

**Institute for Alternative Futures**  
**Foresight Seminars on Health and Innovation**

**SUMMARY**

FORESIGHT SEMINAR ON ANIMAL TESTING  
AND NEW DRUGS  
November 16, 1982

**BACKGROUND**

Issues in the use of animal testing in scientific research have received growing Congressional attention, highlighted by a variety of hearings in recent years and the introduction by Congressman Doug Walgren of the "Humane Care and Development of Substitutes for Animals in Research Act" (H.R.6928). Basic questions regarding animal rights, research economics and government/industry responsibility are at issue. A primary focus of these questions has been on the development and use of alternatives to animal testing. The November 16 seminar brought together a panel whose expertise led to contrasting viewpoints on these questions. The panel was asked to forecast how the issues would appear five to ten years from now. David Phelen, D.V.M., Director of Laboratory Animal Science for Smith, Kline and French spoke from a viewpoint within the pharmaceutical industry. Andrew N. Rowan, D.Phil., Associate Director of The institute for the Study of Animal Problems presented a perspective held by many animal welfare advocates. A.M. Guarino, Ph.D., Review Scientist for New Drug Evaluation at the National Center for Drugs and Biologics gave his view from within the FDA. Finally, Franklin M. Loew, D.V.M., Ph.D., Dean of Tufts University School of Veterinary Medicine addressed the issues as an academic expert.

**DAVID PHELEN, D.V.M.**

Dr. Phelen argued that animal testing is vital to the introduction of drugs, which protect both human beings and animals. Sulfa Drugs, tuberculosis tests and polio vaccines are among the medical advances that required animal use. Without drug development, Phelen argued, domesticated animals would suffer numerous diseases and humans would have a reduced life span with a third of our babies dying at birth. The concern over animal welfare. Phelen suggested, is unlikely in a society that does not have the advantages which scientific research has provided, and most people would want more research rather than less animal testing. As an industry representative, he finds it unfortunate that animal rights groups and industry must turn to "political and legislative persuasion in an attempt to dominate each other." Ultimately, the loser in the dispute may be the nation insofar as the issue involves both health and the economy.

In looking specifically at where and why animals must be utilized in research, Dr. Phelen emphasized the need for models of human physiological systems. This allows an understanding of how diseases and abnormalities work. Differences between species allow more specific modeling; for example, the hypertensive rat serves as the dominant model for blood pressure in man. Another use of animals is for screening new drugs. Theory and

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computer models are not enough. Ultimately, we have to find out if a drug is active by administering it to animals. Understanding the physiological mechanism of how a drug works is necessary to the marketing of new drugs. Pharmacokinetics, knowing where a drug goes in the body; efficacy, knowing how well a drug performs; and toxicology, knowing the safety and side effects of drugs: these are all tests that demand the use of animals.

Dr. Phelen noted that in vitro and other nonanimal methods can sometimes be used in his tests. Computer and mathematical models do sometimes provide a faster and more economical means of predicting drug action than widespread or random animal testing. Cell and organ test systems offer still another alternative, as do microbial test systems. But these are only extensions of the final need to test with animals. They are useful and consequential, but he sees a more important development in improvements in the breeding and care of laboratory test animals. Fewer animals need be tested if they are healthy to begin with. Dr. Phelen believes scientists must be responsible by doing all they can to insure the safety of the public, including the conduct of appropriate animal testing.

The scientist's responsibility should not remove him from public scrutiny, according to Phelen. Standards for animal care should be held for both research institutions and animal shelters. Current standards for scientific institutions and industry include conformance with USDA Animal Welfare Act, Public Laws 89544 and 91579; conformance with the American Association for the Advancement of Laboratory Animal Care (ALAC) standards by member companies; conformance with in-house animal care committees or attending veterinarian reviews; and finally, company demands for effective expenditures.

The economic interests of the company may cause expenditure review to have a greater impact on animal conservation than is generally recognized. Pharmaceutical companies routinely spend from thirty to fifty million dollars to research and market major compounds. An estimated ten to fifteen percent of this total, an average of \$4.8 million, is spent on animal tests. Companies won't spend this money, according to Phelen, unless there is scientific justification or regulatory need. Some of the regulations should be examined to see if they are really needed, but Dr. Phelan urges that we be careful; "we don't want to return to the days of thalidomide."

In examining the Walgren proposal, H.R. 6928, Dr. Phelen noted that there is a great deal of concern within industry over various aspects of the bill. Although privately funded research appears to be exempt from the bill, there is fear that the legislation would be extended in the future. There is also fear that the funding of studies for alternatives to animal testing would "unfortunately, if not tragically, divert funds from other vital studies." Mother criticism is that the bill overlaps existing regulation and it is therefore an example of over-legislating. The effect is felt to be punitive, particularly insofar as the costs to affected research institutes have not been fully explored. Dr. Phelen believes that the goals of the legislation can be adequately met through existing regulation and he notes that private enterprise has already developed alternatives to animal testing on its own. He agrees with the philosophy of awarding research funds to sound research proposals for

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establishing alternative methods to animal research, but he believes that these proposals must meet the same criteria for classical science that other proposals face.

In his conclusion, Dr. Phelen affirmed shared goals with animal welfare groups that want to reduce or eliminate the use of animals in research. He noted, however, that industry scientists have a different expectation of when this can be accomplished. They feel animals must be used to maintain a healthy society. Veterinarians are often caught between the two sides. Dr. Phelen said, however, that the oath veterinarians take includes not only the relief of animal suffering but the promotion of public health and the advancement of medical knowledge.

#### **ANDREW N. ROWAN, D.PHIL.**

Dr. Rowan said the Humane Society does not argue that the alternative concept implies the elimination of all animals testing. Instead, support for the concept means reducing where possible the number of animals used, replacing animals with other methods when appropriate and refining techniques to reduce the suffering of animals. As an example, he cited the safety test for tetanus anti—toxin. The standard pharmacopoeia test in Britain used to require a lethal end-point (the animal was killed). The test has now been changed to use a mildly paralytic end-point. This type of change can be made in other areas to make animal testing more effective and less harmful to animals.

In estimating the scale of animal testing, Dr. Rowan said that somewhere between ten and forty million animals are used for pharmaceutical research and development. About thirty-five percent of these animals, mainly mice and rats, are used in testing. The remainders are used in drug discovery and drug development. Dr. Rowan noted that Britain has reduced the number of animals used in drug screening by using alternatives. In vitro cell cultures and computer models have allowed British pharmaceutical companies to dramatically change the proportion of initial screening tests, which rely on animals.

Unfortunately, compared to the level of knowledge of pharmacology, toxicology and toxicology testing is "in the dark ages." Animal tests are applied by legislative mandate "as a habit." Dr. Rowan described how consumer groups, arguing for more safety, have pushed for more animal testing regardless of whether or not it was better animal testing. For example, he said that there has been a requirement to use pregnant beagles to test oral contraceptives even though the tests were totally unsatisfactory. Although the test is no longer used, it should never have been required in the first place.

Dr. Rowan addressed the question of the status of animal testing in five to ten years. Although animal testing will not be eliminated, there will be major changes, some of which are already becoming apparent. For example, in polio vaccine production, the change has been from 100,000 monkeys used per year in the 1950's to 5,000 monkeys per year used presently. The need for even these monkeys may be eliminated according to Dr. Rowan. Another example cited is the Draize test (for eye irritation). This has been the focus of a major animal welfare campaign in the last few years. There is now research into

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alternatives to this test and regulatory guidelines have been changed to allow the initial use of three animals rather than six or nine as used to be required. Also, if a substance under study contains alkaline or acid, it is not to be placed in the animal 's eye, but merely marked as an irritant. These are changes, which have long been possible, but have taken years because "we continue to function by habit rather than by careful assessment and reevaluation."

Another toxicology test which is strongly opposed by the animal welfare movement is the LD50 test, which identifies what dose of a substance will kill fifty percent of a given population of animals. There is now an international coalition against the LD50 test. The aim is to get regulatory agencies to abolish LD50 data submission unless it is accompanied by scientifically supported evidence stating why the test is necessary. Dr. Rowan said the Pharmaceutical Manufacturer's Association has indicated that it supports this position also. While there will still be a need for toxicity data, it is hoped that the routine use of the LD50 test will soon be a thing of the past. There is also hope in the development of short—term carcinogenicity tests, which use fewer animals and are much cheaper than the animal bioassays.

Dr. Rowan said the pressures for alternatives to animal testing are basically coming from the public. He noted a widespread public disquiet about the use of animals that may make the animal welfare movement a "sleeping giant." This potential has already been mobilized in a campaign against the Draize test and is now being focused against the LD50 test. He spoke of the Walgren Bill as "merely the latest of a long line of legislation that has been before the House." He spoke also of the Drinan Bill and the Research Modernization Act as examples of how the animal welfare movement is making a political impact that will have a shaping effect on how research is performed in the near and long-term future. In the next ten years, safety testing is expected to use human cell culture far more. Regulatory requirements will need to be rationalized to allow more room for scientific judgement. This will lead to fewer animals being used by 1992.

#### **A.M. GUARINO, Ph.D.**

Dr Guarino said he spoke as a scientist who has worked with alternatives to animal testing rather than as a representative of the FDA. Using charts, he divided pharmaceutical animal testing into two important areas: toxicity testing and pharmacologic testing. Toxicity studies usually use approximately two thousand animals per drug. The pharmacologic studies use more animals, but this is not generally recognized. When analogues to existing marketed products are developed, there are various options, some of which are very costly. For example, just recently pharmacologists figured out how aspirin works; basically it is through the inhibition of prostaglandin. Prostaglandin synthetase is an enzyme, which can be isolated, concentrated, and hundreds of tests can be done in vitro to screen out a number of antiarthritics without the need for doing broad testing on animals. There are also dozens of tests which can be done, primarily in rats and mice, to demonstrate the antiarthritic action. Dr. Guarino said that it is a typical example that all of two hundred compounds chemists made were tested in rats and/or mice despite the cheaper in vitro

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method. This indicates an area for improvement, at least where a data base has already been developed. Dr. Guarino distinguished between acute animal toxicity tests and the LD50. Very few of the FDA's regulations demand an LD50; however, they do require evidence of acute toxicity. There is no necessity for having the LD50 tests reported to six decimal points, but he has soon this done.

Looking at what kinds of drugs might be developed in the future is one way to see what kind of animal testing might be needed. Quoting The Qmni Future Almanac, Dr. Guarino noted the expected development of a good number peptides, proteins and converted DNA, which are things we know very little about. If experimental research is being undertaken with man's genetic pool and immune systems, there will be a lot of questions that need answering. Fortunately, in the immunology area there have been pioneers in the development of tissue culture and other in vitro methods and this should continue.

Dr. Guarino's experience with alternatives provides an example of how to reduce animal testing. At the Cancer Institute scientists developed an effective drug that contained platinum, which was curative but damaged the kidney. Several hundreds of these compounds were made and many were tested in tumor systems with positive results. Dr. Guarino tested these for kidney toxicity. He had various optional animal species for study, including dogs or rats, but he knew that flounders are unique as far as the constitution of their kidneys. He was able to dissect out kidney tubules and create a model of a kidney which allowed him to quantify his experiments to identify which compounds were least toxic. This was a relatively cheap way to identify those compounds, which were most promising, so the others did not need to be tested on live animals. The experiment led to an identification of the mechanism involved so that even the flounders became unnecessary for the tests.

Guarino said estimates on the cost of animals used for pharmacological tests may be low as there is no requirement that data be submitted when companies "go fishing" for compounds by using pharmacological studies. He estimated that the number of animals used this way is twice that used in toxicological studies. Alternatives could significantly reduce that number if drug companies stop using standard protocols involving hundreds of animals. Companies also do not need to do a dozen tests when one is sufficient to demonstrate pharmacological activity. As far as toxicological studies, there are very few in vitro target organ tests available; "the state of the art isn't there."

Guarino said that after pouring over the regulatory code for a few days, he found very few requirements, which call for large numbers of animals to be used. In some instances, the FDA plans to publish guidelines to replace animal tests with in vitro tests. The one area where it is important not to handicap research by restricting animal testing is in Phase I studies. Not many animals are used there and it is vital to get all the information possible before clinical trials are done.

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**FRANKLIN M. LOEW, D.V.N., Ph.D.**

Society is uncomfortable with using animals because animals are sentient, feeling creatures; it would be nice not to have to use them or eat them. Animal testing, however, does not conform easily to this view. Recently, there has been increased attention paid to animal testing in popular magazines and in Senate and House hearings. It is worthwhile taking an historical look at how public interest in this area has developed. Dr. Loew views the thalidomide tragedy as the first pivotal event leading to new interest in drug testing. This changed testing as the consumer movement came to insist on increased animal testing. A second watershed was the publishing of *Animal Liberation*, which has the quality of being able to change the world if people adopt its thesis. The book is a key to understanding the motives of the animal welfare movement. Loew said that although there is an element of the anti-science and anti-authority gestalt involved, this is not the basic underpinning of the movement. Animal issues have become very popular, many science magazines have featured the topic over the last eighteen months. A third pivotal event was the raid on Dr. Taub's laboratory in September of 1981. This focused the view of society on the use of animals in research and testing.

Although the number of animals used in research is disputed, there are two sets of official figures, which are of some use. First, there are the annual reports filed with the U.S. Agriculture Department in compliance with the Animal Welfare Act. These reports do not include mice and rats, which constitute the vast majority of animals used in science. They do suggest, however, a magnitude that is small in comparison to the three and a half billion chickens that are eaten in this country. The second set of numbers comes from the National Academy of Sciences' Institute of Laboratory Animal Resources. This is survey data voluntarily given in 1978 which offers a comparison to a similar survey done in 1968. There is a decrease shown in animal use in all categories except large hoofed animals (which is probably due to a widespread substitution of pigs in experiments, which might have used dogs). The decrease is probably not due to ethical concerns but to economics. However, the ethical movement and changes in law may help continue the reduction. Working against this reduction are consumer laws, which tend to increase animal testing. There is a possibility though that society will balance consumer interests with recognition that some products are frivolous and therefore do not merit the cost in animal lives. Alternatives to animal testing have probably not been as significant in the reduction of animal testing but they do offer hope. Epidemiological studies, in vitro tests, computer simulation, microbiology and human experimentation all show promise, but Dr. Loew sees economics and ethical concerns as the primary influences that will continue to affect the numbers of animals used.

Dogs are often painted to when research methods are challenged because dogs are "America's sacred cows." Dogs have made a significant contribution to science but they are also important to people for emotional reasons. For this reason they are useful to those who want to attack the use of animals in research. About 200,000 dogs a year are used in research and while there are no census figures, there are estimated to be thirty or forty million dogs in the country. Every year there are ten to fifteen million dogs and cats killed

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in pounds and animal shelters. This may not justify how dogs are used in research, but it does indicate relative magnitude.

**QUESTION & DISCUSSION**

Dr. Rowan was asked how the number of rhesus monkeys could be further reduced from the present five thousand per year. He said a switch from the live Sabin vaccine to the more expensive Salk vaccine would allow tests using cell cultures. Dr. Phelen added that under pharmaceutical industry initiative a substantial reduction was accomplished in the number of African green monkeys used to test these same vaccines.

Dr. Guarino was asked about ambiguity in FDA requirements. He said there were a number of proposals to issue more specific guidelines, but what he looked for when he reviewed a drug submission was an indication that the sponsor knows more about how the drug works than the FDA reviewer does. When challenged over the possible arbitrariness of FDA guidelines, he specified what the FDA requires: two species studied up to fourteen days. These guidelines may be updated and people interested in clarifying or lessening the requirements should communicate this to the FDA.

Dr. Rowan asked if the FDA shouldn't take the lead in reforming the guidelines. It was noted, however, that this is not part of FDA's mandate. It would be good if a replacement methodology for testing was developed and then it could be up to the FDA to assess whether or not the methods are adequate. A related problem facing advocates of reduced testing is the issue of subsequent company liability. Many companies fear that if they do not perform all of the tests done for the last similar drug, even if the tests are unnecessary, this would be used against them if problems with the drug lead to law suits after it is marketed.

In response to a question about testing with humans instead of animals, Dr. Rowan said that while he wouldn't advocate anything like shifting LD50 tests to prisoners, it is true that a great deal more epidemiological work could be done to reduce the need for animal studies. He added that the FDA role is the arbiter of the public interest. He believes the FDA has the scientific expertise to enhance the level of concern for animals in their policies. On this point, Dr. Guarino said he believes we should get all the information we can from other means before testing with people. He doesn't oppose really good studies that have been done that could replace animal studies. Dr. Loew noted that because we don't have a national health system, we don't have the database that Britain does to develop good epidemiological studies.

When asked about in vitro testing, Dr. Guarino said it cannot replace whole organism tests yet and he doubts if it will ever develop to that extent. Dr. Rowan noted that in 1969 there were similar doubts about cell culture use and that has developed. Dr. Phelen said that in vitro tests are keyed to animal response; the tests serve as a model of how animal systems respond and it will be some time before in vitro testing is sophisticated enough to allow these test results to be assessed on their own merits without reference to the animal

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responses. He also said science is heading into the cellular and subcellular levels and the emphasis on whole animal systems is behind us. The scientific tools are going to be in vitro systems. Parallel animal systems will continue to be studied, probably focusing on rodents and very specialized animals with some genetic characteristic that makes them desirable to study.