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be carried out by a competent person. Many of these procedures are not daily tasks, such as tusk removal in boars or ringing of bulls. On the horizon one sees many objectionable maimings such as amputation of the penis in vasectomized bulls to prevent intromission, amputation of the tongue in calves, and the possible insertion of electronic transponders in cattle. This is an area where we must not abdicate our responsibilities. The role of the practitioner must continue in the future to safeguard the well-being of our livestock by giving advice on care and the prevention of neglect, as well as therapy to the sick and injured.

Welfare is team work. The practitioners will do the forward work, the half back District Veterinary Offices will be at hand in any difficult situation, supported by the talents of Agricultural Development and Advisory Service (ADAS) in the center and the universities on the wings. Very few problems should ever reach the Minister of Agriculture at full back, but if one ever does let us hope he will not put it out of play into touch, but give us an 'up and under' so that we can all bring our expertise together to solve the problem.

Laboratory Animals and Alternatives in the 80's

Andrew N. Rowan

Introduction

In 1969, Sir Peter Medewar, immunologist, Nobel prize-winner and philosopher of science, made the following statement at the Research Defence Society's Annual Meeting:

> *The use of animals in laboratories to enlarge our understanding of nature is part of a far wider exploratory process, and one cannot assay its value in isolation — as if it were an activity which, if prohibited, would deprive us only of the material benefits that grow directly out of its own use. Any such prohibition of learning or confinement of the understanding would have widespread and damaging consequences; but this does not imply that we are forevermore, and in increasing numbers, to enlist animals in the scientific service of man. I think that the use of experimental animals on the present scale is a temporary episode in biological and medical history, and that its peak will be reached in ten years time, or perhaps even sooner. In the meantime, we must grapple with the paradox that nothing but research on animals will provide us with the knowledge that will make it possible for us, one day, to dispense with the use of them altogether (Medewar, 1972).*

It is now just over ten years since Medewar made the prediction that the number of laboratory animals used every year would peak. Figures produced by the U.K. authorities indicate that he was more or less correct. Although the number of recorded animal experiments in the U.K. has stabilized around 5.4 million per annum and may even be falling, it is by no means clear whether this is due to reduced funding and the increasing expense of laboratory animals or to the development and adoption of alternatives (see Box). The most likely explanation is that this peaking is the result of a combination of these and related factors. Whatever the reason, we are entering the 80's amid a flurry of interest in and activity around the idea of "alternatives to laboratory animals."

In this discussion, an *alternative* is defined as any technique which could:

- **REPLACE** the use of animals altogether;
- **REDUCE** the numbers of animals required;
- reduce the amount of stress suffered by the animal by **REFINING** the techniques used.

At the same time, and this is most important, any alternative system must provide data which leads to the same ultimate conclusion with the same or greater degree of confidence as that obtained from the method being replaced.

A clear example of this concept is provided by the experience of an anti-viral screening program in a major pharmaceutical company (Bucknall, R.A., 1980, The use of cultured cells and tissues in the development of anti-viral drugs. In *The Use of Alternatives in Drug Research* [eds A.N. Rowan and C.J. Stratmann] MacMillan: London, pp. 15-27). Over a period of fifteen years (up to 1977), the introduction of cell and organ culture screening techniques reduced the number of mice required per annum from approximately 13,000 to about 2,000. At the same time, the company was able to increase the number of compounds screened for potential anti-viral properties from about 2,000 to about 24,000 per annum. There are a couple of instructive points in this example. First, the laboratory reduced rather than eliminated the use of mice. The cell and organ culture systems could not mimic mammalian metabolism completely and, therefore, the final screening tests still had to be conducted in the whole animal. Second, a great deal of time and money was saved by doing the initial screening of compounds with unknown potential in the faster and cheaper cell system. However, although the time and cost benefits of alternative systems are indisputable, scientists do not always agree that the conclusions derived from them are as valid as those derived from the animal system.

Europe

In Europe, the interest in alternatives has grown steadily ever since the Council of Europe adopted Recommendation 621 in 1971. (The Council of Europe is a loosely-knit treaty organization of 21 European countries). This Recommendation was a radical document which, *inter alia,* called for the drafting of international legislation to set out the conditions under which experiments on live ani-

mals may be authorized and, specifically, for the establishment of a major international clearinghouse on alternatives. At present, the Council of Europe's expert committee is completing a draft treaty on laboratory animals which is considerably watered down from the original Recommendation. Interest in alternatives has, in the meantime, grown significantly, and several of the European nations have publicly supported the concept.

In Britain, Mr. Callaghan, as Prime Minister, issued the following answer to a question in Parliament about his Government's intentions vis-à-vis alternatives:

> *I hope I have indicated that it would certainly be our policy and desire to move to alternatives to animal experiments as quickly as possible, and our efforts must be directed in that way (Hansard, 8 Dec 1977, Cols 1642-1644).*

The Home Office (which administers The Cruelty to Animals Act, 1876) backed up the Prime Minister's statement by sending out a letter exhorting all scientists in Britain who are licensed to perform experiments on living animals to "take every reasonable step to confirm, before using living animals, that their investigations" could not be effectively carried out by other means. The letter continued by urging the licensees "to give thought to the possibilities of developing new alternatives to the use of living animals and to publishing information about successful new methods." According to reports, this letter caused some resentment among biomedical researchers, but it certainly demonstrated the Government's public commitment to the idea.

In continental Europe, the Federal Republic of Germany included a section on alternatives in its Animal Protection Law of 1972 which stated that potentially injurious experimentation would only be authorized if the research could not be done on nonanimal systems or on phyletically lower animals. In Denmark, the 1953 law on experimental animals was amended on May 13, 1977 to forbid painful experiments in schools and to allow experiments on live animals only after due permission is obtained from a national committee composed of four scientists, a lawyer and three representatives from the Danish Society for the Prevention of Cruelty to Animals. Also in 1977, the Dutch Parliament enacted legislation which placed heavy emphasis on the requirement that those dealing with laboratory animals have adequate professional skill and that "no animal experiment shall be conducted for a purpose that, according to the consensus of opinion among experts, could equally well be achieved in some other way." At last year's (1979) meeting of the International Committee for Laboratory Animal Science in Utrecht, the Dutch Minister of Health and Enviromental Protection, Dr. Ginjaar, drew specific attention to this point and stated that "The Netherlands endorses a suggestion made in the Council of Europe's Committee of Experts on the Protection of Animals that the matter of alternatives be promoted at the European level."

Outside the European Economic Community (EEC), Sweden has recently established a governmental advisory Central Committee on Experimental Animals, one of whose responsibilities is the development and promotion of alternatives. Approximately $90,000 has been distributed to research projects dealing with alternatives, and a section on alternatives is to be included in a

course for veterinary students this year. Sweden also passed a law at the end of 1978 making reviews of animal experiments by ethical committees in government institutions mandatory. Elsewhere, the Swiss Federal Assembly passed a new animal welfare law in December 1978 which is expected to be put into force in mid-1980.

Animal welfare and anti-vivisection societies in Europe are not only encouraged by recent government activity, but are themselves encouraging scientists to consider the concept of alternatives by making grant money available for research. One such organization in Britain, the Lord Dowding Fund for Humane Research, held a meeting in the last quarter of 1979 to discuss the results of research which it has been supporting (*New Scientist 84*:271-272, 1979). As is not uncommon in scientific progress, the results were rather mixed.

Dr. Derek Calam of the National Institute for Biological Standards and Control (London) has been working on a high-performance liquid chromatography (HPLC) method for assaying "biological medicines" such as insulin and oxytocin which are currently standardized in potency assays using animals. However, Calam is having difficulty obtaining reproducible results although the HPLC method is potentially sensitive enough (±3% accuracy) to meet the regulatory requirements of ±10% accuracy for oxytocin potency assays.

Dr. Peter Knox of St. George's Hospital Medical School (London) is studying the nutrient requirements of cells in culture. He argues that cell culture technology is still in its infancy and needs to be improved so that it may become a more useful alternative. The blood serum supplement, which normally is added to cell culture nutrient media, contains a large number of constitutents, most of which are unidentified. It is not known which constituents, and in what combination, are essential to normal cell growth. Knox has been working on this very complex problem and has isolated two proteins which appear to play a role in cell adhesion to the petri dish, a vital step in the growth process, and is following up on this finding.

Research on these or similar techniques is, of course, being supported by establishment organizations. However, the animal welfare trusts serve to focus attention on the potential of these techniques as alternatives.

The United States—Arguing the "Alternatives" Concept

The idea of alternatives is coming of age in Europe, but progress in the United States is a little slower. There have been one or two meetings at which the subject has been addressed—notably the ConMed Symposium in Cincinnati last year organized by the Department of Laboratory Animal Medicine at the University of Cincinnati. The National Institutes of Health is also considering a proposal to hold a major conference on the topic.

Furthermore, following the success of the Lord Dowding Fund in Britain, an "alternatives" funding organization has been established in New York (American Fund for Alternatives to Animal Research *[AFAAR]*, 175 West 12th Street, New York, NY 10011). On January 19, 1980, AFAAR organized a small meeting at which two scientists who have received funds for alternatives research described their work. Professor Oscar Frank of the New Jersey Medical School discussed his work on microbial vitamin and amino acid assays, their potential for studying

vitamin deficiency disorders, and the role played by drug anti-metabolites. One protozoan, *Tetrahymena pyriformis* has the same amino acid requirements as man and the rat (the usual laboratory animal for testing protein quality). Professor Frank and his group have developed a technique which allows them to use the protozoan rather than the rat as the test animal for protein quality, and AFAAR is funding research into other applications of the assay. Dr John Petricciani of the Food and Drug Administration's Bureau of Biologics and scientific advisor to AFAAR, described research in his laboratory to develop an organ culture assay (using chick embryonic skin) to measure the tumorigenic potential of cells. Usually, tumorigenic potential is assessed in an immunosuppressed animal or in the nude mouse, but Petricciani argues that the chick embryonic skin test is more sensitive, quicker and less expensive than the animal test. He also stated that there are other areas where animal models are still required; *e.g.*, to assess the metastasis (spreading) potential of a tumor.

Despite these developments, many American research scientists still express some uneasiness about the concept of alternatives. A frequent argument is that one cannot predict the outcome of research and, therefore, allocating funds for the development of alternatives would be a mistake. This argument fails to take into account a number of features about research in general and the alternatives concept in particular. First, funds are allocated for particular areas of research in the hope that this will stimulate the generation of good ideas and research projects. Second, the development and application of new techniques is an important part of the research process and it frequently *is possible to predict* the benefits of better techniques. Conversely, the application of greater resources to a multifaceted research problem, in which not even the correct questions are known, can confound predictions. This is exemplified by the failure of the "war on cancer."

The advance of biomedical knowledge depends on a number of factors including an adequate reserve of imagination and intuition and sufficient funds, equipment and manpower for the critical evaluation and testing of new ideas. Imagination and critical review are the basis of the hypothetico-deductive model of scientific advance, but two other factors must also be included: luck and technique development. The importance of technique development is attested to by the number of awards given to scientists who develop new methods for attacking old problems. For example, Dr. Rosalyn Yalow received a Nobel price in 1977 for her part in the development of the radio-immunoassay technique. This technique has been cited as an alternative because it allows a researcher to assay very small amounts of complex biological molecules which previously could only have been done (if, indeed, it was possible at all) by using living animals.

The alternative technique which has raised the highest hopes among animal welfare organizations is tissue culture. Bernard Dixon argues in his book, *What Is Science For* (Penguin, 1972, pg 31), that when medical researchers look back through the decades, they will select as one of the most important single developments in the 1960's the technical innovations leading to the growth and study of human cells in the laboratory. As stated earlier, the technique is still in its infancy. If more research resources were devoted to improving and developing cell culture techniques, the investigation of many research problems would be simplified. For example, an understanding of the complete growth requirements of

human cells would probably have a major impact on our understanding of differentiation and malignant growth.

The National Institutes of Health already recognizes the importance of supporting technical developments through its Biotechnology Resources program in the Division of Research Resources (DRR). The DRR provided $11.8 million in 1976 to assist in the support and acquisition of complex technological capabilities for qualified research scientists, but a 1976 report on the DRR mission (known as the Bolt, Beranek and Newman Report after the name of the consultancy organization which managed the review), had the following to say about the biotechnology program:

> *The Panel finds this program to be substantially underfunded even for its current portfolio. Furthermore, the Biotechnology Resources Board should address the challenges inherent in biotechnology needs by adding activities in new directions. Specifically, support should be given to preresource development of biomedically-relevant technologies before they are mature enough to serve a user community.*

Therefore, the Bolt, Beranek and Newman report implicitly supports the idea of developing new techniques (which would include alternatives) and also argues that the DRR is not adequately fulfilling its function of conceiving and creating such new resources. The application of funds specifically to the development of cell culture technology, to the training of scientists in tissue culture techniques and to the dissemination of appropriate information on *all* research models (not just animal models as is currently the case) would definitely fall within the purview of the DRR.

The DRR currently provides approximately $14 million per annum to maintain seven primate centers around the country. It is arguable that, if these funds had been devoted specifically to the development and application of cell culture technology, the subsequent advances in biomedical knowledge would have been more significant than those emanating from the primate centers. Animal welfare groups believe that there is too little attention paid to *in vitro* versus animal research models and are therefore attempting to direct research funds to the development and application of alternative techniques via congressional action. As a result, three Bills have been introduced into the U.S. House of Representatives in 1979.

The United States—Legislative Activity

The first Bill, H.R. 282, was introduced by Congressman Drinan (D-MA). This Bill is relatively straightforward and uncontroversial. It calls upon Congress to allocate $12 million to the development of alternative techniques. Most animal welfare advocates consider that the bill is too modest. The second Bill, H.R. 4479, was introduced by Congressman Weiss (D-NY), and it mandates the establishment of a Commission to study alternative methods to the use of live animals in research and testing. The Bill requires that individuals appointed to the Commis-

sion should include representatives from animal welfare groups, biomedical research organizations and veterinarians. The Commission would have a maximum of five years for the investigation and an annual budget of not more than $750,000.

The third and most recent Bill, H.R. 4805, was introduced on July 16, 1979 and is sponsored by Congressmen Richmond (D-NY), Roe (D-NJ), Hollenbeck (R-NJ) and Wolff (D-NY). It is based on a draft bill drawn up by United Action for Animals. This Bill mandates the establishment of a National Center for Alternative Research to increase the use of existing alternatives, to encourage the development of more alternatives, to provide for the training of scientists in the use of such alternatives, to eliminate duplication and repetitive research on live animals, and to disseminate information on alternatives. The National Center, directed by representatives of all the federal agencies who fund animal research, would be required to publish an annual report of how the goals of the Bill are being met. Finally, the Bill mandates the re-allocation of 30-50% of all appropriations for live animal research and testing to the development of alternatives.

The presence of three bills in the House of Representatives promoting the idea of alternatives has generated widespread interest in the subject in the United States. For example, the General Accounting Office has been requested to investigate whether or not research would benefit from the allocation of funds specifically to the development of alternatives and the National Institutes of Health has been conducting its own in-house survey on the extent to which it currently funds research utilizing techniques which fall within the "alternatives" classification. However, scientific organizations are unenthusiastic about all of the Bills. Although the Drinan Bill (H.R. 282) is not controversial and would provide additional funding to scientists, an official letter from the Department of Health, Education and Welfare comments that, although the Department supports the purpose of this bill, it "questions the need for specific authorization." The National Institutes of Health and other scientific organizations are, not surprisingly, much more strongly opposed to the more radical and sweeping H.R. 4805.

A major attraction of H.R. 4805 to members of the present Congress is that the Bill does not require additional funding. However, biomedical research funding agencies are unhappy about the restraints that the bill would place on their activities, and many regard it as being anti-science. United Action for Animals has publicized the Bill widely, and it has vocal support among members of animal welfare organizations, and support from some establishment sources. For example, the Christian Science Monitor carried an editorial about the Bill on October 25, 1979 in which they stated that "such legislation would not inhibit any essential research but might help foster a moral climate in which greater emphasis is placed on humane consideration of the life of all living creatures. It deserves public support." There has been a mixed response from the animal welfare groups themselves. The Society for Animal Rights opposes the Bill because it "clearly implies that the vivisection of animals is acceptable and necessary until such time as alternatives are discovered and put into use" (SAR Report, December 1979). The Humane Society of the United States is committed to support for the principle of alternatives, but considers that H.R. 4805 will have to be modified if it is to have any chance of enactment against the opposition of the

very powerful research lobby.

H.R. 4805 and the other Bills are serving a useful purpose in raising the consciousness of the political public and in forcing scientific organizations to pay greater attention to the question of alternatives. It is not unlikely that some sort of "alternatives" bill could be passed in the next decade as the subject comes under closer and closer scrutiny. In order for such a bill to satisfy the animal welfare community, it would have to contain elements which provided substantial funding for the development of alternatives, which provided for the training of scientists and the dissemination of relevant information, and which tackled the problems of unscientific duplication and repetitive research. On the other hand, if such a bill is to be acceptable to a reasonable proportion of biomedical researchers, then it will have to be perceived as a constructive development. In fact, the research constituency is still apprehensive about the whole concept of alternatives and much groundwork is still required, employing technical and scholarly arguments, to persuade biomedical scientists that the concept is not only valid but that it can also be valuable.

At the very least, generation of a positive attitude toward alternatives should lead to better planning of research and to the use of the most appropriate research models. At the very most, the development of *in vitro* research models can lead to significant new research opportunities. According to Professor Sergey Federoff, past president of the Tissue Culture Association, "the application of tissue cultures to biomedical research is limited only by the imagination of the scientists employing them."

Dr. Rowan is the author of *Alternatives to Laboratory Animals,* which is a review of the scientific and technical aspects of alternatives and an examination of the potential and the limitations of the alternatives concept. The monograph contains detailed information on animal use in various types of biomedical research, a description of alternative techniques and their applicability to specific research areas, as well as extensive references and a selected bibliography covering the ethics, history and legal aspects of animal experimentation. *Alternatives to Laboratory Animals* is available at a cost of $2.00 from the Institute for the Study of Animal Problems, 2100 L St. NW, Washington, DC 20037, USA.