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Relevance of Animal Experiments to Humans

by David P. Rall*

The best evidence of an adverse human health effect is a properly conducted epidemiological study. But human beings should not be the sole test animal. Properly conducted animal studies have been shown to be predictive for carcinogenicity and toxicologic responses in human populations. We need to develop more efficient predictive animal tests for all the common serious toxic effects caused by chemicals.

One particularly important use of epidemiological studies is to validate (or invalidate) the laboratory animal experiments. There is no more powerful tool than the combination of well conducted animal experiments and well conducted epidemiological experiments.

The whole issue of the relevance of the results of laboratory animal toxicology studies to the human experience is a difficult, yet important problem. It is even more difficult when one looks at it in the light of our nation's need for energy from coal. Shy has described most eloquently the complex problems of extracting, transporting, and combusting an intrinsically dirty material like coal (*1*). There are hundreds of potentially toxic compounds involved, although the ones that we think about most commonly in terms of air pollutants affecting the general population are SO_x and NO_x, the trace and heavy metals, oxidants, particulates, etc. There are, in addition, the large number of benzpyrene type compounds which are likely to be hazardous. We also must be concerned about synergistic effects with such a large mixture of compounds. The art and science of predicting synergistic toxic effects of two or more compounds and extrapolating such effects from laboratory animal systems to human populations is primitive. Let me note the studies by Laskin and the New York University group (*2*) in which concentrations of benzpyrene that do not normally cause broncogenic carcinoma in rats will cause broncogenic carcinoma with the addition of inhaled SO_2. This may be true for the general population, and be the cause of the "urban factor" which increases the incidence of lung cancer.

We are dealing here with large human populations and with relatively small differences in exposure. We must ask: Where do we go from here? Can we use experiments with laboratory animals to project what is likely to happen in the human population?

The first thing we ought to do is look at the data. The relatively few data that exist which bear on this particular and critically important problem, I am sorry to say, are not very new. I was involved in a study more years ago than I would like to discuss that looked at anticancer drugs in terms of their toxicity to humans and their toxicity to laboratory animals (*4*). This may seem to be an unusual topic to bring up at this meeting. There were unique advantages of using this class of compounds for this kind of study. Excellent human toxicology studies were available, something that is almost unheard of in any sort of study. Because to be effective these drugs had to be given in dosages that caused rather clear-cut human effects, fairly clear-cut answers were available as to how toxic they were in the patients that were being studied. There were few moral and ethical issues because these were therapeutic agents and they offered hope, in some cases very real hope, of benefit for the patients in this study. In fact, we determined what clinical data were available before we went back to design and perform the animal studies.

It may be expensive to do toxicology studies in animals, but it is much less expensive than doing human clinical trials. The animal studies were designed to mimic as closely as possible the studies we knew were available from the clinic. The route of administration, the dose schedules, and so forth

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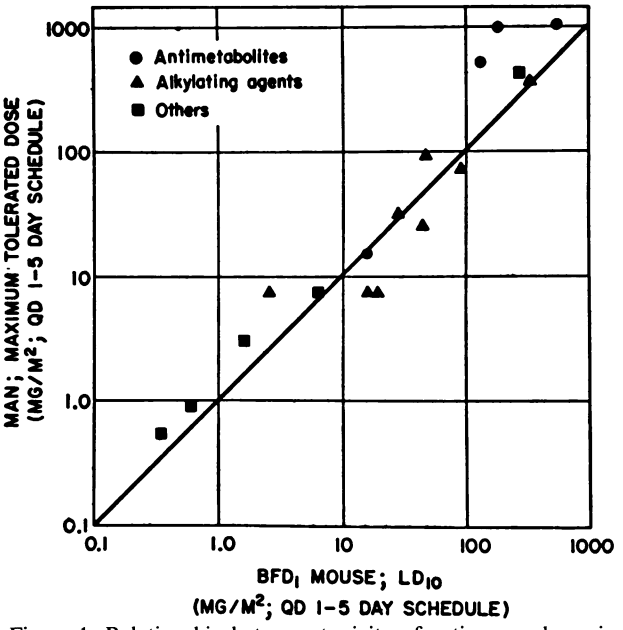

Figure 1. Relationship between toxicity of anticancer drugs in murine and human species.

were as close as possible. The results are easily summarized in Figure 1. Here are plotted the LD_{10}'s levels in one mouse strain against the maximum tolerated dose in the human patients for about 23 compounds. There was a fourfold log range of intrinsic toxicities for the 23 compounds. The points clustered very closely around a line with a 45 degree slope, suggesting there is a good relationship between quantitative toxicity in the mouse and in man for the toxic effects caused by these chemicals.

There are perhaps even fewer clear-cut examples too of carcinogenesis data. Table 1 shows the chemicals that expert groups at the International Association for Research on Cancer (IRC) in Lyon, France, decided can be considered to be carcinogenic in man (*5*). There is as yet no clear-cut evidence in the laboratory animal studies that arsenic and benzene are carcinogenic. I believe that neither of these compounds has been adequately studied. However, there is a study by Maltoni (*6*) suggesting a carcinogenic effect for benzene and an inhalation study at New York University (*7*) which shows leukemias after benzene exposure. Three other compounds, chloramphenicol, oxymetholone, and phenacetin, have not been adequately studied in animals; but for the others there is a very good qualitative relationship. These compounds which are carcinogenic in human populations are also carcinogenic in laboratory animals. There is reasonably close agreement between the laboratory animals and the human population.

The quantitative aspects of comparative carcinogenicity is a much more difficult question. An NAS/NRC group on current pest control practices did look for the first time at quantitative aspects of carcinogenicity in human populations and in laboratory animal studies (*7*). The human data were the best available, but certainly less than desired. The animal data were also of variable quality. In comparing animal and human responses, they used the responses from the most sensitive animal species. With respect to benzidine the predicted human incidence was about the same as what was seen in the most susceptible animal species. This was also true with chlornaphthazine and with cigarette smoke.

The geographic studies which link aflatoxin exposure to liver cancer suggest about a tenfold lower incidence than would have been predicted by the most susceptible animal species. For the other two compounds, diethylstilbestrol and vinyl chloride, the human populations are still at risk, and now it looks like the most sensitive animal species has exaggerated the risk to man. Since these populations are still at risk, the human incidence may increase in the future.

I am convinced that there is a good degree of association between the most sensitive animal species and the human population. I would pause to say that these data obtained after humans had inadvertently been exposed to carcinogens must be among the most precious data we have in the biomedical community. We must always be on the lookout for such data so that we may learn as much as we can from it.

Cancer, of course, is not the only problem, as we all know. More people die of cardiovascular problems. Chronic respiratory disease is one of the most rapidly increasing causes of morbidity in the United States today (*8*). We are seeing more and more evidences of reproductive toxicology and chronic liver and kidney disease. We do not have the data to form any conclusions about how well animal studies pre-

Table 1.

	Predicted human incidence based on most sensitive animal species relative to epidemiological studies
Benzidine	the same as
Chlornaphthazine	the same as
Cigarette smoke	the same as
Aflatoxin B_1	10 × greater than
DES	50 × greater than[a]
Vinyl chloride	500 × greater than[a]

[a]Population still at risk.

dict for man in all toxicological endpoints that toxicologists study. I can phrase this conclusion one of two ways: I could say we have little evidence that animals do *not* predict for man — and that is a perfectly reasonable statement. Or I could say that there is little evidence that animals *do* predict for man — and that is a reasonable statement. It just depends. The proper statement is that there is little evidence one way or the other. This tells us we must focus major research efforts within the scientific community on obtaining answers to these problems.

As I have observed the scientific community over the years I find it convenient to divide scientists into what I call lumpers and splinters. Lumpers and splinters are each very important to successful scientific endeavor, and I do not mean to come out anti-lumper or anti-splinter. But lumpers say: Let's look at the aggregate; let's try to put together all the data and see if we can discern some sort of a pattern. Do we see similarities or do we see only discontinuities? The typical species we use for toxicology studies are mice, rats, and dogs. These species have coexisted with man for many generations. They have shared our bed and board for literally millions of years and they still do. Perhaps it is not surprising that we see some similarities in responses to toxic agents from these mammalian friends of ours that have lived with us for so very long. Splinters, on the other hand, dissect every example, every report of species differences, to try to determine what they can learn, what different mechanisms are used by species that respond differently to accomplish the same basic physiological function. These analytical studies are of immense importance to biomedical science. But when we look for broad guiding principles, it seems to me the lumpers are the more important. When we look at the aggregated science in this way, it seems to me that laboratory animals do predict for human toxicological endpoints. They predict well, but they do not predict perfectly. There is nothing that I know in the biological sciences that is perfect.

What then of epidemiological studies? Now there are many instances when only broad epidemiological studies can give the needed information. The attempts to determine whether the ambient levels of common air pollutants do have any effects on human health must use this sort of broad-scale epidemiological studies. These studies take a long time because chronic effects may take at least a generation to appear. Thus, we are faced with the exposure of a population for at least a generation before an epidemiological study can clearly relate chemical exposure to the toxicological endpoint. They can be very insensitive when there are small differences between exposed and unexposed groups or when essentially all populations exposed with only some gradation between highly and less highly exposed. But clearly they are needed.

Table 2. Hexachlorobenzene in Louisiana cattle.

Projected losses	
Direct	4550 cattle ($2,275,000)
Transactional (unestimated)	—
Actual losses	
Direct	3 cattle ($1,500)
Transactional	($380,000)

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What are our needs? Our needs, I think, are to develop more efficient predictive animal tests for all the common serious toxic effects caused by chemicals. We must be alert to any opportunity to test the hypothesis that a chemical does cause toxicity in man when we are given the opportunity inadvertently. We certainly need to have more dialogue to develop something closer to a concensus on the relavancy of animal testing.

Before I close, I would like to comment on current efforts to look at costs and benefits of various governmental regulatory actions that relate to health. The benefits are presumably the reduction in the burden of disease. This is done in the biomedical community by attempting to match animal experiments with epidemiological data. We publish our hypotheses; these are criticized; we go back to the drawing board; we look for other test systems. We have an iterative system that tries to determine the precision of our estimates of human toxicity based on either animal or epidemiological evidence. I submit we do it pretty well. But let me suggest that I am concerned about the precision of some of the cost estimates in this process. Table 2 depicts one example of a cost estimate developed by David Dominick when he was in the Environmental Protection Agency (EPA) (*9*). The issue was hexachlorobenzene in Louisana cattle. This effluent from a plastics manufacturer contaminated the fields in which the cattle grazed. The cattle were found to have a significant body burden of hexachlorobenzene. EPA picked an action or tolerance level (typically on the basis of inadequate information, since that is about where we are with most chemicals). EPA then carefully projected losses (costs) resulting from this regulatory action.

It was estimated that 4550 cattle, worth well over $2 million, would have to be destroyed. What David Dominick did was to go back to Louisiana after the whole episode was over and try to determine how many cattle were destroyed. It turned out that three head of cattle were destroyed at a cost of about $1500. Much of the same thing happened with regard to estimated compliance costs and actual compliance costs for the workplace standard of 1 ppm for vinyl chloride. I wonder whether the precision of projected costs is in the same ballpark as the precision of predicted health effects based on animal extrapolation and clinical studies.

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