

Chapter Twenty-One

The History of the Public Health Service Policy on the Humane Care and Use of Laboratory Animals

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The National Institutes of Health, a major component of the Public Health Service of the Department of Health and Human Services and the largest federal funder of biomedical research, has functioned as a primary source of animal welfare policies, guidelines, and oversight.

It may not be possible to follow the complete path of progress of the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (PHS Policy), (1) but in this chapter I hope to illuminate the major landmarks. The first was when the director of the Hygienic Laboratory, Dr. Milton J. Rosenau, made an entry into his daily log in 1904 stating, "Animals are to be used in the proper work of the lab, but anything which inflicts pain upon them will not under any circumstances be allowed." A poster, believed to have been displayed in the Hygienic Laboratory during that era, has also been reported. It indicated that the director held himself personally responsible for decisions on the use of animals in given experiments and on the possible exceptions to a general policy on the use of anesthetics.

In 1930 Senator Joseph Ransdell of Louisiana convinced Congress that "fundamental research could lead to cures for diseases," and the resulting Ransdell Act expanded the Hygienic Laboratory and renamed it the National Institute of Health (NIH). The NIH's parent organization, the Marine Hospital Service had also undergone a name change in 1912 and was by this time the Public Health Service (PHS). An administration building and a laboratory were built, but the scientists wanted a building in which they could raise their own pure strains of mice, rats, guinea pigs, and rabbits. Many were being used in studies ranging from psittacosis, encephalitis, and poliomyelitis to Rocky Mountain Spotted fever, and various factors, including

transportation problems and weather conditions, occasionally resulted in failed experiments. In 1935, after much discussion and considerable controversy, philanthropist Luke Wilson sold his estate in Bethesda, Md., to the United States Government for \$10—an estate with the estimated value of almost \$75,000 at that time. Four days later, President Franklin Delano Roosevelt signed the Social Security Act that provided two million dollars per year for "investigation of disease and problems of sanitation." Subsequently, the NIH was relocated to Bethesda in 1937.

Thus, from its embryonic stages, NIH was addressing concerns about the use of laboratory animals. In 1950, the director, Dr. Rolla E. Dyer, issued a single-page "Rules Regarding Animals." These rules covered five items: 1. source of animals only from dealers, with stray dogs to be turned over immediately to Montgomery County authorities; 2. comfort and sanitation, with animals on long experiments to be maintained under veterinary supervision; 3. operations to be performed only under the supervision of the director of the institute concerned; 4. anesthesia requirements; and 5. treatment of an animal at the close of the experiment, with exception to euthanasia. In 1954 an NIH Manual was issued with a chapter on revised requirements relating to animal use in intramural research.

In 1963 the first edition of the *Guide for Laboratory Animal Facilities and Care* was published as Public Health Service Publication Number 1024 (2). It was developed by the Animal Care Panel to "determine and establish a professional standard for laboratory animal care and facilities." More than 35,000 copies were distributed to members of the medical research community. The second edition of the *Guide* was developed in 1965 under the auspices of the National Academy of Sciences Institute for Laboratory Animal Resources (now named Institute for Laboratory Animal Research). It included comments and suggestions solicited from medical researchers. It was intended to play an important role in the PHS's continuing objective of good care and minimal discomfort for animals used in needed research, as expressed by James A. Shannon, MD, then director of NIH. Regarding the *Guide*, then Surgeon General Luther L. Terry was quoted as saying, "... (the *Guide*) reflects a growing recognition that the care of laboratory animals is an institutional responsibility, as well as the responsibility of individual investigators. The animal care programs of most large institutions are based increasingly on this partnership of responsibility, and the recommendations in the *Guide* assume it. The science community has long recognized a scientific and ethical responsibility to provide humane care for experimental animals used in the service of man and animals. This commitment to high standards is expressed in the codes guiding experimentation and care adopted by numerous scientific societies and institutions. The second edition of the *Guide* extends these codes by defining care in professional terms."

The *Guide* was distributed by the Division of Research Grants (DRG, NIH), Dr. Eugene Confrey, Director, to all scientific investigators receiving PHS support for research involving animals. In 1968, the *Guide* was subsequently revised, with a name change to *Guide for the Care and Use of Laboratory Animals*. Further revisions occurred in 1972, 1978, 1985, and 1996 (3). More detailed coverage of the history of the *Guide* is provided elsewhere in this 50th anniversary edition.

The Animal Welfare Act (AWA) was enacted in 1966 (Public Law 89-544) with implementation given to the U.S. Department of Agriculture (USDA) (4). Because the history of the Animal Welfare Act is covered elsewhere in this edition, it will only

be mentioned briefly as needed for chronological points of reference.

NIH issued its first "Policy, Care, and Treatment of Laboratory Animals" in 1971, applicable to "warm-blooded animals" at institutions receiving or about to receive grant or contract awards (5). The Institutional Relations Section of the Division of Research Grants was designated to carry out the terms of the policy on behalf of NIH, a logical assignment since the policy had been developed in that office under the leadership of its director, Dr. Donald T. Chalkley. Although the name of this office was changed in 1972 to Institutional Relations Branch, and in 1974 to Office for Protection from Research Risks, the responsibility for compliance with all subsequent policies was retained throughout by the same office.

In order to determine which institutions would need to comply, the office sent out 2,955 letters to every organization receiving or about to receive financial support at that time. Those who were using laboratory animals had to fill out and submit the first assurance form, and created another NIH record. The policy required a written assurance that institutions receiving or about to receive NIH support had either been accredited by a "professional accrediting body" or had established a committee of three members, of which at least one was a DVM, to evaluate the care of all warm-blooded animals used in research, teaching, or other activities supported by NIH grants or contracts. Annual inspections of facilities were required, with records maintained. Compliance with the AWA was a requirement for this policy as well as for all subsequent policies. The *Guide* was to be used as the basis for annual committee inspections of animal care and facilities.

After the issuance of the 1971 policy, a number of events occurred that warranted a 1973 revision. The PHS had published the newly renamed *Guide*, which was the accepted standard for institutional procedures; the AWA had been amended, which increased the USDA's enforcement responsibilities for research facilities; and the Department of Health, Education, and Welfare (DHEW) ordered the development of a uniform departmental policy. Dr. Charles McPherson of NIH's Division of Research Resources was the NIH representative on the panel that drafted the DHEW policy. Responsibility for carrying out the requirements was again delegated to Dr. Chalkley of the then- Institutional Relations Branch. The 1973 policy was applicable to institutions receiving grant or contract support from any agency of the DHEW for projects involving live vertebrate animals (6). It included animals used for research, training, education, experimentation, and demonstration purposes. During the six years (1973-1979) it was in force, about 800 institutions filed assurances. Applicability of this policy was limited to the United States and its territories or possessions. A distinction was made between animals used in "significant numbers" or "not in significant numbers," but there was no quantitative definition of "significant." For the first time restrictions could be imposed for non-compliance with the terms of the policy. If a grant or contract was found to be unacceptable from an animal care standpoint, or if the procedures of individual investigators were faulty, the assurance approval could be withdrawn from the institution.

If an institution was accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC), now the Association for the Assessment and Accreditation of Laboratory Animal Care, International, institutional components had to be named and records maintained. For non-accredited institutions with significant numbers of animals, compliance rested

with the required committee, again with a minimum of three members—one of which had to be a veterinarian. Facilities and components covered by the assurance had to be named and the records of yearly inspections maintained, as under the original policy. Although the committee was not required to review animal protocols, the procedure was recommended. The 1973 policy included the first set of principles, namely the DHEW "Principles for Use of Laboratory Animals." These included a requirement for animal-related research to be performed by or under the immediate supervision of a qualified scientist and dealt with the purpose and design, and required humane procedures for post-experimental care, anesthetics, and euthanasia.

In the period between the 1973 policy and the next one in 1979, the 1978 version of the *Guide* was published. It included the statement that, although the *Guide* does not apply to facilities for cold-blooded animals, the "Principles for Use of Laboratory Animals" applied to all vertebrates. This was one of the early measures of attention given to the welfare of cold-blooded laboratory animals. In anticipation of a new 1979 policy, a new sample assurance was developed by Dr. Charles McCarthy, director, Office for Protection from Research Risks (whose new title replaced the Institutional Relations Branch), under the leadership of its first animal welfare officer, Dr. Roy Kinard. The process of negotiating more than 800 new assurances started.

On January 1, 1979, the PHS Animal Welfare Policy was issued—the third policy of record. It was adopted as NIH Manual Chapter 4206 and the PHS Grants Manual Chapter 1-43, "Animal Welfare." The policy dealt with animal use for research, experimentation, testing, training, and related purposes. The assurance document provided for three options: 1. AAALAC accreditation; 2. committee's responsibility and judgment of compliance based on inspection at least annually of review and procedures; and, 3. deficiencies found during committee's inspection, specified, and plans for correction. This policy applied to all live vertebrate animals, although the *Guide* still covered only warm-blooded animals. No awards could be made unless the grantee/contractor institution was assured. Review of protocols was still recommended, but not required. Restrictions for non-compliance included potential for suspension or termination of support of a specific project, of projects by a specific investigator, or of all projects involving animals at that institution.

Over the six-plus years that followed, many elements, including the next revision of the *Guide* in 1985, resulted in the publication of another new policy. A special edition of the NIH Guide for Grants and Contracts, "Laboratory Animal Welfare," June 25, 1985, published the new "Policy on the Humane Care and Use of Laboratory Animals by Awardee Institutions." Development of this policy had been performed under the authority and chairmanship of OPRR over a period of almost two years. Members of the drafting committee were representatives not only of OPRR but also other NIH directors' offices, the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), and the Food and Drug Administration (FDA). Other NIH participants were Drs. Joe Held, director of the Division of Research Services; Thomas Malone, NIH deputy director; William Raub, NIH deputy director; Robert Whitney, director of NIH Office of Animal Care and Use; and Thomas Wolfle, Division of Research Services.

Later, on November 20, 1985, Congress passed the Health Research Extension Act (HREA) of 1985 (Public Law 99-158) which became the statutory authority for the PHS Policy for PHS funded research and extended its requirements for the first time to NIH

intramural research facilities (7). Within weeks of passing the HREA, Congress also amended the AWA (Public Law 99-198), with provisions requiring training for all individuals involved in both the care and use of animals, semi-annual rather than annual inspections, and two controversial requirements for the psychological well-being of nonhuman primates and the exercise of dogs (8). One important provision of the new AWA was a requirement for the Secretary of Agriculture to consult with the Secretary of DHHS on the promulgation of specific regulations under the AWA. As a result of this provision, there were extensive consultations between USDA and OPRR so that both the AWA implementing regulations and the PHS requirements would be as consistent as possible, given the two different authorizing statutes. Dr. John Miller, then director of the Division of Animal Welfare, OPRR, and Dr. Dale Schwindeman, then deputy administrator of Regulatory Enforcement/Animal Care, APHIS, USDA, can be credited with the remarkable level of harmonization between the two agencies' regulations and guidelines.

As a result of the HREA, at least four provisions had to be added to the 1985 policy. The final version went into effect on September 16, 1986 and has remained in force. There are requirements that the assurance document be more extensive and include additional specific information. The institutional official with ultimate responsibility for compliance has to be named and the composition of the Institutional Animal Care and Use Committee (IACUC), as appointed by the chief executive officer has to be provided. It now includes a minimum of five members with at least one DVM with program authority, one practicing scientist, one non-scientist and one person not affiliated with the institution in any way except as a member of the committee. The IACUC's major responsibility is the review of all animal protocols of proposals for submission to any of the PHS Agencies, with signed, dated verification of review, and approval. The degree of responsibility and authority delegated to the IACUC is one of the outstanding features of the 1986 policy. Institutions are classified into two categories: Category 1 for AAALAC accredited institutions, and Category 2 for all non-AAALAC accredited institutions. The fact that AAALAC accreditation also depends in large measure on an institution's compliance with the relevant sections of the *Guide* is a major point of similarity between AAALAC and the PHS Policy.

As mandated by PL 99-158, inspections and reports by the IACUC are semi-annual rather than annual, and the training programs for the scientists, technicians and caretakers have to be described. All institutional programs and procedures, including the health programs for personnel, details about facilities, numbers of animals and species by name are all information required by the policy to be included in institutional assurances.

Between 1982 and 1986 a series of periodic site visits was initiated by the NIH's Office of Extramural Research to institutions that conducted animal research with PHS support. The objectives were: 1. to gather data in order to be able to make informed decisions on revisions of animal care guidelines and their impact on institutions; and 2. to review institutions that had been cited for deficiencies in the care of research animals. The site visit teams included a scientist, veterinarian, NIH representative, and an OPRR representative. A continuing goal of 10 site visits per year was set, and by 1990-1991 OPRR was assigned the responsibility of conducting half of them for the purpose of providing technical assistance.

In its role as funder of research, NIH in 1982 developed specific instructions for the reviewers of grants and contracts to pay

increased attention to the appropriateness of species choice; the numbers of animals involved; justification of their use; and an assessment as to whether animals would receive proper care and maintenance and would not suffer unnecessary discomfort, pain, or injury. Special attention was to be directed when the proposed research involved dogs, cats, nonhuman primates, large numbers of animals, or when animals would be in short supply or costly. There have also been Animal Welfare Training Courses for the NIH Scientific Review Administrators (SRAs) who are responsible for the review of research proposals from the extramural community. Among the requirements for the SRAs, in preparing the summary statements after the initial review of applications, is a coding system that was set in place in 1984. Coding is based on whether the awardee institution has or would need an assurance and whether the reviewers expressed animal welfare "comments" or "concerns," the latter requiring resolution as a condition of funding. Although coding of the summary statements, written after the initial review of grants, was not put into place until 1984, OPRR's review of the summary statements tracked and noted animal issues that required further attention. After this practice began, OPRR's routine review revealed a great increase in attention to animal care and experimental procedures by the NIH Initial Review Groups and their Executive Secretaries (predecessors of the SRAs) who prepared the summary statements.

One of the specific duties of OPRR is to advise institutions on the implementation of the PHS Policy. This requirement has evolved into an extensive educational effort, which has become the foundation upon which compliance with the PHS Policy rests. One of the most well known of these efforts is the series of OPRR Animal Welfare Education workshops which are conducted regionally, in conjunction with a PHS assured host institution, several times a year. Other activities include the publication of written material such as the *Institutional Administrator's Manual for Laboratory Animal Care and Use* (9). OPRR has also sponsored or prepared a variety of educational materials, such as computer based self-tutorial exercises, as well as support of lectures and workshops. These serve to illustrate a broad range of basic animal topics for use by IACUC members, investigators, technicians and students. Over the years, OPRR has sent out letters providing specific guidance and PHS Policy interpretation to institutions. It has also developed, in partnership with the organization Applied Research Ethics National Association (ARENA) the *IACUC Guidebook* (10). In addition, OPRR has cooperated with ARENA's parent organization, Public Responsibility in Medicine and Research (PRIM&R), since 1983 in the preparation of meetings focused on animal issues.

In 1982 the Trans-NIH Coordinating Committee for Research Animal Resources was established. Members included individuals involved in intramural animal activities, both research and administrative, as well as both OPRR and other NIH Director's Office representatives. Its chair for several years was Dr. William Gay who, on retirement, was replaced by Dr. Leo Whitehair. Gradually its function was assumed by other NIH and interagency committees.

In 1983, the Interagency Research Animal Committee (IRAC) was established. It replaced the Interagency Primate Steering Committee and was originally composed of representatives of 14 federal entities that used, sponsored, or regulated animal research. Its original charge was to promote primate conservation, but it meets regularly to coordinate federal policies and provide guidance on the care and use of laboratory animals. This body formally adopted the U.S. Government Principles for the Uti-

lization and Care of Vertebrate Animals in Testing, Research, and Training which are part of the current PHS Policy.

Also in 1983, a Memorandum of Understanding was signed to formalize the agreement of NIH, the Animal and Plant Health Inspection Service (APHIS) of the USDA, and the Food and Drug Administration (FDA) to maintain and enhance agency effectiveness while avoiding duplication of efforts to achieve required standards for the care and use of laboratory animals (11). The agreement set forth procedures of reciprocal cooperation which would assist each agency in promoting proper laboratory animal care. Dr. McCarthy of OPRR was chairman of the development committee, Dr. Paul Lepore represented FDA, and Dr. Arnold Matchett represented APHIS. The FDA had issued in 1974 its first Good Laboratory Practice Regulations, so the triple arrangement with NIH, USDA, and FDA was well-conceived. The memorandum was renewed in 1995 with Dr. Nelson Garnett, Dr. James McCormack, and Dr. William (Ron) DeHaven representing NIH, FDA, and USDA respectively (12). The level of interagency cooperation exhibited in the area of laboratory animal welfare during the post-1985 era has been labeled a model for all agencies with overlapping jurisdiction and interests to follow.

Congress became active in the focus on alternatives to animal use in 1984 when its Office of Technology Assessment (OTA) was assigned preparation of a summary of the elements involved with policy issues and options for Congressional action. In addition to the Advisory Panel there was an OTA Project Staff of which Dr. Gary Ellis was project director. Dr. Ellis is now the Director of OPRR. A volume of 441 pages titled "Alternatives to Use of Animals in Research, Testing, and Education" covered the issues thoroughly, but did not envision the elimination of the use of research animals in the foreseeable future. Although there has been some success, the ultimate aim is characterized by frequent references to the "Three Rs—reduction, refinement, and replacement" during the continuing search for the alternatives.

The NIH Revitalization Act of 1993 (PL 103-43) included specific language requiring the NIH director, after consultation with a committee, to prepare a plan for the conduct or support of research into methods of biomedical research and experimentation that do not require the use of animals; that reduce the number of animals used in such research; that produce less pain and distress in such animals; and that involve the use of marine life (other than marine mammals) (13). The plan was also required to address the establishment of the validity and reliability of these methods, encourage acceptance by the scientific community, and train scientists in these methods. The

resulting 1993 NIH Plan for the Use of Animals in Research provides a summary of NIH's activities in this area and a commitment to continue these efforts (14).

In March 1996, the PHS Policy was reprinted with technical corrections such as names and addresses, but was substantively unchanged from the basic 1986 Policy.

References

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