Alternatives to Animal Experimentation

Steven M. Niemi

Steven M. Niemi is a postdoctural associate in the Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, MA 02139. This paper is a winner of the Animal Welfare Science Essay Competition, The Institute for the Study of the Animal Problems, 1981, submitted while Dr. Niemi was a veterinary student in the College of Veterinary Medicine, Washington State University.

Alternatives to animal experimentation are highly touted today by animal welfare advocates. Their campaign for adoption of alternatives has caused much discussion and debate within and outside of the biomedical community. The purpose of this paper was to examine the controversy and assess the more common alternatives, including the bacterial mutagenicity assay or Ames test, cell culture, and mathematical models for toxicity prediction. Safety testing of chemicals is the most promising of the fields for alternatives where laboratory animals are used, and incorporation of alternatives with live-animal assays is increasing. However, due to limitations of alternatives in use currently, there is still considerable need for in vivo systems. The veterinarian is central to the question of alternatives, in terms of humane considerations as well as the usefulness of animals in science. An effective role for the veterinarian is to serve as educator and mediator between the scientist using laboratory animals and the animal welfare proponent.

Zusammenfassung

Alternativen zu Tierversuchen stehen heute sehr in Gunst bei den Fürsprechern des Tierschutzes. Ihre Kampagne für die Akzeptierung von Alternativen gab Anlass zu zahlreichen Diskussionen und Debatten innerhalb und asserhalb biomedizinischer Fachgruppen. Zweck dieses Artikels ist es, diese Kontroverse zu untersuchen und den Wert der wichtigsten Alternativen festzulegen, unter Einbezug der bakteriellen Mutagenitätsprüfung oder des Ames Tests, der Zellkultur und mathematischer Modelle für die Voraussage von Toxizität. Die Sicherheitsprüfung von Chemikalien, bei der Versuchstiere verwendet werden, ist wohl das meistversprechende Anwendungsgebiet für Alternativen und der Einbezug von Alternativen in Proben von lebenden Tieren ist im Wachsen. Jedoch im Hinblick auf die begrenzte Zahl von heute in Venwendung stehenden Alternativen besteht für *in vivo* Systeme noch eine bedeutende Nachfrage Der Veterinär stellt eine Zentralfigur in der Frage der Alternativen dar, sowohl aus Gründen humaner Rücksichtnahmen als auch in Bezug auf die Nützlichkeit von Tieren in der Wissenschaft. Der Veterinär spielt insofern eine wichtige Rolle, da er als Erzieher und Mittelsmann zwischen dem Wissenschaftler, der Versuchstiere verwendet, und dem Vertreter des Tierschutzes steht.

Introduction

Animals have been used by man for at least several centuries to obtain knowledge. As that knowledge further revealed the unity of Earth's life forms, animals were used in increasing numbers in the laboratory as surrogates for humans. Although the benefits of animal experimentation were sometimes not immediately apparent, the laboratory animal has contributed greatly to the welfare of humans as well as other animals (Bustad *et al.*, 1976; Migaki, 1981). Today, animals are used in education, research diagnosis, testing compounds for efficacy and safety, and production of biologics. There are currently 40 to 90 million laboratory animals in use in the United States, 80 to 90 percent of which are rodents (Institute for Laboratory Animal Resources, 1980; Rowan, 1981a).

Opposition to the use of animals for obtaining knowledge is as old as animal research itself. Motives for opposing animal experimentation include belief in the absolute rights of animals, humanitarian motives, scientific motives, economic motives, and legal motives. The moral and ethical arguments of antivivisection and animal welfare advocates center around whether there are any legitimate grounds for inflicting any pain, intentionally or otherwise, on animals for intellectual gain. Other proponents of animal welfare have adopted a more moderate view (Fox, 1981; Rowan, 1981b). While recognizing the contributions science has made to humanity through animal experimentation, this faction is concerned about wasteful, exceptionally cruel, or unnecessary use of laboratory animals, and their aim is to curtail these abuses (Rowan, 1980a). The most eloquent (and least offensive to the biomedical establishment) program for reducing "inhumanity" to laboratory animals was formulated by Russell and Burch (1959). They presented a concept of the "3 R's": *Replacement* of laboratory animals with suitable alternative methods, *Refinement* of research or test protocols to lessen animal suffering, and *Reduction* in the number of animals used. This creed has been adopted by both sides of the laboratory animal welfare issue as a worthwhile goal (Rowan, 1980b; Smyth, 1978).

Traditionally, the antivivisectionist attitude has meant general opposition to biomedical research. This is because there were few adequate substitutes available for the live animal which, historically, was the conventional tool of science. But recent advances in electronic and *in vitro* technology, coupled with a vast extension of our knowledge at the cellular and subcellular levels of biology, have provided substitutes for laboratory animals in many instances. These advances have been seized upon (ironically) by many in the animal welfare community as *complete* replacements for the laboratory animal. Therefore, any further use of animals for science, in their minds, is unnecessary. Moderate voices in the movement have also been encouraged by these scientific achievements, and there is increasing clamor for greater use of these technologies in the place of animals. Scientific and economic motives are also playing an increasing role in the transition from animals to alternatives.

Scientific objections put forward both by researchers and animal welfare advocates include: (1) the variability among mammalian species in anatomy, physiology, and behavior; and (2) the variability among animals of the same species due to genetic and environmental factors, and thus the applicability of the results obtained to human health (Rowan, 1981a; Lang and Vessell, 1976). Economic motives will be addressed later in the paper. Unlike the situation in other nations, there are no legal incentives for adopting alternatives in the United States (Smyth, 1978; Anon., 1981a).

There is another reason for promoting alternatives—namely, the problem of environmental pollution and its effect

on public health. Approximately 63,000 chemicals are in use today, with 1,000 new ones being added each year. It is also estimated that 80 percent of all human cancer is of environmental origin and that only 7,000 chemicals have been tested (adequately or otherwise) for carcinogenicity (Rowan, 1981a). One can thus see the enormous backlog of safety evaluation that needs to be addressed. It has been calculated that with current *in vivo* testing resources, only 500 additional compounds could be tested each year. In addition, animal assays for carcinogenicity and toxicity require an investment of over 800 animals, at least 3 years, and $150,000 to $500,000 per compound (Rowan, 1981a; Muul et *al.*, 1976). To test those compounds commonly exposed to humans as well as compounds new to society would cost over 2 billion dollars and require over 1.6 million animals, using conventional assays (CSPCA, 1980). Therefore, there is a critical need for faster and cheaper tests to detect carcinogens, at least at the initial stages of evaluation. The pressure from these problems will soon supercede the animal welfare argument in hastening any transition to alternative methods of testing.

The purpose of this paper is to discuss the current situation regarding the alternatives controversy and examine strategies used to encourage the adoption of alternative methods in science. Some of the more common alternatives will be mentioned, and comments will be made on the role of the veterinarian regarding this issue.

The concept of alternatives is best defined in the context of the 3 R's (Rowan, 1980b). Replacement is the most obvious and most common goal for those in the animal welfare field, but there are notable examples of alternatives involving different approaches. One example of Reduction is the pooling of resources in nonhuman primate research as described by Moor-Jankowski et *al.* (1980). In this system, the animals serving as negative controls or "sentinels" for infectious agents were used as sources for biological materials by other investigators. An example of Refinement is the alteration of the mouse assay for tetanus antitoxin in Great Britain. Formerly, a lethal end point was required in mouse inoculation tests for the positive controls. But since 1977, the *British Pharmacopoeia* has recommended a paralytic end point, in which the mouse suffers only a temporary and mild hind-limb paralysis and eventually recovers completely (Rowan, 1981a).

While adversaries agree on the attractiveness of the 3 R's, how quickly and by what means they are achieved is a matter of great disagreement. The scientific community has maintained that successful alternatives have arisen from within science by intellectual insight and tedious research, without the need for external prodding. When deemed acceptable, these alternatives have been quickly adopted and, it is argued, this approach will continue to be just as fruitful and dependable in the future (Gowans, 1974; Smyth, 1978; Grafton, 1981).

However, those concerned primarily with animal welfare are not satisfied with the pace of alternatives research and development and have sought other routes to achieve their goals. These routes include confrontation, collaboration, and legislation. Each will be discussed in turn.

Confrontation

An example of confrontation on a national scale is the recent campaign against the Draize test. The Draize test is the accepted eye irritancy test; it is required for all compounds intended for human ocular or conjunctival use, or where exposure to human eyes is likely. The rabbit is the test subject, and the compound to be evaluated is instilled in the conjunctival sac of one eye, the other eye serving as the negative control. Before 1982, standard protocols called for the use of six to nine rabbits per compound, but recent guidelines have

reduced the number required. The eyes are monitored for up to 3 weeks, and any lesions or evidence of irritation that develops is scored quantitatively (Interagency Regulatory Liaison Group, 1981).

Objections to the *in vivo* assay included the facts that: (1) too many rabbits were used repeatedly; (2) at higher doses, some of the compounds were extremely irritating or even necrotizing; and (3) no anesthesia was usually provided to the rabbits. The cosmetics industry was a special target of the anti-Draize campaign because the Draize test was extensively employed in the manufacture of eye makeups, hair sprays, and other similar products. Since there are already many such products available to consumers, Draize opponents felt that subjecting more rabbits to discomfort for the development of new beauty products was a needless consequence of human vanity (Harriton, 1981).

As a result of the anti-Draize campaign, the Revlon Company donated $750,000 to Rockefeller University to finance a 3-year program to develop an alternative to the Draize test. Shortly after Revlon's gift was made, the Cosmetics, Toiletry, and Fragrance Association established a fund, eventually totaling over 1 million dollars, to be managed by the Johns Hopkins Center for Alternatives to Animal Testing (Anon., 1982a).

There are also scientific objections to the Draize test (Simons, 1980). Rabbits are suspect in their ability to detect moderate irritants, although they can be used to distinguish between severe irritants and non-irritants. There is also uncertainty as to the similarity between the human and rabbit eye with regard to sensitivity to irritants. Although there are no alternatives to the Draize test currently available, some techniques are being investigated. These include evaluating *in vitro* cytotoxicity in established cell lines upon exposure to the irritant (Simons, 1980), and measuring serotonin release from irritated rat peritoneal macrophages after *in vitro* exposure (McCormack, 1981).

Collaboration

The second strategy used by animal welfare advocates is collaboration. Certainly this is more palatable to the scientific community and has been more favorably received. Animal welfare organizations have actively participated in recent scientific symposia on laboratory animals and alternatives, e.g., the Animal Welfare Institute, the Canadian Society for the Prevention of Cruelty to Animals, and the Fund for the Replacement of Animals in Medical Experiments, among others (National Academy of Sciences, 1977; Rowan and Stratmann, 1980; CSPCA, 1980).

Another approach involving collaboration is the direct financing by animal welfare organizations of scientific research on alternatives. Most of these ventures have not been as fruitful as hoped, but the mere fact that animal welfare groups are participating in this manner is important and should be encouraged. It indicates a reversal of values, in that organizations that were previously suspicious of science in general are now turning to science for assistance. Even if no breakthroughs are achieved, these sponsors will gain a better understanding of the scientific method, the necessity and value of controlled experimentation, and perhaps an appreciation for the disadvantages as well as the advantages of alternatives in certain situations. One noteworthy contribution arising from private support is the *in vitro* tumorigenicity test developed by Petricciani and others and sponsored by the American Fund for Alternatives to Animal Research (Noguchi *et al.*, 1978).

Legislation

A third strategy employed by animal welfare groups is advocacy for legislation. Presently, there are three sets of

federal regulations pertaining to the husbandry of laboratory animals: the United States Department of Agriculture's Animal Welfare Act, the Food and Drug Administration's *Good Laboratory Practices,* and the National Institutes of Health's *Guide for Grants and Contracts,* which includes animal care policies (Townes, 1980). None of these programs regulates research *per se* but, rather, defines the framework of laboratory animal use within which that research can be conducted.

There are several bills in the current session of the United States congress that pertain to the promotion of alternatives to laboratory animals, and all have originated from or have the support of at least some groups from the animal welfare lobby (Randall, 1981; Anon., 1981b). Advocates of these bills contend that the current level of animal experimentation grossly exceeds the need for such use. They argue that acceptable alternatives exist today and that adoption of these alternatives is slowed by convention, bureaucratic inefficiency, and the lack of "encouragement" for using alternatives (Broad, 1980). Thus, they believe that some central agency or federal directive is needed to expedite the transition to animal replacements.

Many biomedical administrators and scientists oppose such legislation because they feel it is unnecessary, cumbersome, and duplicative. All of the replacements for animals in use today were developed in the laboratory in response to a greater need for specificity and sensitivity. The need still exists but, in their opinion, it would be wrong to believe that by mandating the process and providing more money the system would be any more productive (Broad, 1980; Anon., 1982b).

How Do Alternatives Compare with Animals?

The common alternatives used by science as well as promoted by animal welfare activists can be classified as follows: physicochemical techniques, microbiological systems, *in vitro* eukaryotic systems, *in vivo* eukaryotic systems, computers and mathematical models, and expanded clinical and epidemiological studies in humans.

Physicochemical techniques involve the use of radioactive isotopes, gas-liquid chromatography, and mass spectrometry. It has been argued that these techniques do not substitute for animals, but make results obtained with animals more specific and provide more information (Smyth, 1978). It is also suggested that rather than reduce the number of animals used, physicochemical techniques may actually, in some instances, increase the need for more animals, due to the new questions they may pose to an investigator. However, others have documented examples where physicochemical techniques have replaced animals — as in vitamin A bioassays (Rowan, 1981a).

This illustrates, on a small scale, the problem of determining just how successful computer systems, *in vitro* systems, and clinical studies can be as alternatives to animals. Space is too limited here for detailed analyses, and the reader is referred to several books that have appeared on the subject in recent years (Rowan and Stratmann, 1980; Smyth, 1978; National Academy of Sciences, 1977).

How do *in vitro* systems compare with the laboratory animal in terms of sensitivity or specificity? The most realistic comparison to be made is in the safety testing sector, since the purpose and end points involved here are agreed upon by most. Research, on the other hand, entails more personal choice and therefore more varied endeavors which do not always offer the same opportunities for transposition between animals and alternatives. Most *in vitro* systems for detecting carcinogencity in a compound exhibit 50 to 90 percent agreement with the *in vivo* results (Bridges, 1976; Ames and Hooper, 1978; Anon., 1980a). One study in which one laboratory

performed a comparative survey using the same personnel and same equipment in the same time period (so as to reduce as many external variables as possible) is reported by Bridges (1976). This analysis was performed for 120 chemicals and produced the following results, expressed as percent agreement with animal or human data: bacterial mutation with metabolic activation (Ames test), 90 percent; cell transformation *in vitro*, 83 percent; degranulation of endoplasmic reticulum, 72 percent. Certain assays performed very well for certain classes of compounds, but were quite inaccurate for others. The Ames test was clearly the most accurate of those tested; perhaps 90 percent correlation with *in vivo* results is the best to be expected, given the dissimilarity between the *in vivo* state and that of bacteria or cells in culture, as well as the fact that the animal assay is not foolproof either (Ames and Hooper, 1978). To provide for increased efficiency and maximal accuracy, carcinogenicity and toxicity testing will most likely evolve in the near future to incorporate both *in vivo* and *in vitro* systems (Weisburger and Williams, 1981).

The Bottom Line

To summarize the controversy, there are two points where enlightened spokespersons for and against animal use can agree: (1) animals will be required, if not desired, in the laboratory for some time to come, most notably in research; and (2) no substitute for the entire live animal currently exists because the *in vivo* state is too complex and too poorly understood at this time. It should be appreciated that the greatest promise for alternatives lies in those disciplines that focus on particular biological phenomena not requiring live animal subjects. Much of biology has advanced to a level of sophistication where the animal may serve only as a source of biomaterials for *in vitro* investigations, or where abiotic methods are preferred. An example of the former is the rapid adoption of monoclonal antibody technology, replacing rabbits and other mammals as a means of producing antisera (Kennett, 1981). But there remain fields of study that depend, at least in part, on the live animal and all of its intricate interplay among physiologic systems. These fields include experimental surgery and ethology.

Conversely, the points of disagreement center around (1) the current degree to which animals are used, given that there are alternatives applicable to specific biological processes that we already understand; and (2) the paucity of support given to alternatives in general (Rowan, 1981b).

But a consistently major point of debate is the quality of care that laboratory animals receive, as well as the attitudes of those who use them. In support of those who argue that progress is too slow in providing better care for laboratory animals, a national survey of laboratory animal facilities noted that fewer facilities than expected had become accredited by the American Association for Accreditation of Laboratory Care in the last 10 years (ILAR, 1980). Furthermore, laboratory animal veterinarians have complained of the reluctance of grant recipients or administrators to devote an adequate proportion of their funds to housing and care of animals (Leeper, 1976). On the other hand, the same national survey confidently predicted continued growth of the veterinary labor force in laboratory animal medicine (ILAR, 1980).

The Laboratory Animal Veterinarian

What role should the laboratory animal veterinarian play in the alternatives controversy? Or, should any role be assumed at all? Since his or her position is central to laboratory animal welfare, the veterinarian will become involved by force of circumstance if not by de-

sign. The responsibilities of the laboratory animal clinician have grown enormously in the last decade, partly in response to a greater concern for animal health and welfare from within and outside scientific confines. In addition to managing the laboratory animal colony, he or she may be expected to advise investigators on the appropriateness of particular animals as models and on which ones to use in specific experiments; to instruct investigators on the proper handling of animals; to assess protocols involving animals; to implement and monitor policies to comply with federal regulations on animal care and housing (Bradbury, 1980); and to justify the use of animals in the laboratory. In this last regard, the veterinarian's position has become more politicized and the trend will likely continue. In most instances, the defense of animal experimentation has been retrospective in scope, in that historical examples of biomedical advances that were achieved with animals are offered as evidence. It is then argued that similar advances in the future must also utilize animals (Migaki, 1981).

As more scientists turn to alternatives, for whatever reasons, and as more scientists become sympathetic to the animal welfare "cause," laboratory animal veterinarians will have to adopt new viewpoints, of a *prospective* nature, to be able to discuss intelligently the potential and limitations for both *in vivo* and *in vitro* systems. In addition, they will likely have to work in closer conjunction with animal welfare representatives in performing their duties. This is already being done in Canada on a national scale, outside of any federal directive (Rowsell, 1980; Anon., 1980b). Involvement of the animal welfare community in laboratory animal care and use is an important development, and it is necessary if the two sides are to find common ground or minimize further conflict and misunderstanding. The actual day-to-day activities of biomedical research and testing are often poorly presented to the public (Rowan and Stratmann, 1980). If the public is concerned with the welfare of laboratory animals, their ignorance of what actually occurs in the vivarium and laboratory can only harm the image of biomedical science and further increase the public's suspicions. This is especially true when their suspicions are confirmed, as occurred in the recent Silver Spring animal cruelty case (Kershner, 1982).

As a partial remedy to the information gap, some suggest publishing detailed husbandry protocols in addition to experiments, so as to better inform the reader (and public) on how the animals were cared for and used in the research. Others encourage more interaction between scientists and animal welfare advocates to accommodate the concerns of both sectors of society; again, the laboratory animal clinician's role is pivotal. Public relations and education may well become a major duty of the laboratory animal veterinarian in the near future (Loew, 1981).

The Veterinarian in Private Practice

What of the private veterinary practitioners? They may also become involved in the controversy surrounding alternatives through discussions with concerned clients or in consultations with local humane organizations. Some of the more sensational animal welfare groups distribute literature containing photographs of cute pets or mutilated carcasses of companion animal species, and accuse science of butchery. The client is often the recipient of such literature and will ask his or her veterinarian about the charges. Similar articles in the communications media will also concern the client, as will claims by animal welfare advocates that this destruction of animal life is unnecessary today since cell cultures and computers can substitute *completely* for the laboratory animal. Hope-

fully, the practitioner will seize the opportunity to perform a service for his profession (and the biomedical industry that supports it) by educating the client or the humane society chapter in his town on the complexities of the issue.

Conclusion

In many instances, animal experimentation has been or is being minimized; there are many more opportunities for utilizing alternatives (in *all* aspects of the concept). However, in many cases, animal research still proves to be the best way to approach a problem. Suppression of the utilization of any resources, be they laboratory animals or alternatives, imposes a serious limitation on scientific progress for human welfare.

References

Ames, B. and Hooper, K. (1978) Does carcinogenic potency correlate with mutagenic potency in the Ames assay? *Nature 274*:19-20.

Anonymous (1980a) Alternative carcinogen detection. *Int J Stud Anim Prob 1*: 77-79.

Anonymous (1980b) Surveillance over the care and use of experimental animals in Canada. *J Med Primatol 9*:132-139.

Anonymous (1981a) The law in Sweden. *Int J Stud Anim Prob 2*:150.

Anonymous (1981b) Governmental activities relating to the use of animals in research *ILAR News 24*(2-3):22-27.

Anonymous (1982a) Johns Hopkins to establish Center for Alternatives Testing *ILAR News 25*(3):7-8.

Anonymous (1982b) Modified lab animal bill gains in the House. *ASM News 48*: 466-467.

Bradbury, R.P. (1980) The Good Lab Practice regulations: how to use them. *Lab Anim 9*(4):30-33.

Bridges, B.A. (1976) Short-term screening tests for carcinogens. *Nature 261*:195-200.

Broad, W.J. (1980) Legislating an end to animals in the lab. *Science 208*:575-576.

Bustad, L.K., Gorham, J.R., Hegreberg, G.A., and Padgett, G.A. (1976) Comparative medicine: progress and prospects. *JAVMA 169*:90-105.

CSPCA (1980) *Report of the Workshop on Alternatives to the Use of Laboratory Animals in Biomedical Research and Testing.* Canadian Society for the Prevention of Cruelty to Animals, Montreal, Canada.

Fox, M.W. (1981) The question of animal rights. *Vet Rec 109*:37-39.

Grafton, T.S. (1981) The role of alternatives in biomedical research. *Lab Anim 10* (1):25-30.

Gowans, J.L. (1974) Alternatives to animal experiments in medical research. *Br Med J*, March 23, 1974, pp. 557-559.

Harriton, L. (1981) Conversation with Henry Spira: Draize test activist. *Lab Anim 10*(1):16-22.

ILAR (1980) *National Survey of Laboratory Animal Facilities and Resources, Fiscal Year, 1978.* National Institutes of Health (Pub. No. 80-2091), Public Health Service, Washington, DC.

IRLG (1981) *Acute Eye Irritation Testing.* Interagency Regulatory Liaison Group, Testing Standards and Guidelines Work Group, Washington, DC.

Kennett, R.H. (1981) Hybridomas: a new dimension in biological analyses. *In Vitro 17*(12):1050, 1981.

Kershner, L. (1982) Taub loses NIH grant. *Scientists Center for Animal Welfare Newsletter 4*(3):1, 9.

Lang, C.M. and Vessell, E.S. (1976) Environmental and genetic factors affecting laboratory animals: impact on biomedical research. *Fed Proc 35*:1123-1134.

Leeper, E.M. (1976) New methods may reduce needs, can't replace laboratory animals. *Bioscience 26*:9-12.

Loew, F.M. (1981) Biomedical research and animal welfare: traditional viewpoints and future directions. *Int J Stud Anim Prob 2*:193-198.

McCormack, J. (1981) A procedure for the in vitro evaluation of the eye irritation potential of surfactants, In: *Trends in Bioassay Methodology: In Vivo, In Vitro and Mathematical Approaches.* U.S. Department of Health and Human Services (NIH, Pub. No. 82-2382), Washington, DC, pp. 177-186.

Migaki, G. (1981) Using animals to understand human disease: a history. *Lab Anim 10*(2):30-37.

Moor-Jankowski, J., Goldsmith, E.I., and Wittrup, L. (1980) Humane methodology and conservation of species in maintaining a primate laboratory for biomedical experimentation: twenty years experience, In: *Developments in Biological Standardization, Volume 45: The Standardization of Animals to Improve Biomedical Research, Production and Control.* S. Karger, Basel, Switzerland.

Muul, I., Hegyeli, A.F., Dacre, J.C., and Woodard, G. (1976) Toxicological testing dilemma. *Science 193*:834.

National Academy of Sciences (1977) *The Future of Animals, Cells, Models, and Systems in Research, Development, Education, and Testing.* National Academy of Sciences, Washington, DC.

Noguchi, P.D., Johnson, J.B., O'Donnell, R., and Petricciani, J.C. (1978) Chick embryonic skin as a rapid culture assay for cellular neoplasia. *Science 199*:980-983.

Randall, B. (1981) *Animal Welfare.* Congressional Research Service, Issue Brief Number IB75053. Library of Congress, Washington, DC.

Rowan, A.N. and Stratmann, C.J., (eds.) (1980) *The Use of Alternatives in Drug Research.* Macmillan Press, London, U.K.

Rowan, A.N., (1980a) Animal experimentation and the humane movement in the United States. *J Med Primatol 9*: 108-111.

Rowan, A.N. (1980b) The concept of the three R's—an introduction, In: *Developments in Biological Standardization Biomedical Research, Production and Control.* S. Karger, Basel, Switzerland, pp. 175-180.

Rowan, A.N. (1981a) Alternatives and laboratory animals, In: *Animals in Research* (D. Sperlinger, ed.). J. Wiley and Sons, Chichester, U.K., pp. 257-283.

Rowan, A.N. (1981b) Can alternatives be integrated with animal models? *Lab Anim 10*(2):38-45.

Rowsell, H.C. (1980) The voluntary control program of the Canadian Council on Animal Care. *J Med Primatol 9*:5-8.

Russell, W.M. and Burch, R.L. (1959) *The Principles of Humane Experimental Technique.* Methuen and Co., London, U.K.

Simons, P.J. (1980) An alternative to the Draize test, In: *The Use of Alternatives in Drug Research* (Rowan, A.N., and Stratmann, C.J., eds.). Macmillan, London, U.K., pp. 147-151.

Smyth, D.H. (1978) *Alternatives to Animal Experiments.* Scolar Press, London, U.K.

Townes, J. (1980) Federal regulations and standards: an overview. *Lab Anim 9* (4):16-22.

Weisburger, J.H. and Williams, G.M. (1981) Carcinogen testing: current problems and new approaches. *Science 214*:401-407.