Animal Use and Acceptable Alternatives

A Report from the United States

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The use of animals for food, fiber, companionship and research has traditionally met with acceptance by the majority of the American public. The last decade has seen increasing charges that the use of animals for research and testing is not only irrelevant to our understanding of the human condition but also immoral. Such vocal opposition has resulted in many local and national legislative proposals which could reduce the availability of animals for research purposes. Restrictions on funding for research involving animals, prohibitions against specific research procedures or the use of pound animals, and increased peer or bureaucratic reviews of proposed studies have been considered or passed.

At the same time, vocal proponents point out the critical role that laboratory animals have played in developing our ability to control infectious diseases such as tuberculosis, rabies and polio; to develop new surgical techniques; to understand metabolic disorders such as diabetes, allergies and cancer and to detect harmful chemicals before marketing to the public. The rationalizations, proposals and debates seem and may very well be endless.

An obvious technical approach, which could help decrease the level of hostility, while potentially improving research and testing procedures, is to develop scientifically acceptable substitutes for existing procedures that require the use of animals. Such substitutes – including cell cultures, computer simulation, analysis of chemical structure and use of non-sensate organisms – have acquired the journalistic title of »alternatives«. Discussion of these alternative technologies usually stimulates renewed debate between those who feel such systems can be easily implemented and those who feel that any substitution is impossible.

There are hundreds of applications for the 70 million animals that are used in American laboratories annually. An estimated 40 % of these laboratory animals are used to explore our basic understanding of abnormal biologic conditions, 26 % for evaluating the beneficial effects of new pharmaceutical or other products, 8 % for teaching or experimental surgery, 20 % for evaluating detrimental effects of various chemicals and 6 % for other uses.

Laboratory animal experimental responses involve a complex interaction of many cellular, humoral and organ components. Animals are multi-organ, dynamic interacting systems unlike low density cell cultures of a single cell type in the isolation of a limited supply of man-made culture media. Frequently, scientists are aided by the reduction in complexity achieved by studying

specific well defined biologic functions with in vitro systems. However, when areas of more fundamental biology are initially studied, the use of live research animals with a full complement of interacting systems may be essential. For example, successful kidney transplantation not only required animal experimentation to develop new surgical techniques, but also to develop a fundamental understanding of immunologic mechanisms of tissue rejection. Even today, it is difficult, if not impossible, to evaluate immune induced pathology without intact organ interactions. Elimination of animal studies in fundamental research and new product evaluation would surely prevent scientists from gaining a full understanding of biological activity, unless a large population of human experimental subjects suddenly steps forward.

A number of non-animal systems are already used by the scientific community in basic research and toxicity testing. In 1981 the National Institutes of Health in the United States funded more than 690 million dollars of extramural research exclusively involving alternative technology. This represented 23.4 percent of the funded research projects for that year. Private and commercial toxicology testing institutions in the States also utilize a diverse assortment of in vitro testing techniques, involving isolated DNA repair, bacteria, yeast, fruit flies and animal or human cell culture systems. The 1983 *Directory of Toxicology Testing Institutions in the United States* indicates that 88 of 125 laboratories listing test information, provide one or more in vitro service.

Safety or toxicity studies, unlike fundamental biologic research, involve a limited number of testing techniques, most with observable pathology as the experimental positive. Although the physiologic basis of animal responses to such testing is often complex and frequently the mechanism remains obscure, resulting tissue damage can usually be identified and quantitated in a test animal. In consumer safety evaluations, the relevant question about a new product may not involve fundamental mechanisms such as why an additive causes death but merely if death is a likely by-product of exposure. Because of the similarity in goals and protocols for most toxicity evaluations, many scientists are directing limited alternatives research resources toward new safety toxicology test procedures which will not require the use of whole animals. The development of acceptable non-animal techniques will not be easy. Present day evaluation of safety testing results is frequently based on comparisons of a new product data with previously generated data. For example, we may ascertain by in vivo testing that a newly developed eyewash solution causes less irritation than numerous other compounds that already have moved safely in the public marketplace. This system of comparing benchmark data is not fool proof but has served the scientific and regulatory community for decades. Any changes in the existing test procedures reduce the usefulness of the comparative aspect in this safety evaluation process. Unfortunately such reliance on comparable data does little to en-

hance the development of new testing methodology.

Although cell culture techniques were not established with an eye toward use in toxicity testing, their potential applicability as readily reproducible, cellular systems is very inviting. To begin such development we must determine the type of cell culture that is best suited to replace a particular whole animal test. Primary cell cultures are directly prepared from animal tissues. They have the advantage of still retaining complex metabolic systems similar to those of the original animal tissues. Unfortunately such primary cultures have a limited life span and are not easily passaged or duplicated among laboratories. Genetically transformed tumor cell cultures on the other hand, have the advantages of »eternal life«, unlimited passage and easy exchange but lack many complex metabolic functions found in primary cultures. These metabolic functions could serve as sensitive indicators of toxic affects. Evaluation of cell source, technical design to enhance observable affects, optimal incubation or reaction times, and reproducibility of the system with defined test agents from various chemical classifications must be addressed before developing new in vitro methodology. Although these are difficult problems, they are the type of questions which research scientists can answer if given the opportunity and encouragement.

Industry and government are already hard pressed to meet costly legal and ethical requirements for product testing prior to marketing. Existing whole animal studies for evaluating the carcinogenicity of a single chemical require hundreds of thousands of dollars and several years to complete. A recent study by the National Academy of Sciences, revealed that toxicity data regarding more than 32,000 commercially important industrial chemicals, pesticides, cosmetics, drugs and food additives were inadequate or nonexistent. The monetary and public health benefits of funding the development of rapid, accurate and less expensive non-animal toxicity testing are obvious. Corporations must evaluate the cost and benefit of establishing in house alternative research programs with this year's shareholder dividends in view, while proprietary interests slow the spread of new technology and data produced by industrial research.

Productive research is likely to occur when groups – or even better – individuals can combine a working knowledge of toxicology with expertise in another scientific field. Such useful human hybrids are rare. Unfortunately, excellent industrial salaries budgets and facilities await academically trained individuals willing to direct their efforts toward today's benchmark toxicology requirements for marketing. Government sponsored academic training and research has traditionally emphasized the basic sciences with the assumption that technology will appear as a spin off. Thus, the academic, industrial and government sectors have not supported the type of research and training efforts essential for innovative development of new testing methodology.

The development of substitute techniques for older test systems has revolutionized scientific fields such as

nutrition, immunology, genetics and microbiology over the past century. Numerous testing and research procedures which previously required whole animal use in these fields, now are performed in test tube assays. Despite complex and poorly understood mechanisms, toxicity tests would be substantially improved by the introduction of better defined, more precise and less laborious assay procedures. To accomplish this mutually beneficial goal, government, industry and academic sectors must establish specific assay replacement priorities; develop more attractive research oriented training programs for toxicologists; and commit to long term research funding which will attract more competent scientists to direct their efforts toward new alternative technology. Such efforts will not guarantee success, but a lack of this action will surely impede development of scientifically acceptable non-animal testing techniques. New scientific achievements in areas of safety testing will require extensive research and academia easily could provide the expertise and laboratories for such an effort.

The long term benefits of new alternative technology for industry, science, the public and yes, laboratory animals, are real. For the foreseeable future, many uses of laboratory animals can not be replaced completely, without a significant reduction in benefits to mankind. But use of newly developed in vitro technology as a first course screen of toxic compounds is a real and immediate possibility which will greatly reduce the need and expense of tests using animals. If past experience is any indication, faster, more precise and less expensive technology will replace our existing efforts. This process can be expedited by having industry, government and academia actively address the potential of alternatives with a well coordinated, mutually sponsored, long term training and research program. To date, efforts in this regard have been inadequate.

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