identify those compounds that are most likely to be safe and that can then be put on the back burner.

Second, we need to understand much better how man detoxifies and eliminates these compounds from his body. The main problems are the rates of entrance and egress, the balance of pollutants in man. How rapidly man gets rid of these compounds is of major importance. We need to understand better the mechanisms of toxicity of these compounds. If one can understand the mechanism of toxicity of a class of compounds, then the extensive toxicological testing may not need to be done on the other members of that class when they are present as potential environmental toxins. With this base of knowledge we can begin to predict, not only through the use of in vitro systems but also from inspection of the chemical formula, what agents will likely cause the greatest problem. We will never be totally successful at this effort, but after all nothing in biology really is totally successful. Even the classic toxicological test systems as we all know are imperfect.

The third aspect that needs more emphasis is the possibility of synergistic toxicity. The fact is that two agents, each of very modest toxicity alone, may when combined cause much more severe toxic problems. Many of these can now be predicted by an understanding of the biological detoxification and of the mechanism of action of the individual compounds.

These three points—better testing systems, better understanding of the biology of the compounds, and problems of toxic synergistic action—are what I consider toxicological surveillance. In addition, we need technological surveillance. We must know what is entering the environment. There has been much talk about technological forecasting and assessment. I am concerned not about what is going to enter our environment 20 years hence, but what entered last year, because we do not know that today. And third, we need

MONS 082397

the ecological or environmental surveillance. We must monitor not only for chemicals in the environment but also for biological effects. If one species is shown to be in trouble, we must learn from that. Perhaps it forecasts that other species including man may be on the threshold of unexpected problems. These I think are the research needs, and given money and time and effort we can achieve them.

We also need reason, and I am not so sure we can achieve that. The scientific community, as we all know very well indeed, is very diverse and heterogeneous and contains within its continuum many honest differences of opinion. Let me describe this using as an example carcinogenicity. At one extreme there are scientists to whom any whiff of carcinogenicity is enough to blight a compound permanently. At the other extreme there are scientists who say carcinogenicity must be proved in man. Both these extremes can be, and generally are, represented by some scientists with highly satisfactory credentials. The story, if some confrontation like this occurs in public, in the *New York Times*, the *Washington Post*, or the *Congressional Record*, sounds like a real scientific uncertainty involved in the particular issue being discussed. The answer appears to be determined by counting noses, counting up a score; seven to three for a carcinogenic effect is bad, five to two against is safe. Science operates by a system of eventual consensus and this, in the normal form of scientific development, is quite adequate. There is no time factor; there is no hurry; there is no pressure for immediate regulatory responses. Often there is an adequate base of data to reach a consensus about a new environmental hazard. We need to develop better mechanisms to obtain this data base. Often it must come from very diverse disciplines, disciplines that often do not talk to each other very much under the normal course of events. Scientists from these disciplines must pool their data and work together to reach the consensus as soon as possible. Many issues affecting the environment and man's health are not buttressed by adequate scientific data and here I think is where we are in the most trouble. We must be sure that the American public has a proper view and a balanced view of the potential risks and benefits. We must push harder on a campaign to educate the public, the press, and our legislators; they must better understand problems of risks and benefits—Whose risk? Whose benefit? How are these estimated? What are the elements of error involved in each estimate?

They must understand something about probability: most regulatory decisions are black and white decisions; most scientific knowledge comes in either a graded response or a probablistic response, and it is hard to couple these two together. The public must understand more about dose-response relationships —more is not always better. The public must understand, as I think they are beginning to, that using all chemicals can entail risks. All this, I think, will be a very slow and painful process. FP

RALL: A question to the Panel: How would you suggest that we improve academic, industrial, government, public-at-large interfaces in arriving at solutions of environmental problems that are acceptable to society? It seems to me there are a number of steps to this—first, I think there has to be more interdisciplinary discussion between the scientists in various disciplines and between the scientists in the various fields mentioned. Consider the academic, the government—both research and regulatory—and the industrial scientists. Often these groups of scientists talk only to themselves and not to their counterparts. This would be a beginning. Second, to try to make available to the public summaries of broad, well-balanced views on the current environmental problems that could be published in the lay literature—perhaps the *Readers Digest* as well as the *New York Times*. Third, I think, more scientists who are knowledgeable in these various areas should talk to the public in large or small groups. Fourth, I think there is a need for a broader public education on problems really of understanding the biological effects of chemicals.

MONS 082398