# PRINCIPLES OF ANIMAL RESEARCH: REPLACEMENT, REDUCTION, REFINEMENT, AND RESPONSIBILITY

BY
BRYAN D. OGDEN*

I am not an ethicist, but I am familiar with ethical concerns related to the use of animals in medical research. I am not a lawyer, but I am familiar with the laws which relate to the care and use of laboratory animals. I am not an advocate of animal rights; I am an advocate of animal welfare. I will not argue the moral permissibility of research where animals are used. Rather, I will focus on the principles and laws which guide this activity. Mine is a unique perspective because, while I am not one of the scientists, I am responsible for the care of every animal used in biomedical research at Oregon Health Sciences University (OHSU). I want to share with you some of my understanding and perspective.

I want to address what is called the "three *Rs*:" replacement, reduction, and refinement. Originally proposed by Russell and Birch,[1] these principles are now widely accepted by today's biomedical community. The first of the three Rs, replacement, refers to efforts to use non-animal models—such as *in vitro* tests, tissue culture, and computer models—whenever possible. An example of this is the use of *in vitro* systems rather than mice for mass production of monoclonal antibodies.[2] This also means that we try to replace the more advanced animals with animals lower on the phylogenetic tree. An example of this is the use of horseshoe crabs instead of rabbits for pyrogen testing.[3] The biomedical community is also committed to considering the use of human subjects whenever ethically and legally possible. This is reflected in the fact that, on file at OHSU, there are ten research protocols using humans as research subjects for every one research protocol using animals.

* Clinical Veterinarian, Oregon Health Sciences University; D.V.M. 1980, University of Minnesota. Dr. Ogden is certified as a specialist in laboratory animal medicine.

1 WILLIAM M.S. RUSSELL & REX L. BIRCH, THE PRINCIPLES OF HUMANE EXPERIMENTAL TECHNIQUE (1959)

2 Michael W. McGuill & Andrew N. Rowan, *Refinement of Monoclonal Antibody Production and Animal Well-being*, Institute of Laboratory Animal Resources (ILAR) News, Winter 1989, at 7-10.

3 C. Booth, *The Limulus Amoebocyte Lysate (LAL) Assay—A Replacement for the Rabbit Pyrogen Test*, *in* 64 DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION 271, 271-75 (1986).

The second R, reduction, refers to using fewer animals for each test. For example, there is now more support for the Limit Test[4] to evaluate the toxicity of test substances instead of the classical LD50. It is therefore possible in some situations to use ten animals to obtain information which once required the use of a hundred animals.

The third R, refinement, means that procedures should be altered so that pain and distress to the animal subject can be minimized or eliminated. Where possible, less invasive procedures are employed, and strict attention is paid to adequate anesthesia or analgesia. More sophisticated monitoring equipment, such as end tidal carbon dioxide monitors, pulse oximeters, EKG machines, invasive and noninvasive blood pressure machines, and blood gas machines are being used. These enable us to ensure a better physiologic state for the animals during anesthesia and surgery. Most private practice veterinarians can only envy us because they cannot provide such high-tech patient monitoring.

In addition to the conventional three Rs, there is also a fourth that has been proposed and is receiving interesting attention: responsibility. In a recent article, Dr. Ronald E. Banks stated that the fourth means "responsibility to the research and teaching animals, responsibility to the public, responsibility to scientific and medical integrity, and responsibility to appropriate stewardship of animal resources. Responsibility to research and teaching animals does not suggest equality between humans and animals; rather, it is a commitment to practicing appropriate animal care."[5]

Dr. Banks continues:

> Many [people] have suggested research is inhumane, but I would counter that our adherence to the responsible care of research animals is the ultimate in humaneness; a direct reflection of our own humane nature. . . . Responsibility to research animals means we provide the best care and support possible to research animals in our charge.[6]

Paraphrasing Dr. Banks thoughts, responsibility to the public involves not only educating the public about the benefits obtained through animal facilitated investigation and the challenges and opportunities yet ahead, it also means listening to the public concerns, however ill-founded, and responding in a quiet and gentle manner with the truth. Responsibility to the public means that we continue with determined resolve to address issues of public health, while preparing ourselves for accusations and attacks on our facilities and ourselves. Responsibility to scientific and medical integrity involves optimal protocol design, sufficient data base searching, peer review, and professional oversight. Responsibility to appropriate stewardship of animal resources requires model selection based on the correct

---

[4] J. van Noordwijk & A.J. Seegers, *Reduction of Animal Use for Toxicological Evaluation: The Netherlands Health Council Report on the LD50*, *in* 64 DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION 277, 277-85 (1986).

[5] Ronald E. Banks, D.V.M., *The 4th R of Research*, CONTEMPORARY TOPICS, Jan. 1995, at 50.

[6] *Id.*

model system for specific issues and the use of appropriate numbers of animals—neither too many nor too few—to answer the question at hand. The federal government's principles for the use and care of animals used in testing, research and training reflect the principles of the four Rs.

Laboratory animal veterinarians are committed to these four Rs. In addition to our personal commitments, we also have legal obligations. The Animal Welfare Act and the Health Research Extension Act of 1985 require institutions to employ veterinarians who provide a program of veterinary care.[7] The rules state "each research facility shall assure that the attending veterinarian has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use."[8] The three operative phrases in that quotation are "appropriate authority," "adequate veterinary care," and "oversee other aspects of animal care and use." In overseeing animal care and use, we use as our bible the Public Health Service Guide for the Care and Use of Animals.[9]

While the Animal Welfare Act and the rules promulgated by the U.S. Department of Agriculture do not cover all vertebrate animal species used in research, the NIH Guide does.[10] OHSU is committed to providing the proper care for all animals regardless of which agency covers them. Our facility is subject to inspections by the U.S. Department of Agriculture, National Institutes of Health, and American Association for Accreditation of Laboratory Animal Care (AAALAC), through which we have obtained an excellent reputation for our commitment to proper care and use of animals. The OHSU animal care and use program has been AAALAC accredited since 1966 and was one of the first research facilities in the world to receive this honor.

Laboratory animal veterinarians are not alone in assuring that the spirit and letter of the laws and guidelines are carried out. In 1986, the Public Health Service, through the Office of Protection from Research Risks, published the Public Health Service Policy on humane care and use of animals.[11] This document describes the function of the Institutional Animal Care and Use Committee (IACUC). This IACUC must consist of not less than five members; the IACUC at OHSU has seventeen members. The IACUC must include (1) one doctor of veterinary medicine with training or experience in laboratory science and medicine who has direct or delegated program responsibility for activities involving animals at the institution; (2) one practicing scientist experienced in research involving animals; (3) one member whose primary concerns are in a non-scientific

---

[7] Animal Welfare Act of 1970, 7 U.S.C. §§ 2131-2159 (1994); Health Research Extension Act of 1985, Pub. L. No. 99-158, 99 Stat. 820 (codified in scattered sections of 42 U.S.C.).

[8] PUBLIC HEALTH SERVICE, U.S. DEP'T OF HEALTH AND HUMAN SERVICES, PUBLIC HEALTH POLICY ON HUMAN CARE AND USE OF LABORATORY ANIMALS 28 (1986).

[9] Fred W. Quimby, V.M.D., Ph.D., *The Role of Attending Veterinarians in Laboratory Animal Welfare*, 206 JAVMA 461, 461-64 (1995).

[10] NATURAL RESEARCH COUNCIL ET AL., U.S. DEP'T OF HEALTH AND HUMAN SERVICES, GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS (1985).

[11] PUBLIC HEALTH SERVICE, *supra* note 8.

area; and (4) one individual who is not affiliated with the institution in any other way than as a member of the Committee and is not a member of the immediate family of a person who is affiliated with the institution. At OHSU, we have three veterinarians, ten practicing scientists from a wide range of disciplines, one lawyer, and one ethicist serving on our Committee.

The IACUC oversees the institution's animal program, facilities, and procedures. All projects using animals must first be cleared through the IACUC. The project must be described on a protocol form which requires an explanation of what will happen to the animal during the entire time it is at the institution. The investigator who signs the form must address the legal and ethical issues raised by the Animal Welfare Act and the Public Health Service Policy. These include such questions as: Why must animals be used? Why must this species of animal be used? What has been done to assure that this project cannot be done using a non-animal model? Is the project unnecessarily duplicative? How will this project benefit mankind or animals? Issues such as housing, anesthesia, analgesia, euthanasia, restraint, possible side effects, monitoring, and end points must also be discussed. The number of animals to be used must be justified, and the list goes on. Investigators usually consult with the veterinarian before submitting the protocol, but the veterinarian reviews the protocol before the IACUC discussion. The IACUC reviews the protocol and makes a determination whether to approve the protocol as is, to approve it with certain modifications, or to withhold approval. It should be emphasized that the investigator cannot even order animals until the protocol is approved.

The IACUC also reviews the institution's program for humane care and use of animals and inspects the animal facilities at least every six months, using the Guide as a basis for evaluation. Members of the IACUC at OHSU take their responsibilities very seriously. As a veterinarian, I am proud to be a member of that Committee. The veterinarian's oath advises us to use our scientific knowledge for the benefit of society, for the protection of animal health, for the relief of animal suffering, for the conservation of livestock resources, for the promotion of public health, and for the advancement of medical knowledge. The occupation of a laboratory animal veterinarian is challenging and rewarding, and I take pride in improving the quality of life for research animals, promoting public health, and contributing to the advancement of medical knowledge.